2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

Dominique Farge, Corinne Frère, Jean Connors, Cihan Ay, Alok Khorana, Andres Munoz, Benjamin Brenner, Ajay Kakkar, Hanadi Rafii, Susan Solymoss, et al.

2019 International Clinical Practice Guidelines (ITAC-CPGs) for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer.

Dominique Farge[1]*, MD, Corinne Frere[2]*, MD, Jean M Connors[3], MD, Cihan Ay[4], MD, Alok A Khorana[5], MD, Andres Munoz[6], MD, Benjamin Brenner[7], MD, Ajay Kakkar[8], M.B.B.S., Hanadi Rafii[9], MD, Susan Solymoss[10], MD, Dialina Brilhante[11], MD, Manuel Monreal[12], MD, Henri Bounameaux[13], MD, Ingrid Pabinger[4], MD, James Douketis[14], MD.

* these authors contributed equally to the work

[1] Assistance Publique-Hôpitaux de Paris, Saint-Louis Hospital, Autoimmune and Vascular Disease Unit, Internal Medicine (UF04), Center of reference for rare systemic autoimmune diseases (FAI2R); Université de Paris, EA 3518, Paris, France; Department of Medicine, McGill University, Montreal, QC, Canada.
[2] Sorbonne Université, INSERM UMRS_1166 ; Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Haematology, Paris, France.
[3] Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States
[4] Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria.
[5] Cleveland Clinic, Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland, OH 44106, USA.
[6] Medical Oncology Department, Hospital General Universitario Gregorio Maranon, Universidad Complutense, Madrid, Spain.
[7] Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel.
[8] Thrombosis Research Institute and University College London, London, United Kingdom
[9] Eurocord, Paris-Diderot University EA3518, Saint-Louis Hospital, Assistance Publique-Hôpitaux de Paris, France
[10] Department of Medicine McGill University Montreal Canada.
[11] Francisco Gentil Portuguese Institute of Oncology, Lisbon Center, Lisbon, Portugal.
[12] Department of Internal Medicine, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain. Universidad Católica de Murcia, Spain.
[13] Division of Angiology and Hemostasis, University Hospitals of Geneva, Faculty of Medicine, Geneva, Switzerland.
[14] Department of Medicine, McMaster University, Hamilton, Canada.

Correspondence to:

Dominique Farge : dominique.farge-bancel@aphp.fr; dominique.farge@mcgill.ca Assistance Publique-Hôpitaux de Paris, Saint-Louis Hospital, Autoimmune and Vascular Disease Unit, Internal Medicine (UF04), Center of reference for rare systemic autoimmune diseases (FAI2R); Université de Paris, EA 3518, Paris, France; Department of Medicine, McGill University, Montreal, QC, Canada

Corinne Frere: corinne.frere@aphp.fr Sorbonne Université, INSERM UMRS_1166 ; Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Haematology, Paris, France

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

See Online for appendix

Words count: 4734

Abstract (156 words)

Venous thromboembolism (VTE) is the second-leading cause of death in cancer patients, who are at high risk of VTE recurrence and bleeding during anticoagulant therapy. The International Initiative on Thrombosis and Cancer (ITAC) is an independent academic working group of experts aiming at global consensus for the treatment and prophylaxis of VTE in cancer patients. The ITAC evidence-based Clinical Practice Guidelines (CPGs) were last updated in 2016 with a free web-based mobile application, subsequently endorsed by the International society of Thrombosis and Hemostasis (ISTH). The present 2019 ITAC-CPGs, based on a systematic review of the literature until December 2018 and Grading of Recommendations Assessment Development and Evaluation scale methodology with the support of French Institute of Cancer, were reviewed by an expanded international advisory committee and endorsed by ISTH. Results from head-to-head clinical trials comparing Direct Oral Anticoagulant with Low-Molecular-Weight Heparin and new evidence for the treatment and prophylaxis of VTE in cancer patients are summarized.

Keywords: Cancer, Venous Thromboembolism, Treatment, Prophylaxis, Evidence-based Clinical Practice Guidelines, GRADE methodology, Low Molecular Weight Heparin, Direct Oral Anticoagulant, Vitamin K Antagonist, Central Venous Catheter.

INTRODUCTION

Cancer-associated thrombosis (CAT) is the second leading cause of death after cancer progression.[1] Cancer patients are 4-to 7-times more likely to develop venous thromboembolism (VTE) compared to non-cancer patients and the incidence of CAT is increasing worldwide.[2-4] This is due to multiple factors, which include cancer type and use of central venous catheters (CVC) for chemotherapy and other associated medical and surgical anti-cancer treatments.[5-7]

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

The International Initiative on Thrombosis and Cancer (ITAC) developed the first international evidence-based clinical practice guidelines (CPGs) in 2013[15, 16] to provide clinicians with practical and accessible recommendations for the treatment and prevention of CAT. The ITAC-CPGs use the GRADE methodology[17] and are available through an internationally-accessible, free web-based mobile app (www.itaccme.com). The CPGs and the app were updated in 2016[18] and subsequently endorsed by the International Society of Thrombosis and Hemostasis (ISTH). This 2019 update of the ITAC-CPGs includes a review of new evidence, particularly new data on risk stratification of VTE for decision-making on primary prophylaxis strategies, and the use of DOACs for the prevention and treatment of CAT.

Guideline Development

The guideline development process incorporated measures to ensure impartiality and transparency in the establishment of the recommendations. All iterations of the ITAC-CPGs are an academic initiative by the international branch of the Group Francophone Thrombose et Cancer (GFTC), a not-for-profit organization based at St. Louis Hospital Paris University (www.thrombose-cancer.com). Authors, including the independent external advisory panel, were not paid for their contributions to the preparation of this ITAC-CPG update, and no manuscript preparation services were employed.

Guideline development methodology. The present ITAC-CPG update was prepared by an independent working group of 14 ITAC members, using the GRADE methodology (Panel 1) and support from the Institut National du Cancer (INCa) as with the 2013[15, 16] and 2016 iterations.[18] The ITAC working group is comprised of independent international academic clinicians and methodology experts from various specialties (oncology, hematology, internal medicine, vascular medicine, biology and epidemiology), including two methodologists (CF and HR) and two coordinators (DF and JD). Articles identified for inclusion from the *literature search and selection* process (January 2015 – Dec 2018; see panel 2) underwent a critical appraisal that included an assessment of the articles' methodological strength and clinical relevance by the 2 methodologists (CF and HR), which was then approved by the rest of the working group. All articles identified in the literature search performed with INCA support, were analyzed according to these selection criteria. Every step of the critical appraisal process has been documented and is available for review. Data were independently extracted into evidence tables by the 2 methodologists. Any identified discrepancies were resolved by the working group. Conclusion tables summarizing information from the critical appraisal and data extraction were prepared for each clinical question and were used to develop recommendations according to the GRADE methodology. [17] The ITAC working group convened regularly through teleconferences and meetings at ASH 2017, ISTH 2018 and ASH 2018 to discuss the available evidence (summarized in the Evidence Tables), and formulate the recommendations. Minutes of these meetings have been documented and are available for review. A detailed description of the methodology is provided in the Supplementary Appendix.

Independent external advisory panel. The guidelines were peer-reviewed by an international panel of 83 experts, encompassing all medical and surgical specialties involved in the management of patients with cancer, one nurse, and by two volunteer patient representatives selected from each panelist's patient population or from the patient associations with which the panelists were in contact. Panel experts were identified based on their knowledge, clinical expertise, publication record, and contributions to the field. Panel members were given an evaluation grid (nine-point scale, from don't agree to agree [0–9]) to complete. Feedback was analysed by the working group and revisions were incorporated into this manuscript.

Independent external organization review. The manuscript was then submitted for review to the ISTH Guidance and Guidelines Committee, which subsequently endorsed the ITAC guideline methodology.

RESULTS

GUIDELINE RECOMMENDATIONS

The ITAC CPG uses GRADE methodology to make recommendations for VTE treatment and prophylaxis in patients with cancer. The best quality data are from large phase III randomized clinical trials (RCT) in which patients with less frequently seen cancers were excluded, either because of cancer type or because of other factors such as risk of bleeding and thrombocytopenia. Most patients with primary brain tumors, active central nervous system (CN)S metastases, and hematologic malignancies, especially acute leukemias, did not meet the eligibility criteria for these trials. The limited data available are not sufficient per GRADE methodology to make CPG level recommendations.

Treatment of established VTE

Recommendations for treatment of established VTE in patients with cancer are presented in **Panel 3**. Six randomized clinical trials (RCT) comparing DOACs to VKA have been performed in unselected patients.[19-24] Apixaban, dabigatran, edoxaban, and rivaroxaban have demonstrated a non-inferior efficacy compared to VKAs for the treatment of non-cancer VTE, with similar or

lower rates of major bleeding and clinically-relevant non-major bleeding (CRNMB). The DOACs are endorsed by a number of societies as first-line treatment for VTE in the general population.[25, 26] RCTs having recently assessed their efficacy and safety for CAT are reviewed herein.

Initial treatment of established VTE

LMWH, UFH or Fondaparinux (followed by a VKA). The recommendation on initial treatment with parenteral anticoagulation is unchanged. For the first 5 to 10 days, LMWH is recommended, with fondaparinux and unfractionated heparin (UFH) as alternative treatment options.

Two new studies reported results consistent with previous data.[27, 28] One updated meta-analysis of cancer patient subgroups from 6 studies (446 cancer patients)[27] demonstrated a greater reduction in mortality with LMWH than with UFH treatment (Peto Odds Ratio [OR] 0.53, 95% confidence interval [CI] 0.33-0.85, P = 0.009). Another meta-analysis[28] assessing the first 5-10 days of anticoagulant therapy in cancer patients analysed mortality at 3 months in 5 studies (418 patients), and recurrent VTE in 3 studies (422 patients). Compared to UFH, LMWH was associated with no significant difference in mortality (risk ratio [RR] 0.66, 95% CI 0.40-1.10) and VTE recurrence (RR 0.69, 95% CI 0.27-1.76). Fondaparinux was not statistically different from LMWH or UFH in mortality at 3 months (RR 1.25, 95% CI 0.86-1.81), recurrent VTE (RR 0.93, 95% CI 0.56-1.54), major (RR 0.82, 95% CI 0.40-1.66) or minor (RR 1.53, 95% CI 0.88-2.66) bleeding.

DOACs. Rivaroxaban or edoxaban (after at least 5 days of parenteral anticoagulation) are now recommended as initial treatment options in patients with CAT, who are not at high risk of gastro-intestinal (GI) or genito-urinary (GU) bleeding. The determination of bleeding risk associated with GI or GU cancer types involves consideration of patient-specific factors that may include the extent of the cancer and its propensity for bleeding.

There are differences across DOACs in anticoagulant initiation within the first days of treatment. In the RCTs involving non-cancer patients, 5 days of a parenteral agent, typically LMWH, is required before initiating dabigatran[21] or edoxaban[24] at standard dosage. For apixaban[23] and rivaroxaban[19, 20] treatment with a parenteral agent is not needed, but a higher

dose is given for the first 7 days with apixaban and the first 21 days with rivaroxaban. Edoxaban[8] and rivaroxaban,[9] are two DOACs with published RCTs of patients with CAT (ECOG ≤2, > 40-60 kg, creatinine clearance [CrCl]>30 mL.min–1), which used a LMWH (dalteparin) as comparator. Edoxaban and rivaroxaban were non-inferior to dalteparin for rates of recurrent VTE and survival at 6 months, with higher rates of bleeding. If the decision to treat the cancer patient with a DOAC has been made, 5 days of a parenteral agent are required before starting edoxaban at standard dose, or reduced dose when specific criteria apply (weight ≤60 kg, CrCl ≤50 mL.min^{-1}, concomitant use of strong P-glycoproteins inhibitors). Rivaroxaban is given at 15 mg twice-daily for the first 21 days of anticoagulation, then switched to 20 mg daily. Preliminary data from a RCT of 300 patients using apixaban for CAT presented as an abstract,[10] suggest that compared to LMWH, apixaban is not associated with a higher risk of bleeding.

Inferior vena cava filters. The recommendation on the use of inferior vena cava filters (IVCFs) for the initial treatment of VTE is unchanged. IVCFs may be considered if anticoagulant treatment is contraindicated or if there is recurrent pulmonary embolism (PE) despite appropriate anticoagulant therapy. Eight new retrospective studies on the use of IVCFs in cancer patients have been published since the 2016 ITAC-CPGs,[18] with similar limitations as previous studies. The findings are consistent with the previous ITAC-CPGs [15] [18] that IVCFs in cancer patients appear to increase the risk of recurrent VTE with no evidence of improvement in survival. One new propensity-matched retrospective cohort analysis examined patients who developed symptomatic VTE recurrence on anticoagulant therapy, including a subgroup of cancer patients who received IVCFs after recurrent VTE in the first 3 months of anticoagulant therapy.[29] For patients with deep vein thrombosis (DVT), propensity score-matched groups with or without filter insertion showed no significant difference in death (17.7% *versus* 12.2%, p = 0.56). For patients with PE, propensity score-matched groups showed a significant decrease in all-cause death with filter insertion (2.1%, 48 patients) *versus* without (2.1% *versus* 25.3%, p = 0.02) but PE-related mortality rate was not significantly different between the groups (2.1% *versus* 17.6%, p = 0.08).

Thrombolysis. There are limited data on thrombolysis in cancer patients. Individual patient decision-making in consultation with clinicians experienced with parenteral or catheter directed thrombolysis is advised.

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

Unchanged from the 2016 CPGs, LMWHs are the preferred treatment for CAT over VKAs. Edoxaban and rivaroxaban are now also recommended for the early maintenance and long-term treatment of VTE in cancer patients without contraindications, including risk of strong drug-drug interactions or impaired GI absorption or excessive bleeding risk, especially those with GI or urogenital malignancies. A list of drugs that can potentially interfere with the action of DOACs is included in the Supplementary Appendix (page 88) and should be considered in clinical decisions about DOAC use. Patients who were receiving these drugs were excluded from the randomized trials assessing DOACs for the prevention and treatment of cancer-associated thrombosis.

LMWH versus VKA. Since the 2016 ITAC-CPGs, no new RCTs comparing LMWH to VKA have been published. LMWH is preferred over VKA for early maintenance treatment of CAT. The 2016 CPGs reviewed 5 RCTs in cancer patients (CANTHANOX, CLOT, LITE, ONCENOX, CATCH), 2 RCTs in unselected patients with cancer patient subgroups, and 9 meta-analyses that reported on the benefits and risks of LMWH *versus* short-term heparin followed by VKA in the early maintenance and long-term treatment of confirmed VTE.[18] One new meta-analysis reported on the risk of intracranial haemorrhage (ICH) with LMWH compared to VKA in cancer patients (n=2089).[30] There were no significant differences in risk of major bleeding between the 2 anticoagulant therapies during the first 6 months of treatment (RR 0.49, 95 % CI 0.10-2.3).

DOAC versus VKA. Several RCTs have assessed DOACs in the treatment and prevention of VTE in the general population.[19-24] DOACs have been shown to be non-inferior to VKAs for treatment and prevention of recurrent VTE with similar or lower rates of bleeding. Consistent with results obtained in studies of predominantly non-cancer patients, DOACs were at least non-inferior to VKAs for the prevention of VTE recurrence in cancer patient subgroups

(approximately 5% of patients) from these trials (OR 0.63, 95% CI 0.37-1.10), with no difference in major bleeding or CRNMB (OR 0.77, 95% CI 0.41-1.44).[31]

DOAC versus LMWH. Two RCTs comparing DOACs and LMWH (dalteparin) for CAT have been published.[8, 9] DOACs were at least as effective as dalteparin at reducing VTE recurrence, but with an increased risk of bleeding. In the Hokusai VTE Cancer trial,[8] 1050 cancer patients with symptomatic or incidentally diagnosed VTE were randomized to receive edoxaban (dalteparin for at least 5 days, followed by edoxaban 60 mg once daily) or dalteparin (200 IU/kg once daily for 1 month, followed by 150 IU/kg daily), for 6-12 months. The primary outcome was a composite of recurrent VTE or major bleeding within 12 months after randomization, regardless of treatment duration. Edoxaban was non-inferior to LMWH: 67 of 522 (12.8%) patients in the edoxaban group, compared to 71 of 524 patients (13.5%) in the dalteparin group developed a primary outcome event (HR 0.97, 95% CI 0.70-1.36, p=0.006 for non-inferiority, p=0.87 for superiority). The rates of VTE recurrence were numerically lower with edoxaban, but this difference did not reach statistical significance (7.9% [edoxaban] *versus* 11.3% [dalteparin], p=0.09). The rate of major bleeding was higher with edoxaban (6.9% *versus* 4.0%, p=0.04). Rates of CRNMB and overall survival were similar between groups. In the SELECT-D trial,[9] 406 cancer patients with symptomatic or incidental PE, or symptomatic lower-extremity proximal DVT were randomized to receive rivaroxaban (15 mg twice-daily for 3 weeks, then 20 mg daily for 2-6 months) or LMWH (dalteparin 200 IU/kg daily during month 1, then 150 IU/kg daily up to 6 months). The primary outcome measure was VTE recurrence in the 6 months after randomization. Notably, the Data Safety Monitoring Board decided to exclude patients with upper GI malignancy after the trial was in progress. The 6-month cumulative rate of VTE recurrence with rivaroxaban was significantly lower than with dalteparin (4% [rivaroxaban] *versus* 11% [dalteparin], hazard ratio [HR] 0.43, 95% CI 0.19-0.99). The rate of CRNMB was significantly higher with rivaroxaban (13% [rivaroxaban] *versus* 4% [dalteparin], HR 3.76, 95% CI 1.63-8.69). A non-statistically significant increase in major bleeding was observed with rivaroxaban (6% [rivaroxaban] *versus* 4% [dalteparin]). Overall survival was similar between groups.

Preliminary results from the ADAM VTE trial[10] were presented at the 2018 ASH meeting. Three hundred patients with various types of CAT including upper extremity and splanchnic vein thrombosis were randomized to apixaban (10 mg twice-daily for 7 days followed by 5 mg twice-daily thereafter) *versus* dalteparin (200 IU/kg daily for 1 month, followed by 150 IU/kg daily thereafter) for 6 months. Rates of the primary outcome of major bleeding were low, with no significant difference between treatments (0 [apixaban] *versus* 3/142 (2.1%) [dalteparin], p=0.9956). Rates of a secondary safety composite endpoint of major and CRNMB were equivalent at 9% for both groups. Recurrent VTE, a secondary efficacy outcome, occurred in 5 patients (3.4%) in the apixaban group compared to 20 patients (14.1%) in the dalteparin group (HR 0.26, 95% CI 0.09-0.80, p=0.0182).

Duration of anticoagulation. The updated evidence review supports the use of LMWH or DOAC for at least 6 months for CAT and we have extended the Grade 1A recommendation on the duration of anticoagulation (LMWH or DOAC) from 3 to 6 months. One meta-analysis of 16 RCTs (5167 cancer patients) assessed the safety and efficacy of LMWH, VKA, and DOAC for long-term CAT treatment, with 6 RCTs having a 6-12 months follow-up. Eight studies compared LMWH with VKAs (2327 patients). LMWH was associated with a 42% reduction in VTE recurrence compared to VKAs (RR 0.58, 95% CI 0.43-0.77).[32] No difference was found in rate of major (RR 1.09, 95% CI 0.55-2.12) or minor bleeding (RR 0.78, 95% CI 0.47-1.27), 12-month mortality (RR 1.00, 95% CI 0.88-1.13), or thrombocytopenia (RR 0.94, 95% CI 0.52-1.69). Five studies compared DOACs with VKAs (982 patients). The meta-analysis could not exclude a beneficial or harmful effect of DOACs compared to VKAs on VTE recurrence (RR 0.66, 95% CI 0.33-1.31), major (RR 0.77, 95% CI 0.38-1.57) and minor (RR 0.84, 95% CI 0.58-1.22) bleeding, or mortality (RR 0.93, 95% CI 0.71-1.21).

VTE recurrence in patients with cancer on anticoagulation. No new studies have investigated VTE recurrence under anticoagulant treatment since the 2016 ITAC-CPGs.

Treatment of established central venous catheter-associated thrombosis in patients with cancer. No new studies on established CVC-associated thrombosis were found. The 2016 ITAC-CPG recommendation is unchanged.

VTE Prophylaxis in Patients with Cancer

Recommendations for VTE prophylaxis in patients with cancer are presented in **Panel 4**. The literature search did not identify any specific data on the perioperative management of anticoagulation in cancer patients with established VTE who are already receiving anticoagulant treatment. In the absence of specific data, the perioperative management of anticoagulation in these patients was not addressed in this review. Risk factors and assessment models to identify high-risk patients that could benefit from primary thromboprophylaxis are summarized in **Panel 5**. The most widely used model was developed by Khorana et al.[33] for ambulatory patients receiving chemotherapy.

VTE prophylaxis in patients undergoing cancer surgery

LMWH versus UFH. A previous expanded meta-analysis (12890 patients with cancer),[34] consistent with its earlier version[35] and a meta-analysis in general surgery,[36] indicated that perioperative prophylaxis with daily LMWH was similar to UFH thrice-daily (RR 0·78, 95% CI 0·53–1·15), and superior to UFH twice-daily (RR 0·66, 95% CI 0·44–0·99). A new meta-analysis of 12 studies (10 RCTs, 2 retrospective),[37] confirmed that LMWH was associated with a decreased risk for DVT compared with UFH (175 events in 5002 cancer patients *versus* 164 events in 2717 cancer patients, RR 0.81, 95% CI 0.66-1.00), with no significant differences in rates of bleeding (RR 0.73, 95% CI 0.49–1.08). Daily LMWH is more convenient than twice- or thrice-daily UFH and may be cost-neutral or cost-saving compared with UFH.

Since the 2016 ITAC-CPGs, there is no new evidence that would support the use of fondaparinux as an alternative to LMWH thromboprophylaxis.

Comparison between doses of LMWH. The updated literature search found no new studies comparing different doses of LMWH in surgical cancer patients. As recommended in the 2016 ITAC-CPGs, the highest prophylactic dose of LMWH studied should be used in clinical practice.

Extended-duration (4 weeks) thromboprophylaxis*.* The 2016 ITAC-CPGs for extended prophylaxis with LMWH in cancer patients undergoing laparotomy and laparoscopic surgery remains unchanged, with 4 new supporting meta-analyses changing the grade of the recommendation from Grade 1B to 1A. In the first meta-analysis,[38] extended-duration prophylaxis (2-6 weeks) significantly reduced the risk of any VTE (2.6 *versus* 5.6%, RR 0.44, 95%

CI 0.28-0.70), proximal DVT (1.4 *versus* 2.8%, RR 0.46, 95% CI 0.23-0.91), but not symptomatic PE (0.8 *versus* 1.3%, RR 0.56, 95% CI 0.23-1.40). There was no significant increase in major bleeding (1.8 *versus* 1.0%, RR 1.19, 95% CI 0.47-2.97). In the second meta-analysis,[37] extended-duration thromboprophylaxis was associated with a significant decrease in the incidence of DVT (RR 0.57, 95% CI 0.39-0.83), without significant increase in bleeding (RR 1.48, 95% CI 0.78-2.8). Three observational studies (2 prospective, 1 retrospective) provided evidence for extended-duration prophylaxis after radical cystectomy[39, 40] and liver resection.[41] There is strong evidence supporting extended-duration prophylaxis for 4 weeks after cancer surgery provided that patients are not at high risk of bleeding. A third meta-analysis reported that extended-duration prophylaxis significantly reduced the rate for all VTE (OR 0.38, 95% CI 0.26-0.54), all DVT (OR 0.39, 95% CI 0.27-0.55), and proximal DVT (OR 0.22, 95% CI 0.10-0.47), with a non-significant reduction in symptomatic VTE (OR 0.30, 95% CI 0.08-1.11) and a non-significant increase in major bleeding (OR 1.10, 95% CI 0.67-1.81).[42] A fourth meta-analysis provided corroborating findings.[43]

***Mechanical methods of prophylaxis*.** Since the 2016 ITAC-CPGs, one RCT assessed the clinical effectiveness of mechanical methods of thromboprophylaxis in 682 cancer patients.[44] Patients with intermittent pneumatic compression (IPC) alone had a higher rate of VTE compared to IPC plus LMWH (3.6% [IPC] *versus* 0.6% [IPC+LMWH], $p = 0.008$), although bleeding rates were higher (9.1 v*ersus* 1.2%, $p < 0.001$). Two small randomized studies involving 30 patients[45] and 90 patients[46] found no benefit of adding LMWH to mechanical methods of prophylaxis. Unchanged from the 2016 ITAC-CPGs, the use of mechanical methods of prophylaxis as monotherapy is not recommended, except when pharmacological methods are contraindicated.

Inferior vena cava filter placement. No additional studies were available since the 2016 ITAC-CPGs. The recommendation against the routine use of IVC filters as primary VTE prophylaxis is unchanged.

VTE prophylaxis in hospitalized medically-treated patients with cancer

No new studies have been published that addressed prophylaxis in patients with cancer

who are hospitalized with an acute medical illness.

VTE prophylaxis in ambulatory cancer patients receiving systemic anti-cancer therapy. The risk for symptomatic VTE is approximately 5-10% in ambulatory patients receiving chemotherapy; the risk of VTE and of bleeding vary by cancer type, cancer treatment, and patient characteristics.[47] Unchanged from the 2016 ITAC-CPGs, primary prophylaxis is not recommended routinely in all ambulatory cancer patients receiving systemic anti-cancer therapy. The recommendation relating to primary prophylaxis in medical cancer patients should consider *only small numbers of patients with certain common cancer types were included in the trials* (i.e., breast, colorectal, prostate) and that the results may pertain only to specific DOACs (i.e., apixaban, rivaroxaban).

The updated search identified 5 RCTs and 7 meta-analyses (738-12352 patients) comparing anticoagulant prophylaxis to no intervention or placebo in ambulatory patients receiving systemic anticancer therapy. The duration of thromboprophylaxis in medical cancer patients is uncertain and has not been evaluated for more than a 6-month duration, and should be re-evaluated periodically based on individual patient risk-benefit assessment.

LMWHs. A randomized trial[48] assessed 12 weeks of prophylaxis with LMWH (dalteparin 5000 IU daily) *versus* no prophylaxis in 117 cancer patients with a Khorana score ≥3. A non-significant reduction in a composite measure of symptomatic and asymptomatic VTE (detected by weekly lower limb ultrasound) was observed with LMWH compared to placebo (12% *versus* 21%, HR 0.69, 95% CI 0.23-1.89), with no difference in major bleeding (1 event in each group). A second open-label trial[49] assessed an increased dose of LMWH (enoxaparin 1 mg/kg daily) in 390 patients with small cell lung cancer. The trial was designed to assess the effect of LMWH on mortality. No benefit was shown in overall and progression-free survival, but there was a significant reduction in VTE events (HR 0.31, 95% CI 0.11-0.84). A third RCT investigating the impact of LMWH on survival of patients with resected non-small cell lung cancer (NSCLC) reported no significant difference in 5-year survival (HR 1.24, 95% CI; 0.92-1.68) or occurrence of symptomatic VTE (SHR 0.94, 95% CI 0.68-1.30) between patients with resected NSCLC receiving tinzaparin versus no treatment.[50] An updated meta-analysis assessed 26 RCTs

comparing any oral or parenteral anticoagulant or mechanical intervention to no thromboprophylaxis or placebo (12352 patients).[47] LMWH reduced the rate of symptomatic VTE (RR 0.54, 95% CI 0.38-0.75) compared to no prophylaxis, with a non-significant increase in major bleeding (RR 1.44, 95% CI 0.98-2.11). In a subgroup of patients with multiple myeloma, LMWH was associated with a significant reduction in the rate of symptomatic VTE compared with VKA (RR 0.33, 95% CI 0.14- 0.83), while the difference between LMWH and aspirin was not statistically significant (RR 0.51, 95% CI 0.22-1.17). A second new meta-analysis involving 18 RCTs (9575 patients) reported that prophylaxis with a parenteral anticoagulant (UFH, LMWH, fondaparinux) in all ambulatory cancer patients receiving chemotherapy was associated with a reduced risk for symptomatic VTE (RR 0.56, 95% CI 0.47-0.68) and a statistically significant increase in minor bleeding risk (RR 1.70, 95% CI 1.13-2.55). Major bleeding was not increased (RR 1.30, 95% CI 0.94-1.79).[51]

DOACs. Since the 2016 ITAC-CPGs, two RCTs assessed DOACs for the primary prevention of VTE in selected ambulatory cancer patients at intermediate-to-high risk for VTE, defined by a Khorana score ≥2.[11, 12] In such patients observational studies have shown a 8-12% risk for VTE during the period of chemotherapy.[52] The CASSINI trial, [11] compared up to 6 months of thromboprophylaxis with rivaroxaban (10 mg daily) to placebo in 841 cancer patients initiating chemotherapy after excluding 4.5% of eligible patients found to have lower extremity VTE at the time of enrollment**.** Patients with primary or metastatic brain cancer were also excluded. The primary endpoint was a composite measure of symptomatic or asymptomatic DVT or PE, and VTE-related death. Patients receiving rivaroxaban experienced fewer primary endpoint events compared to placebo while *on-treatment* (HR 0.40, 95% CI 0.20-0.80), whereas the difference between the groups was non-significant over the entire 6-month observation period (HR 0.66, 95% CI 0.40-1.09, p = 0.10). When combining the composite primary endpoint with all-cause of mortality, using a pre-specified intention-to-treat analysis, patients on rivaroxaban experienced fewer events compared to placebo (23.1% *versus* 29.5%, HR 0.75, 95% CI 0.57-0.97). There was no difference in major bleeding (HR 1.96, 95% CI 0.59-6.49). The AVERT trial[12] compared apixaban, 2.5 mg twice-daily, with placebo for 6 months in 573 cancer patients initiating chemotherapy. Based on the modified intention-to-treat analysis, there was a lower

risk of the primary outcome of symptomatic and incidental VTE with apixaban (4.2% *versus* 10.2%, HR 0.14, 95% CI 0.26-0.65, p<0.001), but an increased risk of major bleeding (3.5% *versus* 1.8%, HR 2.00, 95% CI 1.01-3.95, p = 0.046). Both studies excluded patients considered at increased risk of bleeding and also had a high rate of discontinuation of medication (36% to 50%) for both active drug and placebo. The CASSINI[11] and AVERT[12] trials indicate a net clinical benefit of initiating anticoagulant prophylaxis with a DOAC (rivaroxaban 10 mg daily or apixaban 2.5 mg twice-daily) in selected cancer patients initiating chemotherapy, prompting a new ITAC-CPGs recommendation (see panel 4).

Anticoagulant thromboprophylaxis in selected patients according to tumor types

***Lung cancer patients*.** Two new meta-analyses consistently showed that in lung cancer patients, LMWH confers a relative VTE risk reduction,[53, 54] with an increase in bleeding. Another meta-analysis of 6 RCTs in ambulatory lung cancer patients receiving chemotherapy (4315 patients)[55] reported a 4.0% incidence of VTE with LMWH compared to 7.9% in groups without prophylaxis or placebo (risk ratio 0.51, 95% CI 0.40-0.65), with no significant difference in major bleeding (pooled risk ratio 1.47, 95% CI 0.79-2.75) and a significant increase in CRNMB (RR 3.2, 95% CI 2.09-5.06). Overall survival was not increased with LMWH (pooled risk ratio 1.02, 95% CI 0.94-1.11).

Pancreatic cancer patients. One new meta-analysis reported a significant VTE rate reduction in patients with pancreatic cancer (RR 0.18, 95% CI 0.08-0.40), without significant increase in bleeding events.[56] The best net clinical benefit of thromboprophylaxis with LMWH is observed in pancreatic cancer patients receiving chemotherapy, whereas in other patient groups, including lung cancer, this benefit appears to be offset by an increased risk for bleeding. The use of VTE prophylaxis with LMWH for ambulatory cancer patients with pancreatic cancer receiving chemotherapy is supported by 2 RCTs and remains a Grade 1B recommendation in the updated 2019 ITAC-CPGs.

***Unselected cancer types*.** One new meta-analysis of 7 RCTs assessed the effects of oral anticoagulants (VKAs or apixaban) versus placebo or no intervention of primary VTE prophylaxis in cancer patients (1486 patients).[57] In the 6 RCTs comparing a VKA to no prophylaxis, there was

no survival advantage with VKA therapy, but a significant increase in major (RR 2.93, 95% CI 1.86-4.62) and minor (RR 3.14, 95% CI 1.85-5.32) bleeding was observed.

Myeloma patients treated with IMIDs. No new studies have assessed LMWH or DOAC thromboprophylaxis in this specific population since the 2013 ITAC CPG. The recommendation remains unchanged.

Prophylaxis of Central Venous Catheter (CVC)-related VTE

The recommendation against routine primary prophylaxis of CVC-related VTE remains unchanged. One new meta-analysis of 13 studies (3420 patients) in cancer patients with a CVC did not confirm or exclude a beneficial or detrimental effect of low-dose VKA compared to no VKA on mortality, symptomatic catheter-related VTE, major bleeding, minor bleeding, or premature catheter removal, but found moderate-certainty evidence that LMWH reduced CVC-related thrombosis compared to no LMWH (RR 0.43, 95% CI 0.22-0.81) without increase in major or minor bleedings.[58] One systematic review and meta-analysis showed that centrally inserted CVCs were associated with a decrease in CVC-related VTE compared with peripherally inserted CVCs (OR 0.45, 95% CI 0.32–0.62).[59]

VTE treatment in special cancer situations

Recommendations on VTE prevention and treatment for patients in special clinical situations are presented in **panel 6**.

Patients with Brain Tumors. Since the 2016 ITAC-CPGs, one retrospective study[60] found that the rate of recurrent VTE did not significantly differ between cancer patients with or without primary or metastatic brain tumors (364 patients, 11 [95 % CI 6.7–17.9] per 100 patient-years *versus* 13.5 [95 % CI 9.3–19.7] per 100 patient-years), but that rates of intracranial bleeding were higher (4.4 % *versus* 0 %, p=0.004). One new meta-analysis based on 9 retrospective studies[61] reported that the risk of ICH in patients with brain tumors was increased by 2-fold with compared to without anticoagulation (OR 2.13, 95% CI 1.00–4.56), and more than 3-fold in patients with glioma (OR 3.75, 95% CI 1.42–9.95). In patients with brain metastases, therapeutic anticoagulation was not associated with an increased risk of ICH (OR 1.07, 95% CI 0.61–1.88). A second new meta-analysis of 10 RCTs[62] assessed the benefit-to-risk ratio of several methods of VTE prophylaxis in 1263 patients with brain tumor undergoing

craniotomy. Prophylactic measures conferred a significant reduction in VTE risk, with no increase in major bleeding. UFH alone showed a stronger reduction in VTE risk compared to placebo (RR 0.27, 95 % CI 0.10–0.73), and LMWH combined with mechanical prophylaxis showed a lower VTE risk compared to mechanical prophylaxis alone (RR 0.61, 95 % CI 0.46–0.82).

Patients with Thrombocytopenia. The recommendation for anticoagulant treatment of established VTE in cancer patients with thrombocytopenia is unchanged. Since the 2016 CPGs, one retrospective study[63] reported VTE recurrence rates in 47 patients with hematologic malignancy and thrombocytopenia (platelets $<50\times10^9$/L) and 81 patients with hematologic malignancy without thrombocytopenia. One systematic review[64] of 121 patients with CAT and thrombocytopenia reported a high risk of recurrent VTE (27%) and bleeding (15%), but available data do not support one management strategy over another to treat CAT in patients with thrombocytopenia.

Patients with Renal Failure. The recommendation for anticoagulant treatment of established VTE in cancer patients with renal failure is unchanged. Since the 2016 CPGs, a *post-hoc* analysis of data from the CLOT study[65] compared dalteparin with VKA for the prevention of recurrent VTE in a patient subgroup with renal failure (CrCl<60 $mL.min^{-1}$, 162 out of 676 patients). Compared to VKA, dalteparin conferred a significantly reduced risk of recurrent VTE (HR 0.15, 95% CI 0.03-0.65, p = 0.01), with a similar safety profile. Second, a *post-hoc* analysis of patients with renal failure (GFR-MDR<60 $mL.min^{-1}$/1.73m) in the CATCH study (131 out of 733 patients),[66] reported a statistically significant increase in risk of recurrent VTE (RR 1.74, 95%CI 1.06-23.85) and major bleeding (RR 2.98, 95% CI 1.29-6.90) compared to patients without renal failure, with no significant difference in clinically relevant bleeding or mortality observed between LWMH treated or VKA treated patients.

Obese patients. Consideration for a higher dose of LMWH should be given in obese cancer-surgery patients. In non-cancer surgical patients, empirically derived higher LMWH dosing regimens have been used for thromboprophylaxis although the evidence to support this practice is limited.[67]

CONCLUSION

CAT is a concerning problem for cancer patients, increasing both morbidity and mortality. The DOACs have changed the approach to care for patients in atrial fibrillation and VTE, and new data now suggest a role for DOACs in CAT treatment and prophylaxis. The 2019 updated ITAC-CPGs following a strong methodology place these data in the framework of established approaches to all aspects of treatment and prophylaxis of CAT. The ITAC-CPGs accompanying free ITAC-CME web-based mobile App (for iOS and Android see http://www.itacccme.com) will assist the practicing clinician with decision making at a variety of levels to provide optimal care of cancer patients to prevent and treat VTE.

Contributors

The Institut National du Cancer (INCa) designed the methods used to develop the clinical practice guidelines and provided logistical support by doing the MEDLINE OVID reference searches. The guidelines were developed by an independent working group of academic clinicians, researchers, and experts (all authors of this Review). DF and JD were the acting coordinators for the working group. They coordinated the preparation of the manuscript, and the contribution of the authors. CF and HR were the methodologists. They assessed the methodological strength and clinical relevance of the articles identified by the literature search (critical appraisal), the article selection, and the extraction of the data into evidence tables. All authors reviewed and approved the INCa literature search, the critical appraisal of articles, the article selection, the data extraction, and the evidence tables. DF, CF, JMC, CA and JD wrote the first draft of the literature review. All working group members edited and contributed to the development of the literature review. Guideline consensus was achieved during two meetings, at which the working group collectively drafted and ranked the recommendations. The manuscript was reviewed by a multidisciplinary advisory panel of 83 experts (eg, oncology, haematology, palliative medicine, internal medicine, vascular medicine, biology, and epidemiology). All working group members approved the final recommendations and the manuscript.

This study was not NIH funded. None of the authors are employed by NIH. Dr A Khorana is the recipient of an NIH grant (UO1 HL 144302-01)

Conflict of interest

DF reports non-financial support from Leo Pharma, Aspen Pharmacare and Pfizer, outside the submitted work. JD participates in Advisory Boards or Educational Activities for Astra-Zeneca, Bayer, Biotie, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Pfizer, Portola, Sanofi, The Medicines Company, was consultant to Actelion, AGEN Biomedical, Boehringer-Ingelheim, Janssen Research and Development, Ortho-Janssen Pharmaceuticals, Sanofi, was Chair of the MARINER trial (NCT02111564) Clinical Endpoint Committee, was Employee of the Merck Manual , of Up-to-Date , reports grants from Boehringer-Ingelheim and other from Educational Program - CME for Reviewers – Journal of Thrombosis and Haemostasis 2018, outside the submitted work. CA reports personal fees from Bayer and Daiichi-Sankyo, outside the submitted work. HB reports grants and personal fees from Thrombosis Research Institute (London), personal fees from Bayer AG, outside the submitted work. BB was a member of an advisory board or similar committee for Aspen Pharmacare, Bayer, Daiichi-Sankyo, Pfizer, ROVI Laboratories, Sanofi, outside the submitted work. DD reports no conflict of interest. JMC reports personal fees from Bristol-Myer Squibb and Portola. CF reports personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Bayer, personal fees and non-financial support from Aspen Pharma Care, personal fees and non-financial support from Pfizer, outside the submitted work. AAK reports personal fees and non-financial support from Janssen, personal fees and non-financial support from Bayer, personal fees and non-financial support from Halozyme, personal fees and non-financial support from AngioDynamics, personal fees and non-financial support from Pfizer, personal fees from TriSalus, personal fees from Incyte, personal fees from Pharmacyclics, personal fees from Pharmacyte, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Parexel, personal fees and non-financial support from Seattle Genetics, personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Medscape, grants from Merck, grants from Array, grants from Bristol Myers,

grants from Leap, outside the submitted work. AK reports grants and personal fees from Bayer AG, personal fees from Boehringer-Ingelheim Pharma, personal fees from Daiichi Sankyo , personal fees from Janssen Pharma, personal fees from Pfizer, personal fees from Sanofi S.A, personal fees from Verseon, outside the submitted work . MM reports grants from Sanofi and Bayer, outside the submitted work. AMM reports non-financial support and other from Celgene, grants, non-financial support and other from Sanofi, non-financial support and other from Pfizer-BMS, grants, non-financial support and other from LEO Pharma, non-financial support and other from Daiichi Sankyo, non-financial support and other from Bayer, non-financial support and other from Halozyme, other from Rovi, outside the submitted work. IP reports personal fees from Bayer, personal fees from Boehringer-Ingelheim, personal fees from Daiichi-Sanchyo, personal fees from Pfizer, outside the submitted work. HR reports no conflict of interest. SS reports no conflict of interest.

Appendix. List of the advisory committee members

ARGENTINA : Patricia Casais, Academia Nacional de Medicina de Buenos Aires, Buenos Aires; AUSTRIA : Clemens Feistritzer, Medizinische Universität Innsbruck, Innsbruck; Thomas Gary, Medizinische Universität Graz, Graz; Christine Marosi, Medizinische Universität Wien, Wien; Florian Posch, Medizinische Universität Graz, Graz; Matthias Preusser, Medizinische Universität Wien, Wien ; BRAZIL : Cynthia Rothschild, Fundação Faculdade de Medicina, São Paulo; CANADA : Thierry Alcindor, McGill University, Montreal; Marc Blostein, McGill University, Montreal; Russel D Hull, University of Calgary, Calgary; Maral Koolian, McGill University, Montreal; Andre Roussin, CHUM University of Montreal, Montreal; Vicky Tagalakis, McGill University, Montreal; CHINA, HONG KONG : Raymond Wong, The Chinese University of Hong Kong, Hong Kong; FRANCE : Thierry Andre, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Antoine, Paris; Eric Assenat, St-Eloi University Hospital- Montpellier School of Medicine, Montpellier; Ilham Benzidia, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Barbara Bournet, CHU de Toulouse, Hopital Rangueil, Toulouse; Antoine Carpentier, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Jérôme Connault, CHU de Nantes, Nantes; Ludovic Doucet, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Cécile

Durant, CHU de Nantes, Nantes; Joseph Emmerich, Hôpital Saint-Joseph, Paris; Jean-Christophe Gris, CHU de Nimes, Nimes; Adrian Hij, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Claire Le Hello, CHU Saint Etienne, Saint-Etienne; Isabelle Madelaine, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Zora Marjanovic, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Antoine, Paris; Emmanuel Messas, Assistance Publique Hôpitaux de Paris, Hôpital Européen George Pompidou, Paris; Arlette Ndour, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; Stéphane Villiers, Assistance Publique Hôpitaux de Paris, Hôpital Saint-Louis, Paris; GERMANY : Jan Beyer-Westendorf, University Hospital Dresden, Dresden; Florian Langer, University Medical Center Hamburg, Hamburg; Hanno Riess, Charity University, Berlin; INDIA : Joydeep Chakbrabartty, Vivekananda Institute of Medical Science, Kolkata; Sanjith Saseedharan, S.L Raheja Hospital Raheja Rugnalaya Marg, Mumbai; ISRAEL : Dorit Blickstein, Rabin Medical Center, Ze'ev Jabotinsky, Petah Tikva; Sharf Giorfa (patient), Ellis Martin, Meir medical center, Kfar Saba ; ITALY : Walter Ageno, University of Insubria Varese, Varese; Anna Falanga, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo; Mario Mandala, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo; IVORY COAST : Michel Nguessan, CHU de Treichville, Abidjan; Toutou Toussaint, CHU de Treichville, Abidjan; JAPAN : Takayuki IKezoe, Fukushima medical University Hikarigaoka, Fukushima; Norizaku Yamada, Kuwana city medical center, Kunawana; LEBANON : Ali Bazarbachii, American University of Beirut, Beirut; Ali Shamseddine, American University of Beirut, Beirut; Ali Taher American University of Beirut, Beirut; PORTUGAL : Fernando Ajauro, Centro Hospitalar de São João, Porto; Isabel Bogalho, Instituto Superior Técnico, Lisboa; Hugo Alexandre Clemente, Instituto Português de Oncologia Lisboa Francisco Gentil, Lisboa; Luisa Lopes Dos Santos, Instituto Português de Oncologia Porto, Porto; Durate Henrique Machado, Instituto Português de Oncologia Lisboa Francisco Gentil, Lisboa; Antonio Moreira, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa; Ana Pais, Instituto Português de Oncologia Coimbra Francisco Gentil, Coimbra; QUATAR : Kamal R Al-Aboudi , National Center for Cancer Care and Research (NCCCR), Doha; El Omri Halima, National Center for Cancer Care and Research (NCCCR), Doha; REPUBLIC OF SINGAPORE : Lai Heng Lee, Singapore General Hospital, Singapore; RUSSIA : Viktoria Bitsadze, Sechenov First Moscow Medical University, Moscow; Alexander Makatsariya,

Sechenov First Moscow Medical University, Moscow; Jamilya Khrizroeva, Sechenov First Moscow Medical University, Moscow; SERBIA : Darko Antic, Medical Faculty, University of Belgrade, Belgrade; SPAIN : Juan I Arcelus, University of Granada, Granada; Carme Font, Hospital Clinic de Barcelona, Barcelona; Enrique Gallardo, Hospital Universitari Parc Taulí, Sabadell; Luis Juan-Palomares, Hospital Universitario Virgen del Rocio, Sevilla; Ramos Lecumberri, Clinica Universidad de Navarra, Pamplona; Remedios Otero-Candelera, Hospital Universitario Virgen del Rocio, Sevilla; Vanessa Pachon Olmos, Hospital Ramon y Cajal, Madrid; José Antonio Rueda-Camino, Hospital Universitario de Fuenlabrada, Madrid; Pedro Ruiz-Artacho, Clínica Universidad de Navarra, Madrid; Javier Trujillo-Santos, Universidad Católica de Murcia, Murcia ; SWITZERLAND : Marc Righini, University Hospitals of Geneva; Hans Stricker, Ospedale La Carità, Locarno; THAILAND : Pantep Angchaisuksiri, Ramathibodi Hospital, Mahidol University Bangkok, Bangkok ; TURKEY : Ahmet Muzaffer Demir, Trakya University, Erdine; UK : Anthony Marayevas, Hull York Medical School, Heslington, York ; UNITED MEXICAN STATES : Gabriela Cesaraman, National Cancer Inst, México, México; Luis Meillon, Universidad Nacional Autónoma de México; URUGUAY : Cecilia Guillermo, Universidad de la República Oriental del Uruguay, Montevideo; USA : Kenneth A Bauer, Harvard Medical School, Boston; Charles Francis, University of Rochester, Rochester; Nigel S Key, The University of North Carolina at Chapel Hill, Chapel Hill; Howard Liebman, University of Southern California, Los angeles; Robert Hokanson (patient), Gerald Soff, Memorial Sloan Kettering Cancer Center, New-York.

REFERENCES

1. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore)* 1999; 78: 285-291. 1999/09/28.
2. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med* 2006; 166: 458-464. 2006/03/01. DOI: 10.1001/archinte.166.4.458.
3. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; 5: 632-634. 2007/02/27. DOI: 10.1111/j.1538-7836.2007.02374.x.

4. Heit JA, Spencer FA and White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016; 41: 3-14. 2016/01/19. DOI: 10.1007/s11239-015-1311-6.
5. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. *Blood* 2013; 122: 1712-1723. 2013/08/03. DOI: 10.1182/blood-2013-04-460121.
6. Ahlbrecht J, Dickmann B, Ay C, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol* 2012; 30: 3870-3875. 2012/09/26. DOI: 10.1200/JCO.2011.40.1810.
7. Trinh VQ, Karakiewicz PI, Sammon J, et al. Venous thromboembolism after major cancer surgery: temporal trends and patterns of care. *JAMA Surg* 2014; 149: 43-49. 2013/11/08. DOI: 10.1001/jamasurg.2013.3172.
8. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med* 2018; 378: 615-624. 2017/12/13. DOI: 10.1056/NEJMoa1711948.
9. 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: 2017-2023. 2018/05/11. DOI: 10.1200/JCO.2018.78.8034.
10. McBane R, Wysokinski W, Le-Rademacher J, et al. Apixaban, Dalteparin, in Active Cancer Associated Venous Thromboembolism, the ADAM VTE Trial. In: *American Society of Hematology* San Diego, CA, 2018.
11. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med* 2019; 380: 720-728. 2019/02/21. DOI: 10.1056/NEJMoa1814630.
12. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med* 2019; 380: 711-719. 2018/12/05. DOI: 10.1056/NEJMoa1814468.
13. Short NJ and Connors JM. New oral anticoagulants and the cancer patient. *Oncologist* 2014; 19: 82-93. 2013/12/10. DOI: 10.1634/theoncologist.2013-0239.
14. Bellesoeur A, Thomas-Schoemann A, Allard M, et al. Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: Clinical consequences. *Crit Rev Oncol Hematol* 2018; 129: 102-112. 2018/08/12. DOI: 10.1016/j.critrevonc.2018.06.015.
15. 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. 2012/12/12. DOI: 10.1111/jth.12070.
16. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. *J Thromb Haemost* 2013; 11: 71-80. 2012/12/12. DOI: 10.1111/jth.12071.
17. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ* 2008; 336: 1049-1051. 2008/05/10. DOI: 10.1136/bmj.39493.646875.AE.
18. 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-e466. 2016/10/14. DOI: 10.1016/S1470-2045(16)30369-2.
19. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499-2510. 2010/12/07. DOI: 10.1056/NEJMoa1007903.

20. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366: 1287-1297. 2012/03/28. DOI: 10.1056/NEJMoa1113572.
21. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361: 2342-2352. 2009/12/08. DOI: 10.1056/NEJMoa0906598.
22. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014; 129: 764-772. 2013/12/18. DOI: 10.1161/CIRCULATIONAHA.113.004450.
23. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; 369: 799-808. 2013/07/03. DOI: 10.1056/NEJMoa1302507.
24. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; 369: 1406-1415. 2013/09/03. DOI: 10.1056/NEJMoa1306638.
25. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; 149: 315-352. 2016/02/13. DOI: 10.1016/j.chest.2015.11.026.
26. Mazzolai L, Aboyans V, Ageno W, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European society of cardiology working groups of aorta and peripheral circulation and pulmonary circulation and right ventricular function. *Eur Heart J* 2017 2017/03/23. DOI: 10.1093/eurheartj/ehx003.
27. Robertson L and Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2017; 2: CD001100. 2017/02/10. DOI: 10.1002/14651858.CD001100.pub4.
28. Hakoum MB, Kahale LA, Tsolakian IG, et al. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev* 2018; 1: CD006649. 2018/01/25. DOI: 10.1002/14651858.CD006649.pub7.
29. Mellado M, Pijoan JI, Jimenez D, et al. Outcomes Associated With Inferior Vena Cava Filters Among Patients With Thromboembolic Recurrence During Anticoagulant Therapy. *JACC Cardiovasc Interv* 2016; 9: 2440-2448. 2016/11/14. DOI: 10.1016/j.jcin.2016.08.039.
30. Rojas-Hernandez CM, Oo TH and Garcia-Perdomo HA. Risk of intracranial hemorrhage associated with therapeutic anticoagulation for venous thromboembolism in cancer patients: a systematic review and meta-analysis. *J Thromb Thrombolysis* 2017; 43: 233-240. 2016/10/06. DOI: 10.1007/s11239-016-1434-4.
31. Vedovati MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest* 2015; 147: 475-483. 2014/09/12. DOI: 10.1378/chest.14-0402.
32. Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev* 2018; 6: CD006650. 2018/06/20. DOI: 10.1002/14651858.CD006650.pub5.
33. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008; 111: 4902-4907. 2008/01/25. DOI: 10.1182/blood-2007-10-116327.
34. Akl EA, Kahale L, Sperati F, et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. *Cochrane Database Syst Rev* 2014: CD009447. 2014/06/27. DOI: 10.1002/14651858.CD009447.pub2.

35. Akl EA, Terrenato I, Barba M, et al. Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Arch Intern Med* 2008; 168: 1261-1269. 2008/06/25. DOI: 10.1001/archinte.168.12.1261.
36. Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; 88: 913-930. 2001/07/10. DOI: 10.1046/j.0007-1323.2001.01800.x.
37. Guo Q, Huang B, Zhao J, et al. Perioperative Pharmacological Thromboprophylaxis in Patients With Cancer: A Systematic Review and Meta-analysis. *Ann Surg* 2017; 265: 1087-1093. 2016/11/17. DOI: 10.1097/SLA.0000000000002074.
38. Fagarasanu A, Alotaibi GS, Hrimiuc R, et al. Role of Extended Thromboprophylaxis After Abdominal and Pelvic Surgery in Cancer Patients: A Systematic Review and Meta-Analysis. *Ann Surg Oncol* 2016; 23: 1422-1430. 2016/02/19. DOI: 10.1245/s10434-016-5127-1.
39. Schomburg J, Krishna S, Soubra A, et al. Extended outpatient chemoprophylaxis reduces venous thromboembolism after radical cystectomy. *Urol Oncol* 2018; 36: 77 e79-77 e13. 2017/11/04. DOI: 10.1016/j.urolonc.2017.09.029.
40. Pariser JJ, Pearce SM, Anderson BB, et al. Extended Duration Enoxaparin Decreases the Rate of Venous Thromboembolic Events after Radical Cystectomy Compared to Inpatient Only Subcutaneous Heparin. *J Urol* 2017; 197: 302-307. 2016/08/30. DOI: 10.1016/j.juro.2016.08.090.
41. Kim BJ, Day RW, Davis CH, et al. Extended pharmacologic thromboprophylaxis in oncologic liver surgery is safe and effective. *J Thromb Haemost* 2017; 15: 2158-2164. 2017/08/29. DOI: 10.1111/jth.13814.
42. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev* 2018; 11: CD004318. 2018/11/28. DOI: 10.1002/14651858.CD004318.pub3.
43. Carrier M, Altman AD, Blais N, et al. Extended thromboprophylaxis with low-molecular weight heparin (LMWH) following abdominopelvic cancer surgery. *Am J Surg* 2018 2019/01/01. DOI: 10.1016/j.amjsurg.2018.11.046.
44. Jung YJ, Seo HS, Park CH, et al. Venous Thromboembolism Incidence and Prophylaxis Use After Gastrectomy Among Korean Patients With Gastric Adenocarcinoma: The PROTECTOR Randomized Clinical Trial. *JAMA Surg* 2018; 153: 939-946. 2018/07/22. DOI: 10.1001/jamasurg.2018.2081.
45. Nagata C, Tanabe H, Takakura S, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. *J Obstet Gynaecol Res* 2015; 41: 1440-1448. 2015/06/27. DOI: 10.1111/jog.12740.
46. Dong J, Wang J, Feng Y, et al. Effect of low molecular weight heparin on venous thromboembolism disease in thoracotomy patients with cancer. *J Thorac Dis* 2018; 10: 1850-1856. 2018/05/01. DOI: 10.21037/jtd.2018.03.13.
47. Di Nisio M, Porreca E, Candeloro M, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev* 2016; 12: CD008500. 2016/12/03. DOI: 10.1002/14651858.CD008500.pub4.
48. Khorana AA, Francis CW, Kuderer NM, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: A randomized trial. *Thromb Res* 2017; 151: 89-95. 2017/02/01. DOI: 10.1016/j.thromres.2017.01.009.
49. Ek L, Gezelius E, Bergman B, et al. Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial. *Ann Oncol* 2018; 29: 398-404. 2017/11/07. DOI: 10.1093/annonc/mdx716.

50. Meyer G, Besse B, Doubre H, et al. Antitumor Effect of Low Molecular Weight Heparin in Localised Lung Cancer A Phase III Clinical Trial. . *Eur Respir J* 2018; in press.
51. Akl EA, Kahale LA, Hakoum MB, et al. Parenteral anticoagulation in ambulatory patients with cancer. *Cochrane Database Syst Rev* 2017; 9: CD006652. 2017/09/12. DOI: 10.1002/14651858.CD006652.pub5.
52. Lyman GH, Eckert L, Wang Y, et al. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist* 2013; 18: 1321-1329. 2013/11/12. DOI: 10.1634/theoncologist.2013-0226.
53. Yu Y, Lv Q, Zhang B, et al. Adjuvant therapy with heparin in patients with lung cancer without indication for anticoagulants: A systematic review of the literature with meta-analysis. *J Cancer Res Ther* 2016; 12: 37-42. 2016/10/11. DOI: 10.4103/0973-1482.191627.
54. Fuentes HE, Oramas DM, Paz LH, et al. Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. *Thromb Res* 2017; 154: 28-34. 2017/04/14. DOI: 10.1016/j.thromres.2017.03.024.
55. Thein KZ, Yeung SJ and Oo TH. Primary thromboprophylaxis (PTP) in ambulatory patients with lung cancer receiving chemotherapy: A systematic review and meta-analysis of randomized controlled trials (RCTs). *Asia Pac J Clin Oncol* 2018; 14: 210-216. 2017/09/28. DOI: 10.1111/ajco.12770.
56. Tun NM, Guevara E and Oo TH. Benefit and risk of primary thromboprophylaxis in ambulatory patients with advanced pancreatic cancer receiving chemotherapy: a systematic review and meta-analysis of randomized controlled trials. *Blood Coagul Fibrinolysis* 2016; 27: 270-274. 2016/03/11. DOI: 10.1097/MBC.0000000000000413.
57. Kahale LA, Hakoum MB, Tsolakian IG, et al. Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database Syst Rev* 2017; 12: CD006466. 2017/12/30. DOI: 10.1002/14651858.CD006466.pub6.
58. Kahale LA, Tsolakian IG, Hakoum MB, et al. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database Syst Rev* 2018; 6: CD006468. 2018/06/02. DOI: 10.1002/14651858.CD006468.pub6.
59. Lv Y, Hou Y, Pan B, et al. Risk associated with central catheters for malignant tumor patients: a systematic review and meta-analysis. *Oncotarget* 2018; 9: 12376-12388. 2018/03/20. DOI: 10.18632/oncotarget.24212.
60. Chai-Adisaksopha C, Linkins LA, SY AL, et al. Outcomes of low-molecular-weight heparin treatment for venous thromboembolism in patients with primary and metastatic brain tumours. *Thromb Haemost* 2017; 117: 589-594. 2017/01/13. DOI: 10.1160/TH16-09-0680.
61. Zwicker JI and Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation: reply. *J Thromb Haemost* 2016; 14: 2082. 2016/10/28. DOI: 10.1111/jth.13429.
62. Alshehri N, Cote DJ, Hulou MM, et al. Venous thromboembolism prophylaxis in brain tumor patients undergoing craniotomy: a meta-analysis. *J Neurooncol* 2016; 130: 561-570. 2016/09/07. DOI: 10.1007/s11060-016-2259-x.
63. Khanal N, Bociek RG, Chen B, et al. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. *Am J Hematol* 2016; 91: E468-E472. 2016/10/21. DOI: 10.1002/ajh.24526.
64. Samuelson Bannow BR, Lee AYY, Khorana AA, et al. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: A systematic review. *Res Pract Thromb Haemost* 2018; 2: 664-669. 2018/10/24. DOI: 10.1002/rth2.12111.
65. Woodruff S, Feugere G, Abreu P, et al. A post hoc analysis of dalteparin versus oral anticoagulant (VKA) therapy for the prevention of recurrent venous thromboembolism (rVTE) in patients with

cancer and renal impairment. *J Thromb Thrombolysis* 2016; 42: 494-504. 2016/06/28. DOI: 10.1007/s11239-016-1386-8.
66. Bauersachs R, Lee AYY, Kamphuisen PW, et al. Renal Impairment, Recurrent Venous Thromboembolism and Bleeding in Cancer Patients with Acute Venous Thromboembolism-Analysis of the CATCH Study. *Thromb Haemost* 2018; 118: 914-921. 2018/04/05. DOI: 10.1055/s-0038-1641150.
67. Bartlett MA, Mauck KF and Daniels PR. Prevention of venous thromboembolism in patients undergoing bariatric surgery. *Vasc Health Risk Manag* 2015; 11: 461-477. 2015/09/01. DOI: 10.2147/VHRM.S73799.
68. Pirri C, Katris P, Trotter J, et al. Risk factors at pretreatment predicting treatment-induced nausea and vomiting in Australian cancer patients: a prospective, longitudinal, observational study. *Support Care Cancer* 2011; 19: 1549-1563. 2010/09/03. DOI: 10.1007/s00520-010-0982-y.
69. Verso M, Agnelli G and Prandoni P. Pros and cons of new oral anticoagulants in the treatment of venous thromboembolism in patients with cancer. *Intern Emerg Med* 2015; 10: 651-656. 2015/04/05. DOI: 10.1007/s11739-015-1233-5.
70. Lee AY and Carrier M. Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants. *Thromb Res* 2014; 133 Suppl 2: S167-171. 2014/05/28. DOI: 10.1016/S0049-3848(14)50027-8.
71. Ay C, Pabinger I and Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. *Thromb Haemost* 2017; 117: 219-230. 2016/11/25. DOI: 10.1160/TH16-08-0615.
72. Pabinger I, Thaler J and Ay C. Biomarkers for prediction of venous thromboembolism in cancer. *Blood* 2013; 122: 2011-2018. 2013/08/03. DOI: 10.1182/blood-2013-04-460147.
73. Mauracher LM, Posch F, Martinod K, et al. Citrullinated histone H3, a biomarker of neutrophil extracellular trap formation, predicts the risk of venous thromboembolism in cancer patients. *J Thromb Haemost* 2018; 16: 508-518. 2018/01/13. DOI: 10.1111/jth.13951.
74. Geddings JE and Mackman N. Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. *Blood* 2013; 122: 1873-1880. 2013/06/27. DOI: 10.1182/blood-2013-04-460139.
75. Riedl J, Preusser M, Nazari PM, et al. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. *Blood* 2017; 129: 1831-1839. 2017/01/12. DOI: 10.1182/blood-2016-06-720714.
76. Unruh D, Schwarze SR, Khoury L, et al. Mutant IDH1 and thrombosis in gliomas. *Acta Neuropathol* 2016; 132: 917-930. 2016/09/25. DOI: 10.1007/s00401-016-1620-7.
77. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010; 116: 5377-5382. 2010/09/11. DOI: 10.1182/blood-2010-02-270116.
78. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica* 2017; 102: 1494-1501. 2017/05/28. DOI: 10.3324/haematol.2017.169060.
79. Mansfield AS, Tafur AJ, Wang CE, et al. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016; 14: 1773-1778. 2016/06/09. DOI: 10.1111/jth.13378.
80. Bezan A, Posch F, Ploner F, et al. Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. *PLoS One* 2017; 12: e0176283. 2017/04/22. DOI: 10.1371/journal.pone.0176283.

81. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. *Intern Emerg Med* 2012; 7: 291-292. 2012/05/02. DOI: 10.1007/s11739-012-0784-y.
82. Pelzer U, Sinn M, Stieler J, et al. [Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?]. *Dtsch Med Wochenschr* 2013; 138: 2084-2088. 2013/10/03. DOI: 10.1055/s-0033-1349608.
83. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: The Prospective COMPASS-Cancer-Associated Thrombosis Study. *Oncologist* 2017; 22: 1222-1231. 2017/05/28. DOI: 10.1634/theoncologist.2016-0414.
84. Cella CA, Di Minno G, Carlomagno C, et al. Preventing Venous Thromboembolism in Ambulatory Cancer Patients: The ONKOTEV Study. *Oncologist* 2017; 22: 601-608. 2017/04/21. DOI: 10.1634/theoncologist.2016-0246.
85. Munoz Martin AJ, Ortega I, Font C, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. *Br J Cancer* 2018; 118: 1056-1061. 2018/03/29. DOI: 10.1038/s41416-018-0027-8.
86. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol* 2018; 5: e289-e298. 2018/06/11. DOI: 10.1016/S2352-3026(18)30063-2.

PANELS AND TABLES

Panel 1. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scale and additional economic considerations

Levels of Evidence

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

Levels of recommendation

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

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

- The price of a drug varies in different countries and in different regions of the world.
- In the case of a strong recommendation, the benefit to the patient outweighs health economics considerations.
- Costs of anticoagulants are negligible compared to the cost of cancer treatment.

Panel 2. Search strategy and selection criteria

The update literature search for all studies published between January 2015 and Dec 2018 was performed by INCa using MEDLINE and several other databases (eg EMBASE, CCTR), with the following subject headings: cancer, venous thromboembolism, and anticoagulant drugs and devices. The literature search was limited to publications in English or French. Members of the working group had the opportunity to add additional references that the bibliographic search did not identify. Meta-analyses, systematic reviews, randomized clinical trials, or non-randomized prospective or retrospective studies in the absence of randomized clinical trials, were included. Articles were selected for potential inclusion based on article selection grids designed for each clinical question. For inclusion in the analysis, studies had to focus on the therapeutic management of confirmed VTE in cancer patients, prophylaxis of VTE in cancer patients in the surgical and medical settings, or on the treatment and prophylaxis of thrombosis related to central venous catheter placement in cancer patients. Studies in patients with thrombosis related to tumor material or a history of cancer in remission for more than 5 years were excluded from the analysis. Studies which 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 and minor bleeding, thrombocytopenia and death.

Panel 3. Treatment of established VTE

Initial treatment of established VTE (~~first 10 days~~)

1. LMWH is recommended for the initial treatment of established VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1} 1 **[Grade 1B]**.
   Values and preferences: LMWH is easier to use than UFH. A once per day regimen of LMWH is recommended, unless a twice per day regimen is required due to patient characteristics.
2. In patients not having a high risk for gastro-intestinal or genito-urinary bleeding, rivaroxaban (in the first 10 days) or edoxaban (started after at least 5 days of parenteral anticoagulation) can be also used for the initial treatment of established VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1} **[Grade 1B].**
3. UFH can be also used for the initial treatment of established VTE in cancer patients when LMWH or DOACs are contraindicated or not available **[Grade 2C].**
4. Fondaparinux can be also used for the initial treatment of established VTE in cancer patients **[Grade 2D]**.
   Values and preferences: fondaparinux is easier to use than UFH.
5. Thrombolysis in cancer patients with established VTE may only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk (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 performed in centers with healthcare practitioners who have the appropriate expertise.
6. In the initial treatment of VTE, IVC filters may be considered when anticoagulant treatment is contraindicated or in the case of PE recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended, and anticoagulation should be resumed when safe **[Guidance, based on evidence of very low quality and an unknown balance between desirable and undesirable effects]**.

International Advisory Panel ranking: 8.18 out of 9.0

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

1. LMWHs are preferred over VKAs for the treatment of VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1} **[Grade 1A]**.
   Values and preferences: daily subcutaneous injection may represent a burden for patients.
2. DOACs are recommended in cancer patients when creatinine clearance ≥30 mL.min^{-1} in the absence of strong drug-drug interactions or of gastro-intestinal absorption impairment. **[Grade 1A]**. Use caution in patients with gastro-intestinal tract malignancies, especially upper gastro-intestinal tract malignancies, as the currently available data demonstrate increased risk of GI tract bleeding with edoxaban and rivaroxaban. Data for other DOACs are needed as it is not clear whether other DOAC will have the same risk profile.
3. LMWH or DOACs should be used for a minimum of 6 months to treat established VTE in cancer patients **[Grade 1A]**.
4. After 6 months, termination or continuation of anticoagulation (LMWH, DOACs or VKAs) 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]**.

International Advisory Panel ranking: 8.09 out of 9.0

Treatment of VTE recurrence in cancer patients under anticoagulation

1. In the event of VTE recurrence, management depends on the initial treatment: (i) if LMWH, increase LMWH dose by 20%-25% or switch to DOACs; (ii) if DOACs, switch to LMWH; (iii) if VKA, switch to LMWH or DOACs **[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.

International Advisory Panel ranking: 8.0 out of 9.0

Treatment of established catheter-related thrombosis

1. For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months and as long as the CVC is in place; in this setting, LMWHs are suggested and direct comparisons between LMWHs, DOACS and VKAs have not been made **[Guidance]**.
2. In cancer patients with CRT, the CVC can be kept in place if it is functional, well positioned, and non-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]**.

International Advisory Panel ranking: 8.19 out of 9.0

Table 1 Characteristics of direct oral anticoagulants (DOACs) used or being investigated in cancer patients					
		Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Target		FIIa	FXa	FXa	FXa
Dosing		**Therapeutic** 150 mg twice a day; 110 mg twice a day for ages ≥80 years following at least 5 days of parenteral anticoagulant	**Therapeutic** 15mg BID for 3 weeks followed by 20 mg OD	**Therapeutic** 10 mg BID for 7 days, followed by 5 mg BID	**Therapeutic** 60 mg OD following at least 5 days of parenteral anticoagulants
Prodrug		Yes	NO	NO	NO
Bioavailability		3–7%	10 mg dose: 100% 20 mg dose: 100% when taken together with food; 66% under fasting conditions inter-individual variability: 30-40%	~50% interindividual variability: 30%	~62%
Activity onset		1–3 h	2-4 h	3-4 h	1-2 h
Half-life		12–18 h	5-13 h	12 h	10-14 h
Excretion (% of administered dose)		80% renal (unchanged), 20% liver	66 % renal (half active drug unchanged and half inactive metabolites) 33% feces (inactive metabolites)	25% renal 75% feces	50%, renal (unchanged) 50% biliary /intestinal
Considerations for renal insufficiency		**Mild or moderate*:*** Dose adjustment recommended **Severe*:*** Contraindicated if GFR <30 mL.min^{-1}	**Moderate** **(GFR 30-49mL.min^{-1}) :** Dose adjustment recommended **Severe**: Dose adjustment recommended (GFR 15-29 mL.min^{-1}) Not recommended if GFR <15 mL.min^{-1}	**Mild/Moderate** **or if GFR > 25-30 mL.min^{-1}:** **n**o dose adjustment required **Severe:** Not recommended if GFR < 15 mL.min^{-1} *No data available in patients with end-stage renal disease*	**Moderate** **(GFR 30-50 mL.min^{-1})** Dose adjustment recommended **Severe:** Dose adjustment recommended (GFR 15-29 mL.min^{-1}) Not recommended if GFR < 15 mL.min^{-1} *No data available in patients with end-stage renal disease or on dialysis*
Considerations for hepatic insufficiency		Liver enzymes twice normal limit or if acute liver diseases: not recommended	**Moderate hepatic impairment**: Caution **Hepatic disease with caoagulopathy and clinically relevant bleeding risk:** Contraindicated	**Mild or moderate hepatic impairment:** Caution, but no dose adjustment required **Severe hepatic impairment**: Not recommended **Hepatic disease with caoagulopathy and clinical relevant bleeding risk:** Contraindicated	**Mild hepatic impairment**: No dose reduction **Moderate or severe hepatic impairment**: Not recommended
Interaction		P-gp inducers/inhibitors	P-gp inducers/inhibitors CYP3A4 CYP2j2	P-gp inducers/inhibitors CYP3A4	P-gp inducers /inhibitors CYP3A4
SPECIFIC TRIALS IN CANCER PATIENTS		**NONE**	**SELECT D [YOUNG2018]** **CASSINI [KHORANA2018]**	**ADAM-VTE [MCBANE2018]** **AVERT [CARRIER 2018]**	**HOKUSAI [RASKOB2018]**
Specific Antidote		Idarucizumab Aripazine	Andexanet alfa Aripazine	Andexanet alfa Aripazine	Andexanet alfa Aripazine

DOACs are oral anticoagulants which offer an easier route of administration compared to LMWHs (oral). Their absorption may be affected by vomiting, which occurs in up to 50% of patients.[68] The DOACs are administered as fixed dose regimens with predictable anticoagulant effects.[69] P-glycoprotein (P-gp) transport and CYP 3A4 metabolic pathways are inhibited by tyrosine-kinase inhibitors and hormonal therapies, and induced by doxorubicin, vinblastine and dexamethasone.[70] Concomitant administration of chemotherapy agents or anti-angiogenic therapies with DOACs may result in reduced responses to these anti-cancer treatments and an increased risk of bleeding. LMWH is not associated with risk of interaction with chemotherapy, and does not rely on oral intake or gastrointestinal absorption.[69] LMWH has a more onerous route of administration, requires weight adjustment of the dose, and can be associated with heparin-induced thrombocytopenia.

Idarucizumab is a humanized monoclonal antibody fragment which targets oral direct thrombin inhibitors (DTI). Idarucizumab is approved for use in the European Union, UK, Canada and US. Andexanet alfa (PRT064445 or PRT4445) is a modified recombinant FXa protein, which can target oral FXa inhibitors, injectable LMWH, and fondaparinux. In May 2018, the FDA approved andexanet alfa for reversing the anticoagulant effect of apixaban and rivaroxaban during serious bleeding events. Andexanet alfa is currently undergoing regulatory evaluation in Canada, the EU and the UK. Aripazine (PER977) is a synthetic small molecule that can target oral FXa inhibitors, DTIs, injectable UFH, LMWH, and fondaparinux. Aripazine is currently in Phase II trials, and was granted fast-track status in the US in April 2015.

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

	Treatment of acute CAT			VTE prophylaxis	
	HOKUSAI VTE-CANCER [RASKOB2017]	**SELECT-D [YOUNG2018]**	**ADAM-VTE [MCBANE2018]**	**CASSINI [KHORANA2018]**	**AVERT [CARRIER2018]**
Number of randomized Patients	**1050**	**406**	**300**	**841**	**574**
Trial design	• Non-inferiority	• Pilot	• Superiority	• Superiority	• Superiority
DOAC	• **Edoxaban** Dalteparin for at least 5 days, followed by edoxaban 60 mg once daily, for 6-12 months	• **Rivaroxaban** 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 2-6 months	• **Apixaban** 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months	• **Rivaroxaban** 10 mg once daily	• **Apixaban** 2.5 mg twice daily
Comparator	• **LMWH** Daltaparin 200 IU/kg once daily first 30 days, followed by 150 IU/kg daily	• **LMWH** Daltaparin 200 IU/kg once daily first 30 days, followed by 150 IU/kg daily	• **LMWH** Daltaparin 200 IU/kg once daily first 30 days, followed by 150 IU/kg daily	• **Placebo**	• **Placebo**
inclusion criteria	• Patients with cancer and symptomatic or incidental acute VTE	• Patients with cancer and symptomatic or incidental acute VTE DVT	• Patients with cancer and symptomatic or incidental acute VTE	• Ambulatory cancer patients at intermediate-to-high risk for VTE (Khorana score, ≥2) who were initiating chemotherapy	• Ambulatory cancer patients at intermediate-to-high risk for VTE (Khorana score, ≥2) who were initiating chemotherapy
Cancers included	• Cancer other than basal-cell or squamous-cell skin cancer	• Active solid or hematological cancers, other than basal-cell or squamous-cell skin carcinoma. Patients with upper GI malignancy were also excluded from the trial	• Active solid or hematological cancers, other than basal-cell or squamous-cell skin carcinoma.	• Solid tumors or lymphomas with locally advanced or metastatic disease. Primary brain tumor, known brain metastases, or hematologic malignancies (except lymphoma) were excluded	• Cancer other than basal-cell or squamous-cell skin carcinoma, acute leukemia, or myeloproliferative neoplasms
Primary outcome measures	• Composite measure of recurrent VTE or major bleeding within 12 months after randomization	• VTE recurrence in the 6 months after randomization	• Major bleeding including fatal bleeding	• Composite measure of DVT, PE, and VTE-related death • Major bleeding	• Objectively documented VTE (proximal DVT, PE) over a 6-month follow-up period • Major bleeding
Primary outcome results	• Edoxaban: 12.8% • Dalteparin:13.5%	• Rivaroxaban: 4% • Dalteparin: 11%	• Apixaban: 0% • Dalteparin: 2.1%	*Composite on-treatment* • Rivaroxaban: 2.6% • Placebo: 6.4% *Composite – up to 6-months* • Rivaroxaban: 6.0% • Placebo: 8.8% *Major bleeding* • Rivaroxaban: 2.0% • Placebo: 1.0%	*VTE* • Apixaban: 4.2% • Placebo: 10.2% *Major bleeding* • Apixaban: 3.5% • Placebo: 1.8%
Major secondary Outcomes	*Recurrent VTE* • Edoxaban: 7.9% • Dalteparin: 11.3% *Major bleeding* • Edoxaban: 6.9% • Dalteparin: 4.0%	*Major bleeding* • Rivaroxaban: 13% • Dalteparin: 4% *CRNMB* • Rivaroxaban: 6% • Dalteparin: 4%	*Recurrent VTE (DVT.PE, fatal PE)* • Apixaban: 3.4% • Dalteparin: 14.1% • Major + Fatal + CRNMB • Apixaban: 9.0% • Dalteparin: 9.0%	*CRNMB* • Rivaroxaban: 2.7% • Placebo: 2.0%	*CRNMB* • Apixaban: 7.3% • Placebo: 5.5%

Panel 4. Prophylaxis in VTE cancer patients

Prophylaxis of VTE in surgical cancer patients

1. Use of LMWH once per day (when creatinine clearance ≥30 mL.min^{-1}) or low-dose UFH three times per day (is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 hours preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another **[Grade 1A]**.
   Values and preferences: LMWH once per day is more convenient.
2. There is insufficient evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients **[Grade 2C]**.
   Values and preferences: similar.
3. Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended **[Grade 1A]**.
   Values and preferences: equal.
4. Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in cancer patients is indicated in patients with a high VTE risk and low bleeding risk **[Grade 1A]**.
   Values and preferences: longer duration of injections.
5. Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery is recommended in the same way as for laparotomy **[Grade 2C]**.
   Values and preferences: daily injections. Costs: In some countries, the price of LMWH may influence the choice.
6. Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated **[Grade 2B]**.
   Values and preferences: no injection.
7. IVCs are not recommended for routine prophylaxis **[Grade 1A]**.

International Advisory Panel ranking: 8.63 out of 9.0

Prophylaxis of VTE in medical cancer patients

1. We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance ≥30 mL.min^{-1}min, or UFH in hospitalized medical patients with cancer and reduced mobility **[Grade 1B]**. In this setting, DOACs are not recommended routinely **[Guidance]**.
   Values and preferences: subcutaneous injections.
   Costs: In some countries price differences between LMWH, UFH or fondaparinux may influence the choice.
2. Primary prophylaxis with LMWH, VKA or DOACs in ambulatory patients receiving systemic anti-cancer therapy is not recommended routinely **[Grade 1B]**.
   Values and preferences: subcutaneous injections.
3. Primary pharmacological prophylaxis of VTE with LMWH is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anti-cancer therapy and having a low bleeding risk **[Grade 1B]**.
   Values and preferences: subcutaneous injections.
4. Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside in a clinical trial for patients with locally advanced or metastatic lung cancer treated with systemic anti-cancer therapy, including patients having a low bleeding risk **[Guidance]**.
5. Primary prophylaxis with DOAC (rivaroxaban or apixaban) is recommended in ambulatory patients receiving systemic anti-cancer therapy at intermediate-to-high risk of VTE, identified by cancer type (i.e., pancreatic) or by a validated risk assessment model (i.e. Khorana score≥2), and not actively bleeding or not at high risk for bleeding [**Grade 1B**].
6. In patients treated with IMiDs combined with steroids and/or other systemic anti-cancer therapies, VTE primary pharmacological prophylaxis is recommended **[Grade 1A]**; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses, and low-dose aspirin can be used and have shown similar effects with regard to preventing VTE **[Grade 2C]**.
   Values and preferences: subcutaneous injections.

International Advisory Panel ranking: 8.00 out of 9.0

Prophylaxis of catheter-related thrombosis

1. Use of anticoagulation for routine prophylaxis of CRT is not recommended **[Grade 1A]**.
   Values and preferences: bleeding risk with anticoagulants.
2. Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium **[Grade 1B]**.
3. In patients requiring CVC, we suggest the use of implanted ports over PICC lines **[Guidance].**

International Advisory Panel ranking: 8.51 out of 9.0

Panel 5. Risk stratification schemes for prophylaxis of venous thromboembolism in patients with cancer

Patients with cancer are at increased risk of VTE, which is determined by the clinical setting and the presence of various risk factors.[71] A time-dependent association between VTE and cancer has also been observed, with most VTE events occurring within the first 6 months after cancer diagnosis.

Risk factors for VTE in cancer

- **Risk factors associated with the tumor characteristics**: primary site, histological grade, Tumour Node Metastasis (TNM) staging
- **Risk factors associated with the cancer treatments:** surgery and/or hospitalization; central venous catheters; systemic anti-cancer therapy, including radiotherapy, chemotherapy (e.g. cisplatin), anti-angiogenesis agents, immunomodulatory drugs (IMIDs), hormonal therapy, erythropoiesis-stimulating agents, red blood cell or platelet transfusions.
- **General individual VTE risk factors:** history of previous VTE, advanced age, obesity, immobility, prothrombotic variants (e.g. factor V Leiden), and comorbidities.

Emerging biomarkers[72-76]

- Blood-count parameters: platelets, leukocytes
- Markers of activation of blood coagulation and platelets: D-dimers, high endogenous thrombin generation potential, soluble P-selectin
- Markers of neutrophil extracellular trap (NETs) formation (i.e. citrullinated histone H3)
- Microvesicles-associated tissue factor (MV-TF) activity
- High podoplanin expression and iscocitrate dehydrogenase 1 (IDH1) mutation (in brain tumors only)

Risk assessment models

The **Khorana Risk Scoring Model[33]** was developed for VTE risk assessment in patients receiving chemotherapy. This risk score was externally validated in the Vienna CATS study and other studies[77] although recent publications questioned its reproducibility in certain patient populations.[78-80] *Several variations of the Khorana risk score have been performed to improve risk assessment, including 1) the extended "Vienna CATS Score"[77] 2) the PROTECHT[81], and 3) the CONKO score*.[82]

KHORANA Score and expanded models				
	Khorana score	Vienna CATS score	PROTECHT score	CONKO score
Very high-risk tumors†	**+2**	**+2**#	**+2**	**+2**
High risk tumors‡	**+1**	**+1**	**+1**	**+1**
▪ Hemoglobin <10 g/dl ▪ Erythropoietin stimulating agents	**+1**	**+1**	**+1**	**+1**
White blood cell count >11 x 10^9/L	**+1**	**+1**	**+1**	**+1**
platelet count ≥350 x 109/L	**+1**	**+1**	**+1**	**+1**
BMI >35 kg/m2	**+1**	**+1**	**+1**	**+1**
D-dimer >1.44 µg/L		**+1**		
Soluble P-selectin >53.1 ng/L		**+1**		
Gemcitabine chemotherapy			**+1**	
Platinum-based chemotherapy			**+1**	
WHO performance status				**+1**

†Very high-risk tumors: pancreatic, gastric; ‡high risk tumors: lung, lymphoma, bladder, testicular or gynecological; # The Vienna CATS score added primary brain tumor patients (glioma) to the list of very high-risk tumors; BMI, body mass index; WHO, world Health Organization

The **COMPASS-CAT risk assessment model[83]** was developed for use in only breast, colorectal, lung, and ovarian cancer and includes the following variables: anthracycline or anti-hormonal therapy, time since cancer diagnosis, central venous catheter, stage of cancer, presence of cardiovascular risk factors, recent hospitalization for acute medical illness, personal history of VTE and platelet count.

The **ONKOTEV[84]** score is based on a Khorana score of >2, then adds metastatic disease, previous VTE, and vascular/lymphatic compression.A combination of genetic and clinical factors was used to develop the **TiC-Onco** score[85], which performed better than the Khorana risk score in identifying cancer patients at risk of VTE

Pabinger et al. followed a pre-specified process to develop and externally validate in a single prospective cohort (MICA) of 832 cancer patients a simple clinical prediction model that only includes the tumor site category (very-high and high versus intermediate or low) and D-dimer levels as a continuous variable, and a nomogram and online risk calculator (http://catscore.meduniwien.ac.at) is provided for estimating an individual cancer patient´s VTE risk.[86]

Panel 6. Special situations

1. For the treatment of established VTE in cancer patients with a brain tumor, LMWHs or DOACs can be used **[Grade 2B]**.

2. We recommend the use of LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery **[Grade 1A]**.

3. Primary pharmacological prophylaxis of VTE in medical cancer patients with brain tumor who are not undergoing neurosurgery is not recommended **[Grade 1B]**.

4. In the presence of severe renal failure (creatinine clearance < 30 $mL.min^{-1}$) we suggest using UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE **[Guidance, in the absence of data and an unknown balance between desirable and undesirable effects]**.

5. In patients with severe renal failure (creatinine clearance < 30 $mL.min^{-1}$), an ECD may be applied, and pharmacological prophylaxis may be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance < 30 mL.min–1), UFH can be used on a case-by-case basis **[Guidance, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk]**.

6. In cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is > 50 $G.L^{-1}$ and there is no evidence of bleeding; for patients with a platelet count below 50 $G.L^{-1}$, decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution **[Guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk versus VTE risk]**.

7. In cancer patients with mild thrombocytopenia, platelet count > 80 $G.L^{-1}$, pharmacological prophylaxis may be used; if the platelet count is below 80 $G.L^{-1}$, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended **[Guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk versus VTE risk]**.

8. In pregnant cancer patients, we suggest the use of LMWH for treatment of established VTE and for VTE prophylaxis and avoidance of VKAs and DOACs **[Guidance, in the absence of data and based on the contraindication of VKA and DOACs during pregnancy]**.

9. In obese cancer patients, consideration for a higher dose of LMWH should be given for cancer surgery. **[Guidance]**

International Advisory Panel ranking: 8.12 out of 9.0