Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

An overview of the 2022 International Clinical Practice Guidelines (CPGs) for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

A slide set developed by the International Initiative on Thrombosis and Cancer (ITAC)

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2022 - 4th International CPGs : Update including patients with COVID-19

International working group: 19 multidisciplinary experts, 2 methodologists, 1 nurse, 1 patients, 87 independent reviewers

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GRADE methodology

GRADE

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

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

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2022 - 4th International CPGs : The companion free App

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International Clinical Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

The International Initiative on Thrombosis and Cancer Multi-language Interactive Mobile App provides the most important content of the full International Clinical Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer. The ITAC Interactive Guidelines App is compatible with Android and iOS devices and available for free in English, French, Spanish, Portuguese and Russian versions.

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SCAN ME

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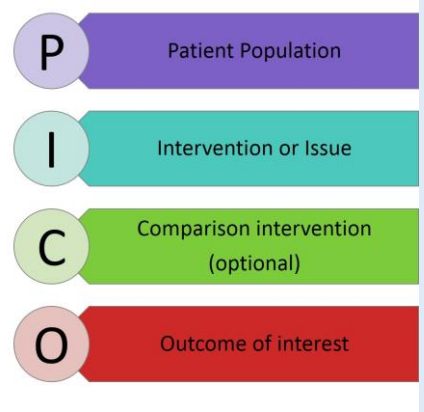
Guidelines Methodology

STEP 1

Establish guideline development group (GDG) and scope

1. Create GDG
2. Define Scope and Topic
3. Identify clinical questions
4. Define PICO*



STEP 2

Systematic review of evidence

1. Systematic search for evidence
2. Identify and select evidence
3. Critical appraisal of methodological quality of included studies
4. Extract data
5. Synthezise data

STEP 3

Formulate CPGs

1. Synthetize evidence
2. Draft recommandations
3. Grade Recommandation
4. Reach consensus among GDG
5. Write Narrative clinical context

Methodology

GRADE

Literature Search

MEDLINE® on Ovid®

Appraisal tools

AGREE REPORTING CHECKLIST

*PICO = P, patient, problem or population; I, intervention; C, comparison, control or comparator; O, outcome.

Adapted from Misso and Teede, Evidence based guideline (EBG) development: A practical guide in knowledge transfer: practices, types and challenges.

GRADE Scale: Going from Evidence to Recommendations

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.

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Major Differences Between 2019 and 2022 International CPGs

- Added results from the recent CARAVAGGIO, CASTA-DIVA and CANVAS randomized clinical trials comparing DOACs with LMWHs for the treatment of venous thromboembolism in patients with cancer
- Added other new evidence to support venous thromboembolism treatment recommendations in patients with cancer
- Added other new evidence to support venous thromboembolism prophylaxis recommendations in patients with cancer
- Added new recommendations for the treatment and prophylaxis of venous thromboembolism in children with cancer
- Added new recommendations for the treatment and prophylaxis of venous thromboembolism in patients with cancer and COVID-19

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Clinical Questions

1. Initial treatment of established Venous thromboembolism (VTE) (up to 10 days)
2. Early maintenance (up to 6 months) and long-term treatment (>6 months) of established VTE
3. Treatment of VTE recurrence in patients with cancer under anticoagulation
4. Treatment of established catheter-related thrombosis
5. Prophylaxis of VTE in surgically-treated patients with cancer
6. Prophylaxis of VTE in in medically-treated patients with cancer
7. Prophylaxis of catheter-related thrombosis
8. Special situations: brain tumor, neurosurgery, thrombocytopenia, renal failure, and pregnancy
9. Treatment and prophylaxis of VTE in patients with cancer and with COVID-19

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Q1: Initial Treatment of Established VTE

• LMWH is recommended for the initial treatment of established VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1}.	**Grade 1A**	**Updated**
• In patients not having a high risk for gastro-intestinal or genito-urinary bleeding, rivaroxaban or apixaban (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 1A**	**Updated**
• 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**	**Unchanged**
• Fondaparinux can be also used for the initial treatment of established VTE in cancer patients.	**Grade 2D**	**Unchanged**
• 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**	**Unchanged**
• 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**	**Unchanged**

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Q2: Early Maintenance and Long-term Treatment of VTE

• LMWHs are preferred over VKAs for the treatment of VTE in cancer patients when creatinine clearance ≥30 mL.min-1.	**Grade 1A**	**Unchanged**
• DOACs (edoxaban, rivaroxaban or apixaban) 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**	**Updated**
• LMWH or DOACs should be used for a minimum of 6 months to treat established VTE in cancer patients.	**Grade 1A**	**Unchanged**
• 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**	**Unchanged**

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Q3: VTE recurrence in patients with cancer under anticoagulation

• In the event of VTE recurrence, management depends on the initial treatment: ✓ If LMWH, increase LMWH dose by 20%-25% or switch to DOACs; ✓ If DOACs, switch to LMWH; ✓ If VKA, switch to LMWH or DOACs.	**Guidance**	**Unchanged**

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Q4: Treatment of Established Catheter-Related Thrombosis Recommendations

• 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**	**Unchanged**
• 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**	**Unchanged**

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Q5: Prophylaxis of VTE in surgically-treated patients with cancer

• 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**	**Unchanged**
• There is insufficient evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients.	**Grade 2C**	**Updated**
• There is insufficient evidence to support DOAC [Grade 2B] as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients.	**Grade 2 B**	**Updated**
• Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended .	**Grade 1A**	**Unchanged**
• Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major abdominal or pelvic surgery (either laparotomy or laparoscopy) is recommended in cancer patients without a high-risk of bleeding [Grade 1A].	**Grade 1A**	**Unchanged**
• Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated.	**Grade 2A**	**Unchanged**
• IVC filters are not recommended for routine prophylaxis.	**Grade 1A**	**Unchanged**

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Q6: Prophylaxis of VTE in medically-treated patients with cancer

• We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance ≥30 mL.min^{-1}, or UFH in hospitalized medical patients with cancer and reduced mobility.	**Grade 1B**	**Unchanged**
• In hospitalized medical patients with cancer and reduced mobility, DOACs are not recommended routinely.	**Guidance**	**Unchanged**
• 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 1A**	**Updated**
• Primary pharmacological prophylaxis of VTE with LMWH with DOAC (rivaroxaban or apixaban) 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**	**Updated**
• Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside 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**	**Unchanged**

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Q6: Prophylaxis of VTE in medically-treated patients with cancer

• Primary prophylaxis with DOAC (rivaroxaban or apixaban) is recommended in ambulatory patients who are receiving systemic anti-cancer therapy and are at intermediate-to-high-risk of VTE, identified by a validated risk assessment model (i.e., Khorana score≥2), and not actively bleeding or not at high-risk for bleeding	**Grade 1B**	**Unchanged**
• In myeloma patients treated with IMiDs combined with steroids and/or other systemic anti-cancer therapies, VTE primary pharmacological prophylaxis is recommended • In this setting, oral anticoagulants (VKA at low or therapeutic doses, apixaban at prophylactic doses) or LMWH at prophylactic doses or low-dose aspirin (100 mg daily) can be used and have shown similar effects with regard to preventing VTE.	**Grade 1A** **Grade 2B**	**Updated**

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Q7: Prophylaxis of catheter-related thrombosis

• Use of anticoagulation for routine prophylaxis of catheter-related thrombosis is not recommended.	**Grade 1A**	**Unchanged**
• 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**	**Unchanged**
• In patients requiring central venous catheters, we suggest the use of implanted ports over PICC lines.	**Guidance**	**Unchanged**

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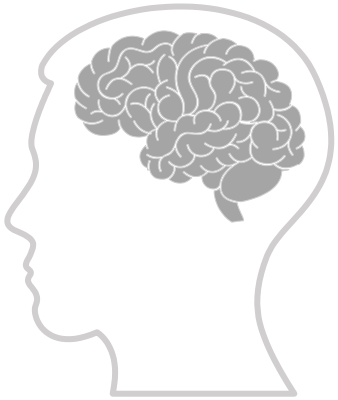
Q8: Special Situations- Brain Tumours

• For the treatment of established VTE in cancer patients with a brain tumor, LMWHs or DOACs can be used .	**Grade 1A**	**Updated**
• We recommend the use of LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery.	**Grade 1B**	**Unchanged**
• Primary pharmacological prophylaxis of VTE in medical cancer patients with brain tumor who are not undergoing neurosurgery is not recommended.	**Guidance**	**Unchanged**



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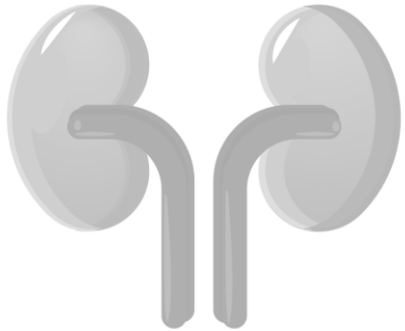
Q8: Special Situations- Severe renal failure

• 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**	**Unchanged**
• 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**	**Unchanged**



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Q8: Special Situations- Thrombocytopenia

• 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**	**Unchanged**
• 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. • In the AVERT and CASSINI trials, patients with a platelet count as low as 50 $G.L^{-1}$ were allowed to receive thromboprophylaxis.	**Guidance**	**Updated**

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Q8: Special Situations- Pregnant cancer patients

• 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**	**Unchanged**

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Q8: Special Situations- Obsese patients

• In obese cancer patients, consideration for a higher dose of LMWH should be given for cancer surgery.	**Guidance**	**Unchanged**

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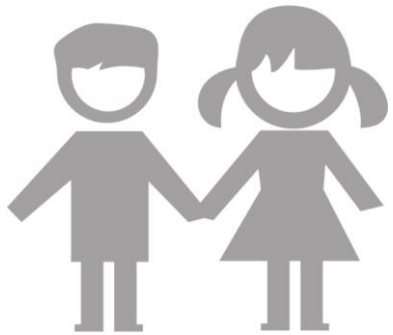
Q8: Special Situations- Children with cancer

• For the treatment of symptomatic catheter-related thrombosis in children with cancer, anticoagulant treatment is recommended for a minimum of 3 months and as long as the central venous catheter is in place; in this setting, direct comparisons between UFH, LMWHs, direct oral anticoagulants, and vitamin K antagonists have not been done.	**Guidance**	**New**
• In children with ALL undergoing induction chemotherapy, we recommend LMWH as thromboprophylaxis.	**Grade 2A**	**New**
• In children requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines.	**Guidance**	**New**



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Q9: Treatment and prophylaxis of VTE in patients with cancer and with COVID-19

• Recommendations for the treatment of established VTE in cancer patients are similar in those with and without COVID-19.	**Guidance**	**New**
• Recommendations for the prophylaxis of VTE in cancer patients are similar in those with and without COVID-19. ✓ Patients with cancer and COVID-19, whether they are hospitalized, post discharge or ambulatory, should be assessed for risk of VTE as any other patient with COVID-19. ✓ Pharmacologic prophylaxis during hospitalization should be given, with the same dose and anticoagulant type as in non-COVID cancer patients, based on current institutional practice. ✓ Post discharge VTE prophylaxis is not advised in cancer patients with COVID-19; as with any cancer patient, individual assessment of benefit-risk ratio should be performed. ✓ Primary pharmacological prophylaxis of VTE in ambulatory cancer patients with COVID-19 is not recommended routinely.	**Guidance**	**New**

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