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International Initiative on Thrombosis and Cancer

Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

An overview of the 2019 International Guidelines 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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2019 – 3rd International CPGs : Update including RCTs comparing DOACs and LMWH

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International working group: 15 multidisciplinary experts, 2 methodologists, 1 nurse, 2 patients, 83 independent reviewers

GRADE methodology

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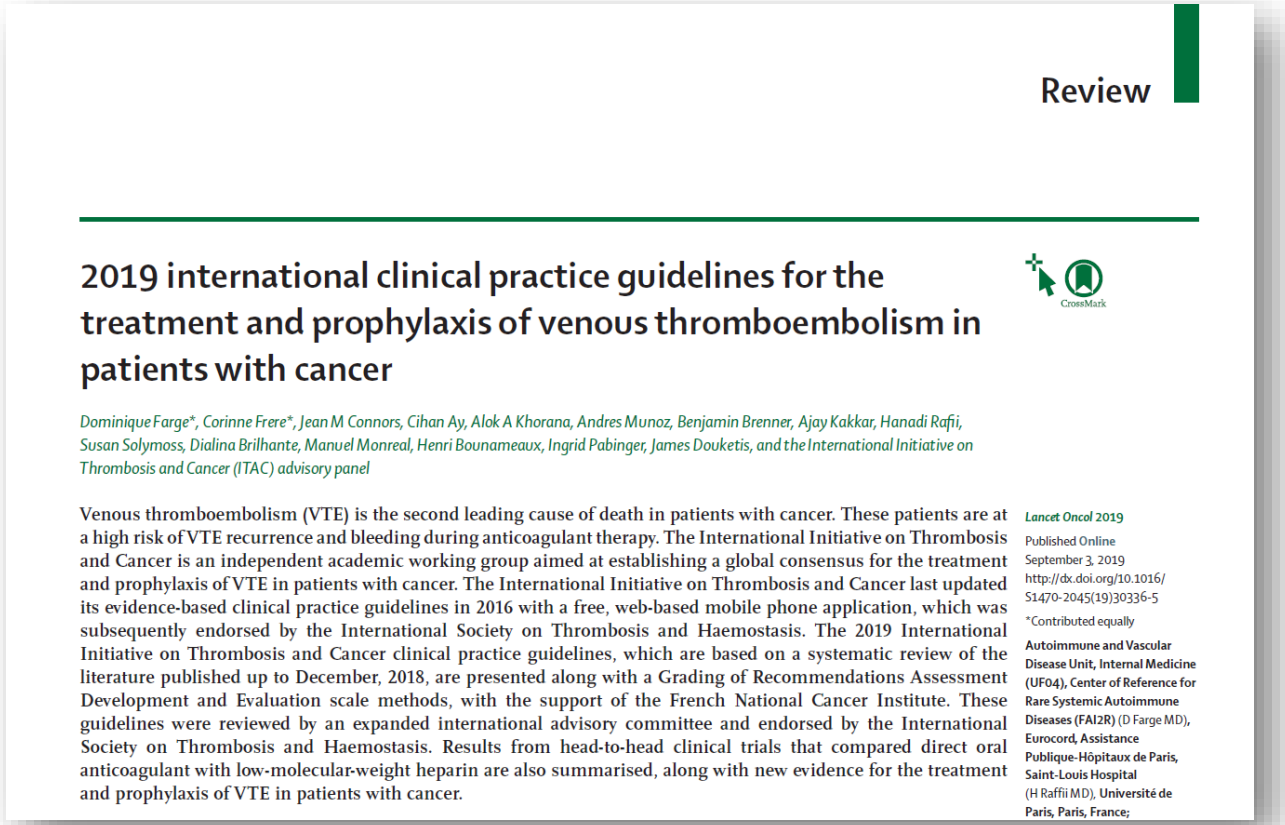

Review

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

Dominique Farge, Corinne Frere*, Jean M Connors, Cihan Ay, Alok A Khorana, Andres Munoz, Benjamin Brenner, Ajay Kakkar, Hanadi Rafii, Susan Solymoss, Dialina Brilhante, Manuel Monreal, Henri Bounameaux, Ingrid Pabinger, James Douketis, and the International Initiative on Thrombosis and Cancer (ITAC) advisory panel*

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

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2019 - International CPGs and Cancer Guidelines App

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- Clinical tool based on the 2019 international CPGs
  - ✓ Decision-tree algorithm to assist clinicians in making treatment strategies
  - ✓ Encourages judicious and appropriate use of anticoagulants as VTE prophylaxis and treatment in patients with cancer

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Guidelines Methodology

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Clinical Questions

1. Initial treatment of established VTE
2. Early maintenance (up to 6 months) and long-term treatment (>6 months) of established VTE
3. Treatment of VTE recurrence under treatment
4. Treatment of established CRT
5. Risk stratification schemes to help assess prophylaxis requirements
6. Prophylaxis of VTE in surgical cancer patients
7. Prophylaxis of VTE in medical cancer
8. Prophylaxis of CRT
9. Special situations: brain tumor, neurosurgery, thrombocytopenia, renal failure, and pregnancy

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Guidelines Methodology

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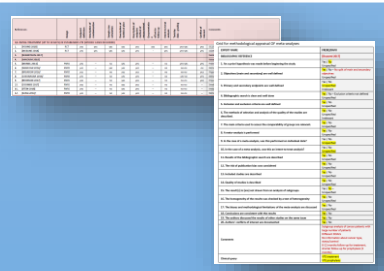
- **Literature review**
  All published studies January 1996-June 2011 (2013 CPGs), June 2011-January 2016 (2016 CPGs), and January 2015- Dec 2018 (2019 CPGs)
- Critical appraisal
  Methodological assessment/clinical relevance



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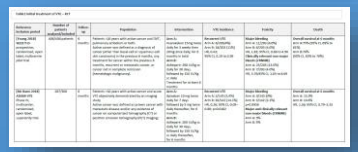
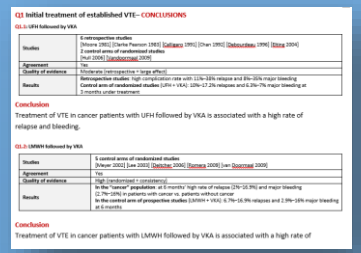


- Conclusion tables



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CPGs, clinical practice guidelines;

Debourdeau P, et al. *J Thromb Haemost*. 2013;11(1):71-80.
Farge D, et al. *J Thromb Haemost*. 2013;11(1):56-70.
Farge et al. *Lancet Oncol* 2016 Oct;17(10):e452-e466.
Farge D, Frère C et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print].

A Summary of the GRADE Approach to Rating Quality of Evidence

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Quality of evidence	Study design	Lower if	Higher if
High (4)	Randomized trial	Study limitations -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
Moderate (3)		Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Low (2)	Observational study	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect when results show no effect
Very low (1)		Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
Adapted from: Balshem H, et al. *J Clin Epidemiol* 2011;64(4):401-6

GRADE Scale: Going from Evidence to Recommendations

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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.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Farge D, et al. *J Thromb Haemost*. 2013;11(1):56-70.
Farge et al. *Lancet Oncol* 2016 Oct;17(10):e452-e466.
Farge D, Frere C et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print].

Major Differences Between 2016 and 2019 International CPGs

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- Added results from the most recent randomized clinical trials (RCTs) comparing DOACs with LMWH for the treatment and prophylaxis of VTE in cancer patients
- Added other new evidence to support treatment and prophylaxis recommendations
- Updated list of risk factors for VTE in patients with cancer
- Updated risk stratification schemes to help determine VTE prophylaxis requirements
- Added 1 table on results from RCTs assessing the efficacy and safety of DOACs in the treatment and prophylaxis of VTE in cancer patients
- Added 1 table on DOAC drug-drug interactions

Farge D et al. *Lancet Oncol* 2016 Oct;17(10):e452-e466.
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Treatment of established VTE in Patients with Cancer

2019 International CPGs
Initial Treatment of Established VTE

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• LMWH is recommended for the initial treatment of established VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1}. [Grade 1B]	Unchanged
• 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]	New
• 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, based on evidence of very low quality and the high bleeding risk of thrombolytic therapy]	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, based on evidence of very low quality and an unknown balance between desirable and undesirable effects].	Unchanged

Farge D , Frère C, et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print]

2019 International CPGs
Early Maintenance and Long-term Treatment of VTE Recommendations

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• LMWHs are preferred over VKAs for the treatment of VTE in cancer patients when creatinine clearance ≥30 mL.min^{-1}. [Grade 1A]	Unchanged
• 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.	New
• LMWH or DOACs should be used for a minimum of 6 months to treat established VTE in cancer patients. [Grade 1A]	Updated
• 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]	Unchanged
VTE Recurrence	
• 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]	Updated

Farge D, Frère C, et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print]

2019 International CPGs
Treatment of Established Catheter-Related Thrombosis Recommendations

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• 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

Farge D , Frère C, et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print]

Prophylaxis of VTE in Patients with Cancer

2019 International CPGs
Prophylaxis of VTE in Surgical Cancer Patients Recommendations

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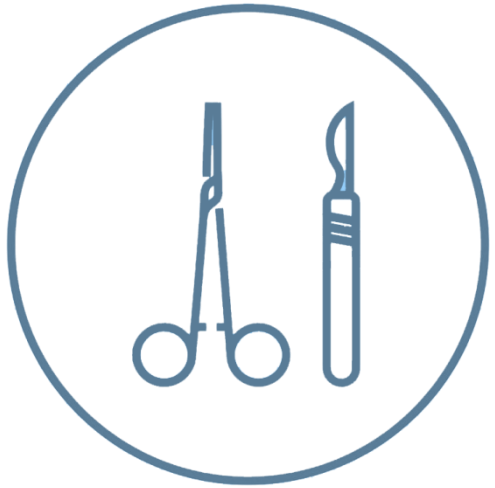
• Use of LMWH once per day (when creatinine clearance ≥30 mL.min^{-1}) or low-dose UFH three times per day (is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 hours preoperatively and continued for at least 7–10 days; there are no data allowing 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]	Unchanged
• Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended. [Grade 1A]	Unchanged



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2019 International CPGs
Prophylaxis of VTE in Surgical Cancer Patients Recommendations

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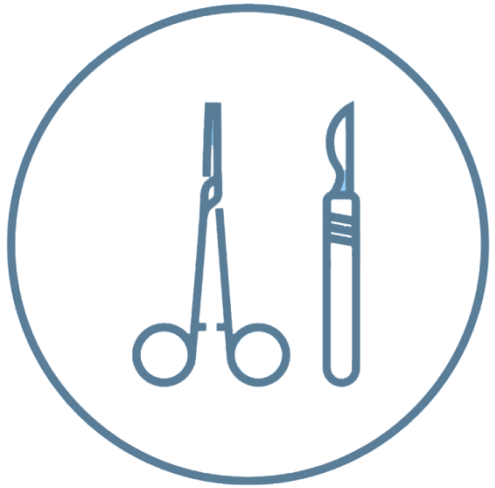
• Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in cancer patients is indicated in patients with a high VTE risk and low bleeding risk. [Grade 1A]	Updated
• Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery is recommended in the same way as for laparotomy. [Grade 2C]	Unchanged
• Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated. [Grade 2B]	Unchanged
• IVCs are not recommended for routine prophylaxis. [Grade 1A]	Unchanged



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2019 International CPGs
Prophylaxis of VTE in Medical Cancer Patients Recommendations

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• 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]. In this setting, DOACs are not recommended routinely [Guidance].	Updated

Farge D, Frere C et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print].

2019 International CPGs
Prophylaxis of VTE in Medical Cancer Patients Recommendations

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• Primary prophylaxis with LMWH, VKA or DOACs in ambulatory patients receiving systemic anti-cancer therapy is not recommended routinely [Grade 1B].		Updated
• 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].		Unchanged
• 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].		Updated

Farge D, Frere C et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print].

2019 International CPGs
Prophylaxis of VTE in Medical Cancer Patients Recommendations

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- 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]

KHORANA score	
Very high-risk tumors (pancreatic, gastric)	+2
High risk tumors ((lung, lymphoma, bladder, testicular, gynecological)	+1
Hemoglobin <10 g/dl and/or erythropoietin stimulating agents	+1
White blood cell count >11 x 109/L	+1
Platelet count ≥350 x 109/L	+1
BMI >35 kg/m2	+1

New

- 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].

Unchanged

Farge D, Frere C et al. *Lancet Oncol* 2019 Sep 3. [Epub ahead of print].

2019 International CPGs
Prophylaxis of CRT in Cancer Patients Recommendations

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• Use of anticoagulation for routine prophylaxis of CRT 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 CVC, we suggest the use of implanted ports over PICC lines. [Guidance]	New

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Special Situations

2019 International CPGs-Special Situations Recommendations

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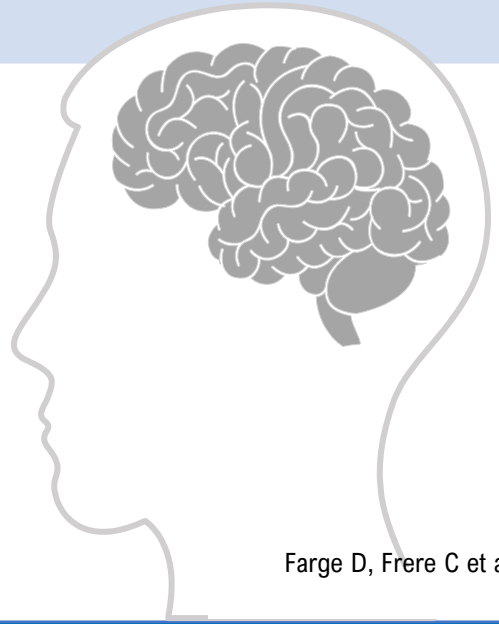
• For the treatment of established VTE in cancer patients with a brain tumor, LMWHs or DOACs can be used. [Grade 2B]	Updated
• We recommend the use of LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery. [Grade 1A]	Unchanged
• Primary pharmacological prophylaxis of VTE in medical cancer patients with brain tumor who are not undergoing neurosurgery is not recommended. [Grade 1B]	Unchanged



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2019 International CPGs
Special Situations Recommendations

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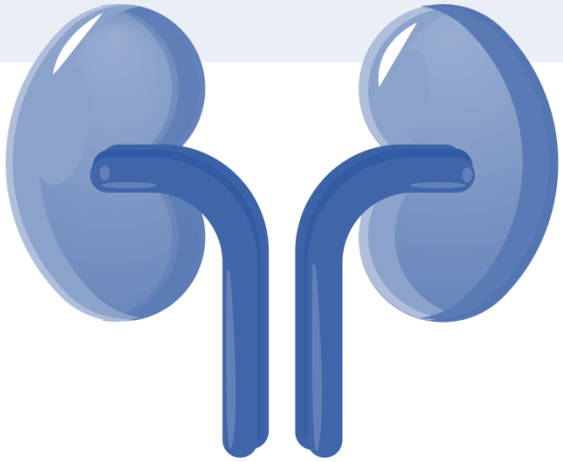
• In the presence of severe renal failure (creatinine clearance < 30 mL.min^{-1}) we suggest using UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE. [Guidance, in the absence of data and an unknown balance between desirable and undesirable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



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2019 International CPGs-Special Situations Recommendations

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• 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]	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. [Guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk versus VTE risk]	Unchanged

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2019 International CPGs-Special Situations Recommendations

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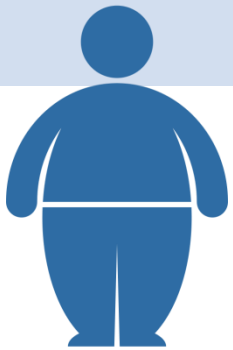
• In pregnant cancer patients, we suggest the use of LMWH for treatment of established VTE and for VTE prophylaxis and avoidance of VKAs and DOACs. [Guidance, in the absence of data and based on the contraindication of VKA and DOACs during pregnancy]	Updated

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



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2019 International Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

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Any VTE and cancer situation

Acknowledgements

- ITAC steering committee

- Knowledge Synthesis team members

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