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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol* 2022; **23:** e334–47.

2022 International Clinical Practice Guidelines (ITAC-CPGs) for the Treatment and Prophylaxis of Venous Thromboembolism in Cancer Patients, including those with Covid-19

Supplementary Appendix

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Appendix 1: Guideline development methodology

The methodology used to prepare the current 2022 update of the International Initiative on Thrombosis and Cancer (ITAC) clinical practice guidelines (CPGs) for the treatment and prevention of venous thromboembolism (VTE) in cancer patients was developed by the Institut National du Cancer (INCa). This methodology was used for the first publication of the ITAC-CPGs in 2013, and their updates published in 2016 and 2019.

Organization, panel composition and coordination.

The panel included independent international academic clinicians from various specialties (hematology, internal medicine, oncology, surgery and vascular medicine), and two methodologists with expertise in evidence appraisal. All panelists were members of the ITAC steering committee. The panel work was coordinated by experts in guideline-development methodology (Dominique Farge and James Douketis) who supported the guideline-development process, prepared agendas and meeting materials using web-based tools (https://www.dispose.aphp.fr). Coordinators also facilitated panel discussions during the online meetings. Minutes from all meetings were documented and are available for review on request.

Panel composition:

- Dominique Farge, MD, PhD, France (coordinator)
- James Douketis, MD, Canada (coordinator)
- Syed A. Abutalib, MD, USA
- Darko Antic, MD, Serbia
- Cihan Ay, MD, PhD, Austria
- Dialina Brilhante, MD, Portugal
- Henri Bounameaux, MD, Switzerland
- Benjamin Brenner, MD, Israel
- Patricia Casais, MD, Argentina
- Jean M. Connors, MD, USA
- Corinne Frere MD, PhD, France (lead methodologist)
- María Cecilia Guillermo Esposito, MD, Uruguay
- Takayuki Ikezoe, MD, Japan
- Ajay Kakkar, B.Sc., M.B.B.S., PhD, UK
- Alok A. Khorana, MD, USA
- Luis A. Meillon-García, MD, United Mexican States
- Andres Munõz Martín, MD, Spain
- Ingrid Pabinger, MD, PhD, Austria
- Pedro H. Prata, MD, Brazil (methodologist)

Search strategy and selection criteria. The panel used the PICO (Population, Intervention, Comparator and Outcomes) model to formulate specific clinical questions and determining outcomes of interest. The updated literature search was performed by the INCa using MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials. The detailed search strategy is shown in Appendix 2. Search was restricted to articles in English published from December 15, 2018, to January 1, 2022. All articles

identified in the literature search were analyzed by two reviewers (DF and CF) who independently screened titles, abstracts, and subsequently full texts for eligibility. The selection criteria are shown in Appendix 3. Briefly, meta-analyses, systematic reviews, randomized clinical trials, or non-randomized prospective or retrospective studies in the absence of randomized clinical trials, were included. Editorials, letters to the editor, case reports, publications without an abstract, press releases and animal studies were excluded. Studies had to focus on the treatment of established VTE in cancer patients (including initial treatment, early maintenance, and long-term treatment, as well as treatment of recurrent VTE) or on the prophylaxis of VTE in cancer patients in both the surgical and the medical settings. When data from studies specific to cancer patients were not available, we selected studies performed in the general population (non-cancer specific data) which included a subset of cancer patients. In this case, the results were extrapolated to cancer patients and methodological bias was considered.

Members of the working group had the opportunity to add any additional references fulfilling the inclusion criteria for the individual questions that may have been missed.

Other CPGs addressing overlapping clinical questions were consulted.

The current review of the literature is added to the previous search of MEDLINE® and of all other databases, in French or English, which spanned from January 1, 1996 to December 31, 2018, and was previously reviewed in the 2013 (J Thromb Haemost. 2013 Jan;11(1):56-70 and J Thromb Haemost. 2013 Jan;11(1):71-80) 2016 and 2019 ITAC-CPGs (Lancet Oncol 2016 Oct; 17(10)e462-466; Lancet Oncol 2019 oct;20(10):e566-e581), also based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Critical appraisal and data extraction. Selected articles underwent a **critical appraisal**, that included an assessment of their methodological strength and clinical relevance, which was independently performed by the two methodologists. Discrepancies between the 2 methodologists were identified and resolved by consensus or discussion with a third reviewer. The decision to include or exclude a study was then approved by the rest of the panelists. Every step of the critical appraisal process has been documented.

Data were extracted into **evidence tables** by the methodologists using standardized forms. All members of the panel had the opportunity to make suggestions for corrections, and to identify missing evidence.

Conclusion tables were assembled by the methodologists and the coordinators to guide the development of the recommendations. These tables summarized the evidence for each clinical question based on the critical appraisal grids and evidence tables. The conclusion table for each clinical question included the list of studies with new evidence highlighted, a summary of findings, rankings of the study quality (low, moderate, high) based on study type, methodological strength, and sample size; the degree of agreement between studies (consistency); and an assessment of the patient population (directness)—*i.e.,* patients with cancer *versus* an unselected study population, which was recorded as a study limitation, and publication bias. These elements were later used to rank the level of evidence according to the GRADE scale. Any disagreements were successfully resolved by group discussion. All evidence and conclusion tables were reviewed and approved on November 29, 2021, and their final version on January 31, 2022, by all working group members.

Consensus development and grading system. Recommendations were drafted over four consensus meetings (June 25, July 30, September 10, and November 29, 2021). Prior to each consensus meeting, working group members were asked to evaluate each recommendation from the 2019 iteration of the ITAC-CPGs against new published data summarized in the conclusion tables. The working group members had to indicate whether the recommendation should remain unchanged or formulate what update they thought should be made, and why. These responses were collected and distributed to the working group for consideration prior to the consensus meeting.

Once drafted, the recommendations were ranked using two different scoring systems within the *Grading of Recommendations Assessment Development and Evaluation (GRADE) scale*: 1) a quality of evidence grade (A-D), and 2) a level of recommendation ranking that reflects the degree of confidence that the benefits of adherence to a recommendation will outweigh any undesirable effects (Grade 1 guideline, strong; Grade 2 guideline, weak). In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the international experts within the working group and defined as “Best Clinical Practice” (Guidance). The international working group including representatives from Europe, Africa, Asia, North and South America took account of additional economic considerations to offer treatment alternatives, when possible, that address potential economic barriers to treatment.

The working group agreed *a priori* that if a consensus could not be reached, this would be reported in the guidelines, with an explanation of the point or points of contention. No such conflict arose, and all recommendations represent a consensus reached by the entirety of the panelists.

The guideline-development process incorporates measures to ensure impartiality and transparency while establishing the recommendations.

Review process The Guidelines were peer-reviewed by an advisory panel of 87 independent international experts, encompassing all medical and surgical specialties involved in the management of patients with cancer, and by 1 patient advocate and 1 nurse. The experts were identified based on their knowledge, clinical expertise, publication records, and contributions to the field. As performed in the previous ITAC-CPGs iterations, advisory panel members were asked to rank their agreement with the recommendations according a nine-point scale (from “strongly disagree” to “strongly agree”) and to provide any insightful comment. Each suggestion was analyzed by the coordinators, then by the working group, and revisions were incorporated into the final review. This last process enabled us to consider both practitioner and patient values and preferences. Any discrepancy in opinion between the advisory panel and the working group members was resolved by consensus during a final meeting.

The International Society on Thrombosis and Haemostasis (ISTH) has reviewed and endorsed the methodology used in creating these guidelines.

Appendix 2: Literature search strategy

Q1: Initial treatment of established VTE (up to 10 days of anticoagulation)
Q2: Early maintenance (3 to 6 months) and long-term (beyond 6 months) treatment of established VTE

Search equation *Medline*® (Ovid)	Search description
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignant$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombosis$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembolism$).ti. 9. or/4-8 10. exp Thrombolytic Therapy/ 11. exp Antithrombins/ 12. exp Heparin, Low-Molecular-Weight/ 13. exp anticoagulants/ 14. ((novel or new) adj2 (anticoag$ or anti coag$)).mp. 15. ((new or novel or direct) adj4 (oral anticoag$ or oral anti coag$)).mp. 16. warfarin.mp. 17. vitamin K.mp. 18. tinzaparin.mp. 19. reviparin.mp. 20. Fondaparinux.mp. 21. dabigatran.mp. 22. rivaroxaban.mp. 23. apixaban.mp. 24. edoxaban.mp. 25. or/10-24	"**Treatment of VTE venous Thromboembolism**" (1)
26. thrombosis/dt, th 27. venous thrombosis/dt, th 28. thromboembolism/dt, th 29. pulmonary embolism/dt, th 30. ((thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembolism$) and (treatment$1 or therapy or therapeutic)).ti. 31. or/26-30	"**Treatment of VTE venous Thromboembolism**" (2)
32. 3 and 9 and 25 33. 3 and 31 34. 32 or 33	"**Treatment of VTE venous Thromboembolism**" (1) or (2)
35. limit 34 to (human and (english or french) and ed=20181215-20220101) 36. editorial.pt. 37. letter.pt. 38. news.pt. 39. case reports.pt. 40. in-vitro.pt. 41. animal/ 42. or/36-41 43. 35 not 42	Limitations (date, language) and exclusion filters
44. randomized controlled trial.pt. 45. random allocation.de. 46. random$.ti. 47. double-blind method.de. 48. or/44-47	Search for randomized trials
49. meta-analysis.pt. 50. meta-analy$.ti. 51. metaanaly$.ti. 52. (systematic adj3 overview$).tw. 53. (systematic adj3 review$).tw. 54. (quantitative adj3 overview$).tw. 55. (quantitative adj3 review$).tw. 56. or/49-55	Search for **Meta-analyses/systematic reviews**

57. 43 and 48 58. 43 and 56	

Q3: Treatment of VTE recurrence – vena cava filters

In patients with cancer

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignan$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 9. Venous Thromboembolism/ 10. or/4-9	Search module **venous thromboembolism**
11. Vena Cava Filters/ 12. (filter$1 adj (umbrella or vena cava)).ti. 13. or/11-12 14. 3 and 10 and 13	"**Vena cava filters**"
15. limit 14 to (human and (english or french) and ed=20181215-20220101) 16. editorial.pt. 17. letter.pt. 18. news.pt. 19. case reports.pt. 20. in-vitro.pt. 21. animal/ 22. or/16-21 23. 15 not 22	Limitations (date, language) and exclusion filters
24. randomized controlled trial.pt. 25. random allocation.de. 26. random$.ti. 27. double-blind method.de. 28. 24 or 25 or 26 or 27	Search for randomized trials
29. meta-analysis.pt. 30. meta-analy$.ti. 31. metaanaly$.ti. 32. (systematic adj3 overview$).tw. 33. (systematic adj3 review$).tw. 34. (quantitative adj3 overview$).tw. 35. (quantitative adj3 review$).tw. 36. or/29-35 37. 23 and 28 38. 23 and 36	Search for **Meta-analyses/systematic reviews**

In patients without cancer

Search equation *Medline*® (Ovid)	**Search description**
1. thrombosis/ 2. venous thrombosis/ 3. thromboembolism/ 4. Pulmonary Embolism/ 5. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 6. Venous Thromboembolism/ 7. or/1-6	Search module: **venous thromboembolism**
8. Vena Cava Filters/ 9. (filter$1 adj (umbrella or vena cava)).ti. 10. or/8-9 11. 7 and 10	"**Vena cava filters**"
12. limit 11 to (human and (english or french) and ed=20181215-20220101) 13. editorial.pt. 14. letter.pt. 15. news.pt. 16. case reports.pt. 17. in-vitro.pt. 18. animal/ 19. or/13-18 20. 12 not 19	Limitations (date, language) and exclusion filters
21. meta-analysis.pt. 22. meta-analy$.ti. 23. metaanaly$.ti. 24. (systematic adj3 overview$).tw. 25. (systematic adj3 review$).tw. 26. (quantitative adj3 overview$).tw. 27. (quantitative adj3 review$).tw. 28. or/21-27 29. 20 and 28	Search for **Meta-analyses/systematic reviews**

Q4: Prophylaxis of VTE in surgical cancer patients
Q5: Prophylaxis of VTE in medical cancer patients

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignan$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 9. or/4-8	Search module **Venous Thromboembolism**
10. thrombosis/pc 11. venous thrombosis/pc [Prevention & Control] 12. thromboembolism/pc [Prevention & Control] 13. Pulmonary Embolism/pc [Prevention & Control] 14. 10 or 11 or 12 or 13 15. ((thrombos$ or DVT or VTE or thromboembol$ or (pulmonary adj1 embolism)) adj4 (recurrence or recurrent or second$) adj2 (risk$ or prevent$ or prophylaxy or prophylaxi$)).ti,ab. 16. (risk$ or prevent$ or prophylaxy or prophylaxi$).ti,ab. 17. ((thrombos$ or DVT or VTE or thromboembol$ or (pulmonary adj1 embolism)) adj4 (recurrence or recurrent or second$)).ti,ab. 18. 3 and 9 and 16 19. 3 and 15 20. 3 and 14 and 17 21. 18 or 19 or 20	**"Venous thromboembolism prophylaxis"**
22. editorial.pt. 23. letter.pt. 24. news.pt. 25. case reports.pt. 26. in vitro.pt. 27. animal/ 28. or/22-27 29. 21 not 28 30. limit 29 to (human and (english or french) and ed=20181215-20220101)	Limitations (date, language) and exclusion filters
31. randomized controlled trial.pt. 32. random allocation.de. 33. random$.ti. 34. double-blind method.de. 35. 31 or 32 or 33 or 34	Search for **Randomized trials**
36. meta-analysis.pt. 37. meta-analy$.ti. 38. metaanaly$.ti. 39. (systematic adj3 overview$).tw. 40. (systematic adj3 review$).tw. 41. (quantitative adj3 overview$).tw. 42. (quantitative adj3 review$).tw. 43. or/36-42	Search for **Meta-analyses/systematic reviews**
44. clinical trials, phase iii/ 45. clinical trial, phase iii.pt. 46. (phase III or phase 3).ti. 47. 44 or 45 or 46	Search for **Phase III Randomized trials**
48. exp "cohort studies"/ 49. prospective stud$.ti. 50. prospective studies/ 51. 48 or 49 or 50 52. 30 and 35 53. 30 and 43 54. 30 and 47 55. 30 and 51	Search for **Prospective studies**

Q6: Treatment of established catheter-related thrombosis
Q7: Prophylaxis of catheter-related thrombosis

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignan$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 9. or/4-8	Search module **Venous Thromboembolism**
10. Catheterization/ 11. Catheterization, Central Venous/ 12. (Catheterization$ or CCV or (central adj1 venous) or catheter$).ti. 13. or/10-12 14. 3 and 9 and 13	Search module **Catheter**
15. limit 14 to (human and (english or french) and ed=20181215-20220101) 16. editorial.pt. 17. letter.pt. 18. news.pt. 19. case reports.pt. 20. in-vitro.pt. 21. animal/ 22. or/16-21 23. 15 not 22	Limitations (date, language) and exclusion filters
24. randomized controlled trial.pt. 25. random allocation.de. 26. random$.ti. 27. double-blind method.de. 28. 24 or 25 or 26 or 27	Search for **Randomized trials**
29. meta-analysis.pt. 30. meta-analy$.ti. 31. metaanaly$.ti. 32. (systematic adj3 overview$).tw. 33. (systematic adj3 review$).tw. 34. (quantitative adj3 overview$).tw. 35. (quantitative adj3 review$).tw. 36. or/29-35 37. 23 and 28 38. 23 and 36	Search for **Meta-analyses/systematic reviews**

Thrombolytics

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignan$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 9. Venous Thromboembolism/ 10. or/4-9	Search module **Venous Thromboembolism**
11. Thrombolytic Therapy/ or thrombolysis.ti. 12. 3 and 10 and 11	Search module **Thrombolysis**
13. limit 12 to (human and (english or french) and ed=20181215-20220101) 14. editorial.pt. 15. letter.pt. 16. news.pt. 17. case reports.pt. 18. in-vitro.pt. 19. animal/ 20. or/14-19 21. 13 not 20	Limitations (date, language) and exclusion filters
22. randomized controlled trial.pt. 23. random allocation.de. 24. random$.ti. 25. double-blind method.de. 26. 22 or 23 or 24 or 25	Search for **Randomized trials**
27. meta-analysis.pt. 28. meta-analy$.ti. 29. metaanaly$.ti. 30. (systematic adj3 overview$).tw. 31. (systematic adj3 review$).tw. 32. (quantitative adj3 overview$).tw. 33. (quantitative adj3 review$).tw. 34. or/27-33 35. 21 and 26 36. 21 and 34	Search for **Meta-analyses/systematic reviews**

Q8: Special situations

(See all above Medline® equations)

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

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignant$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombosis$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembolism$).ti. 9. or/4-8 10. exp Thrombolytic Therapy/ 11. exp Antithrombins/ 12. exp Heparin, Low-Molecular-Weight/ 13. exp anticoagulants/ 14. ((novel or new) adj2 (anticoag$ or anti coag$)).mp. 15. ((new or novel or direct) adj4 (oral anticoag$ or oral anti coag$)).mp. 16. warfarin.mp. 17. vitamin K.mp. 18. tinzaparin.mp. 19. reviparin.mp. 20. Fondaparinux.mp. 21. dabigatran.mp. 22. rivaroxaban.mp. 23. apixaban.mp. 24. edoxaban.mp. 25. or/10-24	"**Treatment of VTE venous Thromboembolism**" (1)
26. thrombosis/dt, th 27. venous thrombosis/dt, th 28. thromboembolism/dt, th 29. pulmonary embolism/dt, th 30. ((thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembolism$) and (treatment$1 or therapy or therapeutic)).ti. 31. or/26-30	"**Treatment of VTE venous Thromboembolism"** (2)
32. 3 and 9 and 25 33. 3 and 31 34. 32 or 33	"**Treatment of VTE venous Thromboembolism**" (1) or (2)
35. covid-19.mp 36. sars-cov-2.mp 37. 35 or 36 38. 34 and 37	"**COVID-19"**
39. limit 38 to (human and (english or french) and ed=20191001-20220101) 40. editorial.pt. 41. letter.pt. 42. news.pt. 43. case reports.pt. 44. in-vitro.pt. 45. animal/ 46. or/40-45 47. 39 not 46	Limitations (date, language) and exclusion filters
48. randomized controlled trial.pt. 49. random allocation.de. 50. random$.ti. 51. double-blind method.de. 52. or/48-51	Search for randomized trials
53. meta-analysis.pt. 54. meta-analy$.ti. 55. metaanaly$.ti. 56. (systematic adj3 overview$).tw. 57. (systematic adj3 review$).tw. 58. (quantitative adj3 overview$).tw. 59. (quantitative adj3 review$).tw. 60. or/53-59 61. 47 and 52 62. 47 and 60	Search for **Meta-analyses/systematic reviews**

Q10: Prophylaxis of VTE in cancer patients with COVID-19

Search equation *Medline*® (Ovid)	**Search description**
1. exp neoplasms/ 2. (cancer$1 or carcinoma$1 or adenocarcinoma$1 or tumour$1 or tumor$1 or malignan$).ti. 3. 1 or 2	Search module **Cancer**
4. thrombosis/ 5. venous thrombosis/ 6. thromboembolism/ 7. Pulmonary Embolism/ 8. (thrombos$ or DVT or (pulmonary adj1 embolism) or VTE or thromboembol$).ti. 9. or/4-8	Search module **Venous Thromboembolism**
10. thrombosis/pc 11. venous thrombosis/pc [Prevention & Control] 12. thromboembolism/pc [Prevention & Control] 13. Pulmonary Embolism/pc [Prevention & Control] 14. 10 or 11 or 12 or 13 15. ((thrombos$ or DVT or VTE or thromboembol$ or (pulmonary adj1 embolism)) adj4 (recurrence or recurrent or second$) adj2 (risk$ or prevent$ or prophylaxy or prophylaxi$)).ti,ab. 16. (risk$ or prevent$ or prophylaxy or prophylaxi$).ti,ab. 17. ((thrombos$ or DVT or VTE or thromboembol$ or (pulmonary adj1 embolism)) adj4 (recurrence or recurrent or second$)).ti,ab. 18. 3 and 9 and 16 19. 3 and 15 20. 3 and 14 and 17 21. 18 or 19 or 20	**"Venous thromboembolism prophylaxis"**
22. covid-19.mp 23. sars-cov-2.mp 24. 22 or 23 25. 21 and 24	"**COVID-19"**
26. editorial.pt. 27. letter.pt. 28. news.pt. 29. case reports.pt. 30. in vitro.pt. 31. animal/ 32. or/26-31 33. 25 not 32 34. limit 33 to (human and (english or french) and ed=20191001-20220101)	Limitations (date, language) and exclusion filters
35. randomized controlled trial.pt. 36. random allocation.de. 37. random$.ti. 38. double-blind method.de. 39. Or/35-38	Search for **Randomized trials**
40. meta-analysis.pt. 41. meta-analy$.ti. 42. metaanaly$.ti. 43. (systematic adj3 overview$).tw. 44. (systematic adj3 review$).tw. 45. (quantitative adj3 overview$).tw. 46. (quantitative adj3 review$).tw. 47. or/40-46	Search for **Meta-analyses/systematic reviews**
48. clinical trials, phase iii/ 49. clinical trial, phase iii.pt. 50. (phase III or phase 3).ti. 51. 48 or 49 or 50	Search for **Phase III Randomized trials**
52. exp "cohort studies"/ 53. prospective stud$.ti. 54. prospective studies/ 55. 52 or 53 or 54 56. 34 and 39 57. 34 and 47 58. 34 and 51 59. 34 and 55	Search for **Prospective studies**

Appendix 3: Article selection

Q1: Initial treatment of established VTE (up to 10 days of anticoagulation)

	Inclusion criteria	Exclusion criteria
Population	Patients with: • cancer (solid tumors) • acute leukemia • multiple myeloma • lymphoma Confirmed VTE (deep-vein thrombosis and pulmonary embolism) Patients treated by all cancer-associated therapies: • chemotherapy • growth factors • hormonal therapy • targeted therapy (anti-angiogenics, monoclonal antibodies) • surgery • radiotherapy Initial treatment of VTE corresponds to the first 10 days of anticoagulation (0 to 10 days)	Patients with a tumor thrombus, or a history of cancer in remission for more than 5 years Patients with no VTE (prophylaxis) Catheter-related thrombosis Superficial-vein thrombosis
Intervention	UFH VKA LMWH Fondaparinux Thrombolytic Vena cava filter External compression device	Drugs or devices that are not marketed
Outcomes	Rates of VTE (*de novo* VTE or VTE extension) Major and minor bleeding Thrombocytopenia Death	Catheter-related thrombosis Superficial-vein thrombosis

Q2: Early maintenance (3 to 6 months) and long-term (beyond 6 months) treatment of established VTE

	Inclusion criteria	Exclusion criteria
Population	Patients with: • cancer (solid tumors) • acute leukemia • myeloma • lymphoma Confirmed VTE (deep-vein thrombosis and pulmonary embolism) Patients treated by all cancer-associated therapies: • chemotherapy • growth factors • hormonal therapy • targeted therapy (anti-angiogenics, monoclonal antibodies) • surgery • radiotherapy	Patients with tumor thrombus, or a history of cancer in remission for more than 5 years Patients with no VTE (prophylaxis) Catheter-related thrombosis Superficial-vein thrombosis
Intervention	VKA LMWH (long-term use) Idraparinux DOAC	Drugs or devices that are not marketed
Outcomes	Rates of VTE: • *de novo* VTE • VTE extension Major and minor bleeding Thrombocytopenia Death	Catheter-related thrombosis Superficial-vein thrombosis

Q3: Treatment of VTE recurrence in cancer patients under anticoagulation

	Inclusion criteria	Exclusion criteria
Population	Patients with: • cancer (solid tumor) • acute leukemia • multiple myeloma • lymphoma Confirmed VTE (deep-vein thrombosis and pulmonary embolism) Patients treated by all cancer-associated therapies: • chemotherapy • growth factors • hormonal therapy • targeted therapy (anti-angiogenics, monoclonal antibodies) • surgery • radiotherapy	Patients with a tumor thrombus, or a history of cancer in remission for more than 5 years Patients with no VTE (prophylaxis) Catheter-related thrombosis Superficial-vein thrombosis
Intervention	VKA Vena cava filter DOACs	Drugs or devices that are not marketed
Outcomes	Rate of VTE: • *de novo* VTE • VTE extension Major and minor bleeding Thrombocytopenia Death	Catheter-related thrombosis Superficial-vein thrombosis

Q4: Prophylaxis of VTE in surgical cancer patients

	Inclusion criteria	Exclusion criteria
Population	Cancer patients in a surgical setting with laparotomy or laparoscopy	Patients with a history of cancer in remission for more than 5 years No cancer Patients with VTE Patients with a full dose of anticoagulant Surgery performed for non-cancer treatment
Intervention	UFH LMWH Fondaparinux External compression device Duration of drug prophylaxis DOAC	Drugs or devices that are not marketed
Outcomes	*De novo* VTE Major and minor bleeding Thrombocytopenia Death	Catheter-related thrombosis Superficial-vein thrombosis

Q5: Prophylaxis of VTE in medical cancer patients

	Inclusion criteria	Exclusion criteria
Population	Hospitalized cancer patients Children with ALL treated with L-asparaginase Ambulatory patients treated with • chemotherapy • thalidomide or lenalidomide	Cancer in remission for more than 5 years Non-cancer patients Patients with VTE Patients treated with a full dose of anticoagulant
Intervention	UFH LMVH Fondaparinux External compression device DOAC	Drugs or devices that are not marketed
Outcomes	*De novo* VTE Major and minor bleeding	Catheter-related thrombosis Superficial-vein thrombosis

	Thrombocytopenia Death	

Q6: Treatment of established catheter-related thrombosis

	Inclusion criteria	Exclusion criteria
Population	Cancer patients with a central venous catheter: • totally implantable venous access system • tunneled catheter • prophetically inserted central catheter • with open-ended or valved distal extremity Patients treated by all cancer-associated therapies: • chemotherapy • growth factors • hormonal therapy • targeted therapy (anti-angiogenics, monoclonal antibodies) • surgery • radiotherapy	Cancer in remission for more than 5 years Central catheter inserted in non-cancer patients Dialysis catheter Peripheral intravenous catheter
Intervention	LMWH VKA CVC removal Systemic thrombolytic DOAC	Catheter flushing with • normal saline or heparinized saline solution • thrombolytic • taurolidine-citrate lock solution
Outcomes	Proven CRT: • *de novo* CRT • CRT extension • PE related to CRT Toxicities: • major and minor bleeding • thrombocytopenia • death	Catheter obstruction without parietal thrombosis DVT of lower limbs PE not related to CRT Superficial-vein thrombosis

Q7: Prophylaxis of catheter-related thrombosis

	Inclusion criteria	Exclusion criteria
Population	Cancer patients with a central venous catheter: • totally implantable venous access system • tunneled catheter • peripherically inserted central catheter • with open-ended or valved distal extremity	Cancer in remission for more than 5 years Central catheter inserted in non-cancer patients Dialysis catheter Peripheral intravenous catheter Patients with VTE or CRT Patients treated with full dose of anticoagulant
Intervention	Low dose of VKA Low dose of UFH Low dose of LMWH Type of CVC + insertion site Thrombolytic	Catheter flushing with • normal saline or heparinized saline solution • thrombolytic • taurolidine-citrate lock solution • antibiotics ull dose of anticoagulant
Outcomes	*De novo* proven CRT PE related to CRT Toxicities: • major and minor bleeding • thrombocytopenia • death	Catheter obstruction without parietal thrombosis DVT of lower limbs PE not related to CRT Superficial-vein thrombosis

Q8: Special situations

	Inclusion criteria	Exclusion criteria
Population	Cancer patients with: • thrombocytopenia • brain tumors • renal failure • Pregnant women with cancer	Not applicable
Intervention	Treatment and prophylaxis of: • DVT • PE • CRT	Exclusion criteria chosen for each specific question (Q1 to Q7)
Outcomes	Selected endpoints chosen for each specific question (Q1 to Q7)	Excluded endpoints chosen for each specific question (Q1 to Q7)

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

	Inclusion criteria	Exclusion criteria
Population	Cancer patients with COVID-19.	Not applicable
Intervention	UFH LMVH Fondaparinux DOAC External compression device	*Drug or devices that are not marketed*
Outcomes	Rates of VTE: • recurrent VTE • VTE extension Major and minor bleeding Thrombocytopenia Death	Catheter related thrombosis Superficial vein thrombosis

Q10: Prophylaxis of VTE in cancer patients with COVID-19

	Inclusion criteria	Exclusion criteria
Population	Cancer patients with COVID-19.	Not applicable
Intervention	UFH LMVH Fondaparinux DOAC External compression device	*Drug or devices that are not marketed*
Outcomes	Rates of VTE: Major and minor bleeding Thrombocytopenia Death	Catheter related thrombosis Superficial vein thrombosis

Update reference list

Q1: Initial treatment of established VTE

- **RCT-randomized controlled trials**

[McBane II 2020] Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost. 2020;18(2):411-421.

[Agnelli 2020] Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med. 2020 Apr 23;382(17):1599-1607.

[Planquette 2021] Rivaroxaban versus Dalteparin in Cancer-Associated Thromboembolism: A Randomized Trial. Chest. 2021 Oct 7:S0012-3692(21)04079-4.

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Q2: Early maintenance and long-term treatment of established VTE

- **RCT-randomized controlled trials**

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[Schrag 2021] The comparative effectiveness of direct oral anti-coagulants and low molecular weight heparins for prevention of recurrent venous thromboembolism in cancer: The CANVAS pragmatic randomized trial. Journal of Clin Oncol 2021 39:15_suppl, 12020-12020

- **Systematic reviews w/wo Meta-Analysis**

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[Moik 2021] Extended anticoagulation treatment for cancer-associated thrombosis - rates of recurrence and bleeding beyond 6 months: A systematic review. J Thromb Haemost. 2021 Nov 24.

- **Comparative/observational – prospective/retrospective**

[Wysokinski 2019] Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism. Am J Hematol. 2019 Nov;94(11):1185-1192.

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Q3: Treatment of VTE recurrence

Q4: Prophylaxis of VTE in surgical cancer patients

- **RCT-randomized controlled trials**

[Hata 2019] Efficacy and safety of anticoagulant prophylaxis for prevention of postoperative venous thromboembolism in Japanese patients undergoing laparoscopic colorectal cancer surgery. Ann Gastroenterol Surg. 2019 Jul 22;3(5):568-575.

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- **Systematic reviews w/wo Meta-Analysis**

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Q5: Prophylaxis of VTE in medical cancer patients

- **RCT-randomized controlled trials**

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Q6: Treatment of established catheter-related thrombosis (CRT)

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Q7: Prophylaxis of CRT

- **RCT-randomized controlled trials**

[Picardi 2019] A Frontline Approach With Peripherally Inserted Versus Centrally Inserted Central Venous Catheters for Remission Induction Chemotherapy Phase of Acute Myeloid Leukemia: A Randomized Comparison. Clin Lymphoma Myeloma Leuk. 2019 Apr;19(4):e184-e194.

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- **Systematic reviews w/wo Meta-Analysis**

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- **Comparative/observational – prospective/retrospective**

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Q8: Questions for specific populations and specific clinical situations

Cancer patients with:

✓ **Brain Tumours**

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✓ **Thrombocytopenia**

[Lecumberri 2020] Management and outcomes of cancer patients with venous thromboembolism presenting with thrombocytopenia. Thromb Res. 2020 Nov;195:139-145.

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✓ **Renal Failure**

✓ **Gender differences**

✓ **Children**

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

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Q10: Prophylaxis of VTE in cancer patients with COVID-19

- **RCT-randomized controlled trials**

[The REMAP-CAP, ACTIV-4a, ATTACC Investigators 2021] Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021 Aug 4. doi: 10.1056/NEJMoa2103417. Epub ahead of print. PMID: 34351722.

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- **Comparative/observational – prospective/retrospective**

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Appendix 4: CRITICAL APPRAISAL SYNTHESIS

References	Design	Endpoint definition	Description of randomization	Sample size calculation	Description of statistical plan	Description of endpoint method of measurement	Documentation of lost to follow-up	Intent-to-treat analysis	Toxicity: data - grading	Conflict of interest	Comments
Q1. INITIAL TREATMENT (UP TO 10 DAYS) OF ESTABLISHED VTE (SPECIFIC CASES EXCLUDED)											
1. [MCBANE II 2020]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	ADAM-VTE
2. [AGNELLI 2020]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	CARAVAGGIO
3. [PLANQUETTE 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	CASTA-DIVA
4. [SCHRAG 2021]	RCT	yes	-	-	-	-	-	-	-	-	CANVAS abstract
5. [KAHALE 2021]											Meta-analysis
6. [BRAILOVSKI 2020]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	catheter-directed thrombolysis
7. [BALABHADRA 2020]	retrospective	yes	-	-	yes	yes	-	-	no	yes	IVC filters
8. [QUEZADA 2020]	prospective	yes	-	-	yes	yes	-	-	Yes-yes	yes	IVC filters
9. [TAKASE 2020]	prospective	yes	-	-	yes	yes	-	-	-	yes	IVC filters
Q2. EARLY MAINTENANCE TREATMENT (3 TO 6 MONTHS) AND LONG-TERM TREATMENT (BEYOND 6 MONTHS) OF ESTABLISHED VTE (SPECIFIC CASES EXCLUDED)											
10. [MCBANE II 2020]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	ADAM-VTE
11. [AGNELLI 2020]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	CARAVAGGIO
12. [PLANQUETTE 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	CASTA-DIVA
13. [SCHRAG 2021]	RCT	yes	-	-	-	-	-	-	-		CANVAS abstract
14. [MOIK 2020]											Meta-analysis
15. [GIUSTOZZI 2020]											Meta-analysis
16. [SAMARANAYAKE 2020]											Meta-analysis
17. [HAYKAL 2020]											Meta-analysis
18. [DONG 2021]											Meta-analysis
19. [ELBADAWI 2020]											Meta-analysis
20. [CAMILLI 2020]											Meta-analysis
21. [MULDLER 2020]											Meta-analysis
22. [SABATINO 2020]											Meta-analysis
23. [DESAI 2020]											Meta-analysis
24. [YAN 2020]											Meta-analysis
25. [FRERE 2021]											Meta-analysis
26. [MOIK 2021]											Systematic Review
27. [WYSOKINSKI 2019]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	Apixaban vs rivaroxaban and enoxaparin in acute CAT
28. [MAHE 2020]	retrospective	yes	-	-	yes	yes			Yes-yes	yes	Treatment duration

References	Design	Endpoint definition	Description of randomization	Sample size calculation	Description of statistical plan	Description of endpoint method of measurement	Documentation of lost to follow-up	Intent-to-treat analysis	Toxicity: data - grading	Conflict of interest	Comments
Q3. TREATMENT OF VTE RECURRENCE (SPECIFIC CASES EXCLUDED)											
Q4. PROPHYLAXIS OF VTE IN SURGICAL CANCER PATIENTS (SPECIFIC CASES EXCLUDED)											
29. [HATA 2019]	RCT	yes	yes	yes	yes	yes	no	yes	yes-yes	yes	Japanese patients undergoing laparoscopic colorectal cancer (CRC) surgery
30. [TANAKA 2019]	RCT	yes	yes	yes	yes	yes	no	yes	yes-yes		Postoperative enoxaparin for the prevention of VTE after esophagectomy in Japan
31. [NAKAGAWA 2019]	RCT	yes	yes	yes	yes	yes	no	yes	yes-yes	no	Postoperative enoxaparin for the prevention of VTE after laparoscopic surgery for colorectal cancer in Japan
32. [GUNTUPALLI 2020]	RCT	yes	no	yes	yes	yes	no	Modified ITT	yes-yes	yes	Safety and efficacy of an oral treatment alternative for thromboprophylaxis in postoperative patients with gynecologic cancer.
33. [OBITSU 2020]	RCT	yes	yes	yes	yes	yes	no	yes	yes-yes	no	Japanese patients undergoing laparoscopic gastrointestinal cancer surgery
34. [PATEL 2020]	RCT	yes	yes	yes	yes	yes	no	yes	yes-yes	yes	Men with prostate cancer undergoing laparoscopic surgery
35. [BISCH 2021]											Meta-analysis
36. [INSIN 2021]											Meta-analysis
37. [KNOLL 2021]											Meta-analysis
Q5. PROPHYLAXIS IN MEDICAL CANCER PATIENTS (SPECIFIC CASES EXCLUDED)											
38. [ZWICKER 2020]	RCT	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	
39. [LI 2019]											Meta-analysis
40. [BARBARAWI 2019]											Meta-analysis
41. [BECATTINI 2020]											Meta-analysis
42. [THEIN 2020]											Meta-analysis
43. [FRERE 2020]											Meta-analysis
44. [XIN 2020]											Meta-analysis
45. [SCHÜNEMANN 2020]											Meta-analysis
46. [RANK 2020]											Meta-analysis

References	Design	Endpoint definition	Description of randomization	Sample size calculation	Description of statistical plan	Description of endpoint method of measurement	Documentation of lost to follow-up	Intent-to-treat analysis	Toxicity: data - grading	Conflict of interest	Comments
Q5. PROPHYLAXIS IN MEDICAL CANCER PATIENTS (SPECIFIC CASES EXCLUDED)											
47. [RUTJES 2020]											Meta-analysis
48. [BOSCH 2020]											Meta-analysis
49. [PEGOURIE 2019]	prospective	yes	-	-	yes	yes	-	-	yes-yes	yes	Apixaban for VTE prevention in myeloma patients treated with IMiDs
50. [SIBAI 2020]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	single-centre retrospective cohort study to determine the effects of LMWH as primary VTE prophylaxis in ALL
51. [CORNELL 2020]	prospective	yes	-	-	yes	yes	-	-	yes-yes	yes	phase IV, single-arm pilot study
52. [VADHAN-RAJ 2020]	retrospective	yes	yes	yes	yes	yes	yes	yes	yes-yes	yes	pre-specified subgroup analysis of the CASSINI trial
Q6. TREATMENT OF ESTABLISHED CATHETER-RELATED THROMBOSIS (CRT)											
Q7. PROPHYLAXIS OF CRT											
53. [PICARDI 2019]	RCT	yes	yes	yes	yes	yes	yes	-	Yes-no	yes	PICC vs CICC
54. [TAXBRO 2019]	RCT	yes	yes	yes	yes	yes	yes	-	Yes-no	yes	PICC vs CICC
55. [IKESAKA 2021]	RCT	yes	yes	-	yes	yes	yes	yes	yes	Yes	Rivaroxaban vs SOC
56. [LIU 2020]											Meta-analysis
57. [LV 2019]	prospective	yes	-	-	-	-	-	-	-	no	Comparison of LMW, rivaroxaban and no intervention
Q8. SPECIFIC CASES: ALL THESE SPECIFIC CASES WHICH WERE NOT STUDIED IN THE ABOVE CLINICAL QUESTIONS											
BRAIN TUMOURS											
58. [CARNEY 2019]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
59. [PORFIDIA 2020]											Meta-analysis
60. [CARNEY 2020]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
61. [SWARTZ 2021]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
62. [WOOD 2021]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
63. [JO 2021]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
64. [LEE 2021]	retrospective	yes	-	-	yes	yes	-	-	yes-yes	yes	retrospective
THROMBOCYTOPENIA											
65. [LECUMBERRI 2020]	prospective	yes	-	-	yes	yes	-	-	Yes-yes	yes	
66. [CARNEY 2022]	prospective	yes	-	-	yes	yes	-	-	Yes-yes	yes	

References	Design	Endpoint definition	Description of randomization	Sample size calculation	Description of statistical plan	Description of endpoint method of measurement	Documentation of lost to follow-up	Intent-to-treat analysis	Toxicity: data - grading	Conflict of interest	Comments
CHILDREN											
67. [GREINER 2019]	RCT	yes	yes	yes	yes	yes	-	yes	yes	yes	Children with ALL
68. [THOM 2020]	retrospective	yes	yes	no	yes	yes	yes	NS	Yes-yes	yes	Prespecified subgroup analysis of EINSTEIN-Jr RCT
69. [PELLAND-MARCOTTE 2019]											Meta-analysis
70. [JAFFRAY 2020]	prospective	yes	-	-	-	-	-	-	-	yes	PICCs vs TLs in children
Q9. TREATMENT OF VTE IN CANCER PATIENTS WITH COVID-19											
Q10. PROPHYLAXIS OF VTE IN CANCER PATIENTS WITH COVID-19											
71. [REMAP-CAP, ACTIV-4A, AND ATTACC INVESTIGATORS 2021]	Multiplatform RCT	yes	yes	-	yes	yes	yes	yes	yes	yes	REMAP-CAP, ACTIV-4a, ATTACC – Critically ill patients
72. [ATTACC, ACTIV-4A, AND REMAP-CAP INVESTIGATORS 2021]	Multiplatform RCT	yes	yes	-	yes	yes	yes	yes	yes	yes	REMAP-CAP, ACTIV-4a, ATTACC– Moderately ill patients
73. [SADEGHIPOUR 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	INSPIRATION
74. [LOPES 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	ACTION
75. [SHOLZBERG 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	RAPID
76. [ESWARAN 2020]	retrospective	yes	-	-	-	-	-	-	-	yes	Thrombosis outcomes following COVID-19 hospital discharge
77. [GIANNIS 2021]	Prospective	yes	-	-	-	-	-	-	-	yes	Thrombosis outcomes following COVID-19 hospital discharge
78. [PEREPU 2021]	RCT	yes	yes	-	yes	yes	yes	yes	yes	yes	
79. [CONNORS 2021]	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	ACTIV-4B
80. [RAMACCIOTTI 2022]	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	MICHELLE

CAT, cancer-associated thrombosis; IVCF, inferior vena cava filters; PNRS/RNRS, Prospective/retrospective Non-Randomized Study; RCT, Randomized Controlled Trial; RDBT, Randomized Double-Blind Trial; RS, Randomized Study.

Appendix 5: Data Extraction Tables

Table1: Initial treatment of VTE – Randomized controlled trials

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Safety	Death
[McBane II 2020] **ADAM-VTE** Phase IV, multicenter, randomized, open label, superiority trial	287/300	6 months	Patients >18 years with active cancer and acute VTE objectively demonstrated by an imaging study. Active cancer was defined as any evidence of cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior six months. 66% of subjects had metastasis; 74% were receiving concurrent chemotherapy.	**Arm A:** Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter, for 6 months. **Arm B:** dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 6 months.	**Recurrent VTE** Arm A: 1/145 (0.7%) Arm B: 9/142 (6.3%) HR 0.099; 95% CI 0.013–0.78; p=0.0281	**Major bleeding** Arm A: 0/145 (0%) Arm B: 2/142 (1.4%) HR not estimable; p=0.138 **Major and clinically relevant non-major bleeds (CRNMB)** Arm A: 9/145 (6.2%) Arm B: 9/142 (6.3%) P=0.8816	**Overall survival at 6 months** Arm A: 23/145(16%) Arm B: 15/142 (11%) p=0.3078
[Agnelli 2020] **CARAVAGGIO** Phase III, multinational, randomized, investigator-initiated, open-label, non-inferiority trial with blinded central outcome adjudication	1155/1170	6 months	Patients >18 years with active cancer and acute symptomatic VTE or incidental proximal (popliteal or a more proximal vein) lower-limb deep-vein thrombosis or pulmonary embolism. Active cancer defined as cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia) that had been diagnosed within the past 6 months, cancer for which anticancer. treatment was being given at the time of enrollment or during 6 months before randomization, or recurrent locally advanced or metastatic cancer. Patients with a history of cancer (as compared with active cancer) included	**Arm A:** Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter, for 6 months. **Arm B:** dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 6 months.	**Recurrent VTE** Arm A: 32/576 (5.6%) Arm B: 46/579 (7.9%) HR 0.63; 95% CI 0.37-1.07; p<0.001	**Major bleeding** Arm A: 22/576 (3.8%) Arm B: 23/579 (4.0%) HR 0.82; 95% CI 0.40-1.69, p=0.60 **Major or clinically relevant non-major bleeds (CRNMB)** Arm A: 70/576 (12.2%) Arm B: 56/579 (9.7%) HR 1.16; 95% CI 0.77-1.75	**Deaths from any cause at 6 months** Arm A: 135/576 (23.4%) Arm B: 153 (26.4%) HR 0.82; 95% CI 0.62-1.09

			those in whom a diagnosis had been made within 2 years before enrollment.				
[Planquette 2021] CASTA-DIVA Phase III, multicenter, randomized, investigator-initiated, open-label, non-inferiority trial with blinded central outcome adjudication	158/158	3 months	Patients >18 years with active cancer, acute proximal DVT and/or PE and a modified Ottawa score ≥1	**Arm A:** Rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily thereafter, for 3 months. **Arm B:** dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 3 months.	**Recurrent VTE** Arm A: 4/74 (6.4%) Arm B: 6/84 (10.1%) HR 0.75; 95% CI 0.21-2.66; p=0.13 for non-inferiority	**Major bleeding** Arm A: 1/74 (1.4%) Arm B: 3/84 (3.7%) HR 0.36; 95% CI 0.04-3.43 **Major or clinically relevant non-major bleeds (CRNMB)** Arm A: 9/74 (12.2%) Arm B: 8/84 (9.8%) HR 1.27; 95% CI 0.49-3.26	**Deaths from any cause at 3 months** Arm A: 19/74 (25.7%) Arm B: 20/84 (23.8%) HR 1.05; 95% CI 0.56-1.97
[Schrag 2021] CANVAS randomized, open-label, non-inferiority trial	638/671 in the randomized cohort	6 months	Patients with any invasive solid tumor, lymphoma, multiple myeloma or CLL and a diagnosis of symptomatic or radiographically detected VTE within 30 days of enrollment	**Arm A:** Any DOAC (rivaroxaban, apixaban, edoxaban, dabigatran) in accordance with the drug's FDA package insert for 6 months **Arm B:** Any LMWH (dalteparin, enoxaparin, or fondaparinux) in accordance with the drug's FDA package insert +/- Warfarin for 6 months.	**Recurrent VTE** Arm A: 6.1% Arm B: 8.8% Difference -2.7%; 90% CI -6.1 to 0.7%	**Major bleeding** Arm A: 5.2% Arm B: 5.6% Difference -0.4 %; 90% CI -3.3 to 2.5% **Clinically relevant non-major** bleeds (CRNMB) Arm A: 5.8% Arm B: 2.6% Difference 3.2 %; 90% CI 0.6 to 5.8%	**Deaths from any cause** Arm A: 21.5% Arm B: 18.4% Difference3.1%; 90% CI-2.1 to 8.3%

Table 2: Initial treatment of VTE – Systematic reviews with or without Meta-analysis

Reference	[Kahale 2021]
Bibliographic search	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid) and Embase (via Ovid), handsearching of conference proceedings; checking of references of included studies; and a search for ongoing studies. This update of the systematic review was based on the findings of a literature search conducted on 14 August 2021.
Included studies	**15 RCTs** (1615 participants with cancer and VTE) **13 studies** compared LMWH with UFH (1025 participants) [Breddin 2001] [Buller 1997] [Duroux 1991] [Hull 1992] [Koopman 1996] [Levine 1996] [Merli 2001] [Prandoni 1992] [Prandoni 2004] [Simonneau 1993] [Simonneau 1997] [Lindmarker 1994] [Lopaciuk 1992] **1 study** compared fondaparinux with UFH and LMWH (477 participants) [Van Doormaal 2009] **1 study** compared dalteparin with tinzaparin (113 participant) [Wells 2005]
Primary endpoint	All-cause mortality
Secondary endpoint	Symptomatic recurrent DVT Symptomatic recurrent PE Major bleeding Minor bleeding Postphlebitic syndrome Quality of life Thrombocytopenia
Results	**Patient or population:** patients with cancer with the initial treatment of VTE; **settings:** inpatient or outpatient **Intervention:** LMWH **Comparison:** UFH Reduced mortality with LMWH at 3 months: RR 0.66, 95% CI 0.40-1.10; risk difference (RD) 57 fewer per 1000, 95% CI 101 fewer to 17 more (moderate certainty evidence). No beneficial/detrimental effect of LMWH over UFH on Recurrent VTE at 3 months: RR 0.69, 95% CI 0.27-1.76; RD 30 fewer per 1000,95% CI 70 fewer to 73 more (moderate certainty evidence). **Intervention:** fondaparinux **Comparison:** heparin (UFH or LMWH) No difference in mortality: RR 1.25, 95% CI 0.86-1.81; RD 43 more per 1000, 95% CI 24 fewer to 139 more (moderate certainty evidence) No difference in recurrent VTE: RR 0.93, 95% CI 0.56-1.54; RD 8 fewer per 1000, 95% CI 52 fewer to 63 more (moderate certainty evidence) Major bleeding: RR 0.82; 95% CI 0.40- 1.66; RD 12 fewer per 1000, 95% CI 40 fewer to 44 more (moderate certainty evidence) Minor bleeding: RR 1.53, 95% CI 0.88-2.66; RD 42 more per 1000, 95% CI 10 fewer to 132 more (moderate certainty evidence) **Dalteparin vs Tinzaparin** No difference in mortality: RR 0.86, 95% CI 0.43-1.73; RD 33 fewer per 1000, 95% CI 135 fewer to 173 more (low certainty evidence) No difference in VTE recurrence: RR 0.44, 95% CI 0.09-2.16; RD 47 fewer per 1000, 95% CI 77 fewer to 98 more (low certainty evidence) Major bleeding: RR 2.19, 95% CI 0.20-23.42; RD 20 more per 1000, 95% CI 14 fewer to 380 more (low certainty evidence) Minor bleeding: RR 0.82, 95% CI 0.30-2.21; RD 24 fewer per 1000, 95% CI 95 fewer to 164 more (low certainty evidence).
Authors' conclusions	Low molecular weight heparin (LMWH) is probably superior to UFH in the initial treatment of VTE in people with cancer. Additional trials focusing on patient-important outcomes will further inform the questions addressed in this review. The decision for a person with cancer to start LMWH therapy should balance the benefits and harms and consider the person's values and preferences.

Table 3: Initial treatment of VTE: Thrombolysis - Comparative/observational – prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Brailovsky 2020] Data were obtained from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project National Inpatient Sample (NIS) files between January 2005 and December 2013	2574/2574	-	Patients identified with a principal discharge diagnosis of proximal lower extremity or caval DVT and diagnosis of cancer	**Group A**: catheter-directed thrombolysis (CDT) and anticoagulation. **Group B:** anticoagulation alone.	-	**Rates of intracranial hemorrhage** Group A: 1.3% Group B: 0.4% p=0.017 **Rates of blood transfusion** Group A: 18.6% Group B: 13.1% p< 0.001 **Rates of procedure-related hematoma** Group A: 2.4% Group B: 0.4% P < 0.001	Group A: 2.6% Group B: 1.9% p=0.23

Table 4: Initial treatment of VTE: Vena Cava filters - Comparative/observational – prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Balabhadra 2020] Retrospective cohort (Inpatient databases for California from 2005 to 2011 and Florida from 2005 to 2014) Propensity-matched cohort	88 585 cancer patients with DVT (33 740 patients with IVC filter versus 54 845 patients without IVC filter)	median follow-up 479 days (IQR, 89-1322 days).	Patients who presented to a health care institution with a diagnosis of DVT and cancer based on ICD-9 codes	**Group A:** IVC filter **Group B:** no IVC filter	**PE-free survival** Significant improvement in PE-free survival in patients who underwent IVC filter placement (HR 0.69; 95% CI 0.64-0.75; p < 0.001). **Recurrent DVT** Group A: 4638/24 857 (18.7%) Group B: 5492/24 857 (22.1%) p < 0.001 **Recurrent-DVT free survival** Significant improvement in recurrent-DVT free survival in	Not reported	Overall in-hospital mortality worse overall in-hospital mortality in patients who underwent IVC filter placement (p < 0.001).

					patients who underwent IVC filter placement (p < 0.001)		
[Quezada 2020] Prospective cohort study of patients with CAT from RIETE Propensity-matched cohort	17,005 cancer patients included in RIETE Matched-cohort: 247 patients treated with IVC filters and 247 patients treated without IVC filters	30 days	Cancer patients with acute VTE included in RIETE	**Group A:** IVC filter **Group B:** no IVC filter	**PE-related death** Group A: 2/247 (0.8%) Group B: 10/247 (4.0%) OR 0.19; 95% CI 0.04–0.89; p=0.04 **Recurrent VTE** Group A: 18/247 (7.3%) Group B: 8/247 (3.2%) OR 2.34; 95% CI 1.00–5.51; p=0.05 **Recurrent PE** Group A: 11/247 (4.5%) Group B: 7/247 (3.6%) OR 1.60; 95% CI 0.61–4.20; p= 0.34	**Major bleeding** Group A: 15/247 (6.1%) Group B: 14/247 (5.7%) OR 1.08; 95% CI 0.51–2.29; p= 0.85	**Death** Group A: 30/247 (12.2%) Group B: 42/247 (17.0%) OR 0.67; 95% CI 0.41–1.12; p= 0.13
[Takase 2020] Retrospective study of patients with CAT from COMMAND VTE registry	150 cancer patients with non-retrieved IVC filter and 454 cancer patients without IVC filter	Median follow-up : 1020 (IQR: 432–1567) days	Cancer patients with acute VTE included in the COMMAND VTE registry	**Group A:** IVC filter **Group B:** no IVC filter	**PE** Group A: 7/150 (4.7%) Group B: 25/454 (5.5%) aHR 0.82; 95% CI .34–1.96; p=0.650 **DVT** Group A: 16/150 (10.7%) Group B: 24/454 (5.3%) aHR 2.47; 95% CI 1.24–4.91; p=0.01	**Major bleeding** Group A: 28/150 (18.7%) Group B: 63/454 (13.9%) aHR 1.78; 95% CI 1.11–2.87; p=0.017	**Death** Group A: 111/150 (74.0%) Group B: 282/454 (62.1%) aHR 1.28; 95% CI 1.02–1.62; p=0.034

Table 5: Early maintenance and long-term treatment of established VTE – RCT

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[McBane II 2020] **ADAM-VTE** Phase IV, multicenter, randomized, open label, superiority trial	287/300	6 months	Patients >18 years with active cancer and acute VTE objectively demonstrated by an imaging study. Active cancer was defined as any evidence of cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior six months. 66% of subjects had metastasis; 74% were receiving concurrent chemotherapy	**Arm A:** Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter, for 6 months **Arm B:** dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 6 months	**Recurrent VTE** Arm A: 1/145 (0.7%) Arm B: 9/142 (6.3%) HR 0.099; 95% CI 0.013–0.78; p=0.0281	**Major bleeding** Arm A: 0/145 (0%) Arm B: 2/142 (1.4%) HR not estimable; p=0.138 **Major and clinically relevant non-major bleeds (CRNMB)** Arm A: 9/145 (6.2%) Arm B: 9/142 (6.3%) P=0.8816	**Overall survival at 6 months** Arm A: 23/145(16%) Arm B: 15/142 (11%) p=0.3078
[Agnelli 2020] **CARAVAGGIO** Phase III, multinational, randomized, investigator-initiated, open-label, non-inferiority trial with blinded central outcome adjudication	1155/1170	6 months	Patients >18 years with active cancer and acute symptomatic VTE or incidental proximal (popliteal or a more proximal vein) lower-limb deep-vein thrombosis or pulmonary embolism. Active cancer defined as cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia) that had been diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrollment or during 6 months before randomization, or recurrent locally advanced or metastatic cancer. Patients with a history of cancer (as compared with active cancer) included those in whom a diagnosis had been made within 2 years before enrollment.	**Arm A:** Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter, for 6 months **Arm B:** dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 6 months	**Recurrent VTE** Arm A: 32/576 (5.6%) Arm B: 46/579 (7.9%) HR 0.63; 95% CI 0.37-1.07; p<0.001	**Major bleeding** Arm A: 22/576 (3.8%) Arm B: 23/579 (4.0%) HR 0.82, 95% CI 0.40-1.69, p=0.60 **Major or clinically relevant non-major bleeds (CRNMB)** Arm A: 70/576 (12.2%) Arm B: 56/579 (9.7%) HR 1.16; 95% CI 0.77-1.75	**Deaths from any cause at 6 months** Arm A: 135/576 (23.4%) Arm B: 153 (26.4%) HR 0.82; 95% CI 0.62-1.09
[Planquette 2021] **CASTA-DIVA** Phase III, multicenter, randomized, investigator-initiated, open-label, non-inferiority trial with	158/158	3 months	Patients >18 years with active cancer, acute proximal DVT and/or PE and a modified Ottawa score ≥1	**Arm A:** Rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily thereafter, for 3 months. **Arm B:**	**Recurrent VTE** Arm A: 4/74 (6.4%) Arm B: 6/84 (10.1%) HR 0.75; 95% CI 0.21-2.66; p=0.13 for non-inferiority	**Major bleeding** Arm A: 1/74 (1.4%) Arm B: 3/84 (3.7%) HR 0.36; 95% CI 0.04-3.43 **Major or clinically relevant non-major bleeds (CRNMB)** Arm A: 9/74 (12.2%)	**Deaths from any cause at 3 months** Arm A: 19/74 (25.7%) Arm B: 20/84 (23.8%) HR 1.05; 95% CI 0.56-1.97

blinded central outcome adjudication				dalteparin 200 IU/kg sc daily for 30 days, followed by 150 IU/Kg sc daily thereafter, for 3 months.		Arm B: 8/84 (9.8%)SHR 1.27; 95% CI 0.49-3.26	
[Schrag 2021] CANVAS randomized, open-label, non-inferiority trial	638/671 in the randomized cohort	6 months	Patients with any invasive solid tumor, lymphoma, multiple myeloma or CLL and a diagnosis of symptomatic or radiographically detected VTE within 30 days of enrollment	**Arm A:** Any DOAC (rivaroxaban, apixaban, edoxaban, dabigatran) in accordance with the drug's FDA package insert for 6 months **Arm B:** Any LMWH (dalteparin, enoxaparin, or fondaparinux) in accordance with the drug's FDA package insert +/- Warfarin for 6 months.	**Recurrent VTE** Arm A: 6.1% Arm B: 8.8% Difference -2.7%; 90% CI -6.1 to 0.7%	**Major bleeding** Arm A: 5.2% Arm B: 5.6% Difference -0.4 %; 90% CI -3.3 to 2.5% **Clinically relevant non-major** bleeds (CRNMB) Arm A: 5.8% Arm B: 2.6% Difference 3.2 %; 90% CI 0.6 to 5.8%	**Deaths from any cause** Arm A: 21.5% Arm B: 18.4% Difference3.1%; 90% CI-2.1 to 8.3%

Table 6: Early maintenance and long-term treatment of established VTE – Systematic reviews with or without Meta-analysis

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[Moik 2020]	Literature search using Medline (PubMed), EMBASE, and CENTRAL (Cochrane Controlled Trials Registry) up to April, 2020	4 studies, 2894 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	CRNMB Mortality Rate of preterm discontinuation of anticoagulation at 6 months	RR determined using Mantel-Haenszel method (random effects model). Risk of bias and strength of evidence assessed by using the Cochrane Collaboration's tool and the GRADE system. Cochrane's test and I^2 statistic to assess heterogeneity between studies. Statistically significant heterogeneity was considered to be high when $p < 0.10$ and $I^2 > 50\%$. Funnel plots were used to assess for publication bias.	**Recurrent VTE** Treated with DOACs: 75/1446 patients (5.2%) Treated with LMWHs: 119/1448 patients (8.2%) RR 0.62; 95% CI 0.43–0.91; I^2=30% ***Recurrent VTE in patients with incidental VTE*** Treated with DOACs: 11/276 Treated with LMWHs: 20/285 RR 0.58; 95% CI 0.28-1.18; I^2= 0% ***Recurrent VTE in patients with symptomatic VTE*** Treated with DOACs: 55/815 Treated with LMWHs: 72/816 RR 0.76; 95% CI 0.55-1.07; I^2=0% **Major bleeding** Treated with DOACs: 62/1446 (4.3%) Treated with LMWHs: 48/1448 (3.3%) RR 1.31; 95% CI 0.83-2.08; I^2=23% ***Major bleeding in GI cancer*** Treated with DOACs: 24/257 Treated with LMWHs: 9/226 RR 2.30; 95% CI 1.08-4.88; I^2=22.9% ***Major bleeding in non-GI cancer*** Treated with DOACs: 16/468 Treated with LMWHs: 14/501 RR 1.22; 95% CI 0.60-2.48; I^2= 0% ***Major bleeding in patients with incidental VTE***	In patients with cancer-associated VTE, DOACs are more effective in preventing recurrent VTE compared to LMWH. However, risk of bleeding is increased with DOACs, especially in patients with GI cancer.

						Treated with DOACs: 14/276 Treated with LMWHs: 13/285 RR 1.11; 95% CI 0.53-2.32; I^2=67% ***Major bleeding in patients with symptomatic VTE*** Treated with DOACs: 32/815 Treated with LMWHs: 23/816 RR 1.50; 95% CI 0.56-4.07; I^2= 67% **CRNMB** Treated with DOACs: 150/1446 Treated with LMWHs: 92/1448 RR 1.65; 95% CI 1.19-2.28; I^2=29% **All-cause death** Treated with DOACs: 346/1446 Treated with LMWHs: 351/1448 RR 0.99; 95% CI 0.83–1.18; I^2= 37% **Pretreatment discontinuation** Treated with DOACs: 572/1446 Treated with LMWHs: 652/1448 RR 0.88; 95% CI 0.81-0.96; I^2= 0%	
[Giustozzi 2020]	Literature search using Medline (PubMed), EMBASE, and CENTRAL (Cochrane Controlled Trials Registry) up to March 30, 2020	4 studies, 2894 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	Recurrent PE Recurrent DVT Fatal PE Clinically relevant nonmajor bleeding (CRNMB), Clinically relevant bleeding (CRB) Fatal bleeding All-cause death.	RR determined using Mantel-Haenszel method (random effects model). Risk of bias and strength of evidence assessed by using the Cochrane Collaboration's tool and the GRADE system. Cochrane's test and I^2 statistic to assess heterogeneity between studies. Statistically significant heterogeneity was considered to be high when $p < 0.10$ and $I^2 > 50\%$ Funnel plots were used to assess for publication bias.	**Recurrent VTE** Treated with DOACs: 75/1446 patients (5.2%) Treated with LMWHs: 119/1448 patients (8.2%) RR 0.62; 95% CI 0.43–0.91; I^2= 30% **Major bleeding** Treated with DOACs: 62/1446 (4.3%) Treated with LMWHs: 48/1448 (3.3%) RR 1.31; 95% CI 0.83-2.08; I^2= 23% **Recurrent PE** Treated with DOACs: 3.2% Treated with LMWHs: 119/1448 patients (4.6%)	In patients with cancer-associated VTE, oral factor Xa inhibitors reduced the risk of recurrent VTE without a significantly higher likelihood of major bleeding at 6 months compared with LMWH.

						RR 0.71; 95% CI 0.49–1.03; I^2= 0% **Recurrent DVT** Treated with DOACs: 2.2% Treated with LMWHs: 3.8% RR 0.60; 95% CI 0.36–1.00; I^2=16% **Fatal PE** Treated with DOACs: 0.3% Treated with LMWHs: 0.3% RR 1.25; 95% CI 0.34-4.67; I^2= 0% **CRNMB** Treated with DOACs: 10.4% Treated with LMWHs: 6.4% RR 1.65; 95% CI 1.19-2.28; I^2= 29% **CRB** Treated with DOACs: 13.7% Treated with LMWHs: 9.3% RR 1.51; 95% CI 1.09-2.09; I^2= 49% **Fatal bleeding** Treated with DOACs: 0.2% Treated with LMWHs: 0.3% RR 0.37; 95% CI 0.07-2.0; I^2= 0% **All-cause death** Treated with DOACs: 23.9% Treated with LMWHs: 24.2% RR 0.99; 95% CI 0.83–1.18; I^2=37%	
[Samaranayake 2020]	Literature search using MEDLINE, EMBASE, CENTRAL through April 1, 2020	4 studies, 2907 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE at 6 months Major Bleeding at 6 months	CRNMB at 6 months All-cause mortality at 6 months	RR determined using Mantel-Haenszel method (random effects model). I^2 statistic to assess heterogeneity between studies. .	**Recurrent VTE** DOACs vs. LMWHs: RR 0.63, 95% CI 0.44-0.91; I^2 = 28% **Major bleeding** DOACs vs. LMWHs: RR 1.31, 95%CI 0.83-2.07; I^2 = 22%	DOACs are effective in treating malignancy associated VTE, however caution is required in patients with high risk of bleeding. Apixaban had lower risk of bleeding compared to other DOACs in this population.

						Major bleeding or CRNMB DOACs vs. LMWHs: RR 1.52, 95%CI 1.09-2.12; I^2 = 51% **All-cause mortality** DOACs vs. LMWHs: RR 1.0, 95% CI 0.84-1.18; I^2=33%	
[Haykal 2020]	Literature search using PubMed, Embase, and COCHRANE from inception to April 2020.	4 studies, 2907 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	Recurrent DVT Recurrent PE CRNMB All-cause mortality VTE-related death Bleeding-related death	RR determined using Mantel-Haenszel method (random effects model) Risk of bias and strength of evidence assessed by the Cochrane Collaboration's tool. I^2 statistic to assess heterogeneity between studies.	**Recurrent VTE** Treated with DOACs: 82/1451 (5.7%) Treated with LMWHs: 132/1456 (9.1%) RR 0.62; 95% CI 0.44–0.87; p=0.006; I^2=25% **Recurrent DVT** Treated with DOACs: 41/1451 (2.8%) Treated with LMWHs: 70/1456 (4.8%) RR 0.61; 95% CI 0.40–0.94; p=0.02; I^2=12% **Recurrent PE** Treated with DOACs: 50/1451 (3.4%) Treated with LMWHs: 70/1456 (4.8%) RR 0.73; 95% CI 0.51–1.04; p=0.08; I^2=0% **Major bleeding** Treated with DOACs: 69/1451 (4.76%) Treated with LMWHs: 52/1456 (3.57%) RR 1.33; 95% CI 0.84-2.10; p=0.22; I^2= 26% *Subgroup of major bleeding per cancer type* Gastro-intestinal cancers Treated with DOACs: 30/256 (11.7%)	Among cancer patients with VTE, treatment with DOACs is associated with a significant reduction of VTE and DVT recurrence, compared to LMWH. These benefits were offset by an increased risk of CRNMB, and major bleeding in gastrointestinal cancer

						Treated with LMWHs: 10/226 (4.4%) RR 2.55; 95% CI 1.24-5.27; p=0.01; I^2= 5% Genitourinary cancers Treated with DOACs: 4/90 (4.4%) Treated with LMWHs: 1/88 (1.14%) RR 2.81; 95% CI 0.45-17.40; p=0.27; I^2= 0% Other cancers Treated with DOACs: 10/388 (2.58%) Treated with LMWHs: 14/435 (3.22%) RR 0.80; 95% CI 0.36-1.77; p=0.58; I^2= 0% **CRNMB** Treated with DOACs: 162/1451 (11.2%) Treated with LMWHs: 107/1456 (7.3%) RR 1.58; 95% CI 1.11-2.24; p=0.01; I^2= 41% **All-cause mortality** Treated with DOACs: 412/1451 (28.4%) Treated with LMWHs: 416/1456 (28.57%) RR 0.99; 95% CI 0.84–1.17; p= 0.92; I^2 = 40% **VTE-related death** Treated with DOACs: 5/1451 (3.45%) Treated with LMWHs: 5/1453 (3.44%) RR 1.00; 95% CI 0.29–3.44; p= 1; I^2=0% **Bleeding-related death** Treated with DOACs: 3/1451(2%)	

						Treated with LMWHs: 5/1456 (3.4%) RR 0.71; 95% CI: 0.17–2.91; p=0.63; I^2 =0%	
[Dong 2021]	Literature search using PubMed, EMBASE, Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov was performed from inception to May 1, 2020	8 studies, 5856 patients [Young 2018] [Prins 2014] [Raskob 2016] [Raskob 2018] [Agnelli 2015] [Mc Bane 2020] [Schulman 2015] [Agnelli 2020]	Recurrent VTE	Major Bleeding CRNMB	RR determined using Mantel-Haenszel method (fixed effects model). I^2 statistic to assess heterogeneity between studies. Funnel plots to assess publication bias.	**Recurrent VTE** **DOACs vs. LMWHs in active cancer:** RR 0.62; 95% CI 0.48-0.81; p=0.0005; I^2= 26% **DOACs vs. VKAs in active cancer:** RR 0.61; 95% CI 0.39-0.96; p=0.03; I^2= 0% **DOACs vs VKAs in history of cancer:** RR 0.49; 95% CI 0.29-0.82; p=0.006; I^2= 35% **Major bleeding** **DOACs vs. LMWHs in active cancer:** RR 1.33; 95% CI 0.94-1.89; p=0.11; I^2= 27% **DOACs vs. VKAs in active cancer:** RR 0.64; 95% CI 0.36-1.12; p=0.12; I^2= 0% **DOACs vs VKAs in history of cancer:** RR 0.56; 95% CI 0.28-1.12; p=0.10; I^2= 8% **CRNMB** **DOACs vs. LMWHs in active cancer:** RR 1.45; 95% CI 1.05-1.99; p=0.02; I^2= 50% **DOACs vs. VKAs in active cancer:** RR 0.91; 95% CI 0.66-1.26; p=0.58; I^2= 33% **DOACs vs VKAs in history of cancer:** RR 0.69; 95% CI 0.41-1.15; p=0.16; I^2= 68%	DOACs have better efficacy to prevent recurrent VTE compared with conventional therapy. Regarding the safety profile, DOACs may carry higher risk of bleeding compared with LMWH but lower risk of bleeding compared with VKAs. Further studies are needed to inform the optimal anticoagulation approach for different types of cancers.

[Elbadawi 2020]	Literature search using MEDLINE, SCOPUS and COCHRANE through April 2020	4 studies, 2907 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	Recurrent DVT Recurrent PE CRNMB All-cause mortality	RR determined using random-effects models by using inverse variance methods Risk of bias and strength of evidence assessed by the Cochrane Collaboration's tool. I^2 statistic to assess heterogeneity between studies.	**Recurrent VTE** Treated with DOACs: 82/1446 (5.7%) Treated with LMWHs: 132/1448 (9.1%) RR 0.62; 95% CI 0.44–0.87; p=0.007; I^2=26% ***Subgroup analysis for recurrent VTE*** Treated with apixaban: 33/721 (4.6%) Treated with LMWHs: 55/721 (7.6%) RR 0.36; 95% CI 0.06-2.13; p=0.26; I^2=68% Treated with non-apixaban DOACs: 49/725 (6.8%) Treated with LMWHs: 77/727 (10.6%) RR 0.64; 95% CI 0.46–0.91; p=0.01; I^2=0% Test for subgroup differences: p=0.53; I^2=0% **Recurrent DVT** Treated with DOACs: 37/1446 (2.6%) Treated with LMWHs: 65/1448 (4.5%) RR 0.60; 95% CI 0.39–0.93; p=0.02; I^2=6% **Recurrent PE** Treated with DOACs: 50/1446 (3.4%) Treated with LMWHs: 70/1448 (4.8%) RR 0.73; 95% CI 0.51–1.04; p=0.46; I^2=0% **Major bleeding** Treated with DOACs: 69/1446 (4.8%)	Among patients with cancer-related VTE, DOACs were associated with lower risk of VTE recurrence and similar risk of major bleeding compared with LMWH. Future studies examining the subset of cancer patients who drive the most benefit are encouraged.

						Treated with LMWHs: 52/1448 (3.6%) RR 1.33; 95% CI 0.84-2.11; p=0.23; I^2= 27% **Subgroup analysis for Major bleeding** Treated with apixaban: 22/721 (3.0%) Treated with LMWHs: 25/721 (3.5%) RR 0.89; 95% CI 0.45-1.75; p=0.73; I^2=3% Treated with non-apixaban DOACs: 47/725 (6.5%) Treated with LMWHs: 27/727 (3.7%) RR 1.75; 95% CI 1.10–2.77; p=0.02; I^2=0% Test for subgroup differences: p=0.11, I^2=61.5% **CRNMB** Treated with DOACs: 162/1446 (11.2%) Treated with LMWHs: 107/1448 (7.4%) RR 1.58; 95% CI 1.11-2.24; p=0.01; I^2= 42% **All-cause mortality** Treated with DOACs: 412/1446 (28.5%) Treated with LMWHs: 416/1448 (28.7%) RR 0.99; 95% CI 0.84-1.16; p=0.91; I^2= 38%	
[Camilli 2020]	Literature search using Medline, Scholar, ClinicalTrials.gov from inception to March 29, 2020	4 studies, 2894 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	CRNMB GI MB Recurrent PE All cause death Recurrent VTE + MB	Quality of randomized studies was assessed by the Risk of Bias Assessment Tool. Frequentist random-effect meta-analysis with Inverse-variance method was used to estimate the incidence rate.	**Recurrent VTE** DOACs vs. LMWHs: IRR 0.62; 95% CI 0.47–0.82; p<0.01; I^2= 0% **Major bleeding** DOACs vs. LMWHs:	In patients with cancer related VTE, NOACs are effective and safe in reducing VTE recurrence compared to LMWH. An increased risk of CNRMB and GI MB should nonetheless be considered

					ratio (IRR) of primary and secondary outcomes with 95 % confidence intervals (95 % CI). I^2 statistic to assess heterogeneity between studies.	IRR 1.33; 95% CI 0.93-1.90; p=0.12; I^2= 0% **CRNMB** DOACs vs. LMWHs: IRR 1.55; 95% CI 1.03-2.32; p<0.01 (fixed effects) or 0.03 (random effects); I^2= 12% **GI MB** DOACs vs. LMWHs: IRR 1.86; 95% CI 1.08-3.20; p=0.03; I^2= 0% **Recurrent PE** DOACs vs. LMWHs: IRR 0.72; 95% CI 0.50-1.03; p=0.07; I^2= 0% **All-cause death** DOACs vs. LMWHs: IRR 0.99; 95% CI 0.87-1.14; p=0.92; I^2= 0% **Recurrent PE + MB** DOACs vs. LMWHs: IRR 0.82; 95% CI 0.66-1.02; p=0.08; I^2= 0%	
[Mudler 2020]	Literature search using Medline (PubMed), Embase, CENTRAL, and conference proceedings until March 29, 2020	3 studies, 2894 patients [Raskob 2018] [Young 2018] [Mac Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding	Composite outcome of first recurrent VTE and major bleeding Clinically relevant non-major bleeding All-cause mortality	Logit transformation and inverse variance weighting to calculate summary estimates using a Knapp-Hartung random-effects model. Between-study heterogeneity was assessed by calculating tau-squared (τ^2) and I-squared (I^2) using restricted maximum likelihood estimations Funnel plots were used to assess for publication bias.	**Recurrent VTE** Treated with DOACs: 5.6% Treated with LMWHs: 8.3% RR 0.68; 95% CI 0.39-1.17 Absolute risk difference with DOACs -2.7%; 95% CI -5.1-1.4% **Major bleeding** Treated with DOACs: 4.8% Treated with LMWHs: 3.5% RR 1.36; 95% CI 0.55 -3.35 Absolute risk difference with DOACs 1.3%; 95% CI -1.6-8.3% **Composite outcome of first recurrent VTE and major bleeding**	DOACs are an effective treatment option for cancer patients with acute VTE, although caution is needed in patients at high risk of bleeding.

						Treated with DOACs: 9.5% Treated with LMWHs: 11.1% RR 0.86; 95% CI 0.60 -1.23 Absolute risk difference with DOACs -1.6%;95% CI -4.4-2.6% **Clinically relevant non-major bleeding** Treated with DOACs: 10.6% Treated with LMWHs: 6.5% RR 1.74, 95% CI 0.64-4.77 Absolute risk difference with DOACs 4.1%; 95% CI -1.8-17.2% **All-cause mortality** Treated with DOACs: 24.7% Treated with LMWHs: 25.7% RR 0.96; 95% CI 0.68-1.36 Absolute risk difference with DOACs -1.0%; 95% CI -8.2-9.3%	
[Sabatino 2020]	Literature search using PubMed, SCOPUS, and Google Scholar electronic databases from September 1, 2007 through March 31, 2020	4 studies, 2907 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding CRNMB	Recurrent PE GI bleeding All-cause death	Quality of randomized studies was assessed by the Risk of Bias Assessment Tool. RR determined using Mantel-Haenszel method (fixed-effect model). I^2 statistic to assess heterogeneity between studies. Funnel plots to assess publication bias.	**Recurrent VTE** Treated with dalteparin: 132/1456 Treated with DOACs: 82/1451 RR 1.55; 95% CI 1.19-2.03; p=0.001; I^2= 24% **Recurrent PE** Treated with dalteparin: 70/1456 Treated with DOACs: 50/1451 RR 1.38; 95% CI 0.96-1.97; p=0.08; I^2= 0% **All-cause death** Treated with dalteparin: 408/1456 Treated with DOACs: 412/1451 RR 0.95; 95% CI 0.73-1.24; p=0.714; I^2= 73% **Major bleeding** Treated with dalteparin: 52/1456 Treated with DOACs: 69/1451 RR 0.74; 95% CI 0.52-1.06; p=0.110; I^2= 26%	DOACs were noninferior to dalteparin in preventing VTE recurrence in patients with cancer without a significantly increased risk of major bleeding. However, DOACs were associated with higher rates of CRNMB compared with dalteparin, primarily in patients with gastrointestinal malignancies.

						GI bleeding Treated with dalteparin: 20/1306 Treated with DOACs: 39/1301 RR 0.53; 95% CI 0.31-0.92; p=0.02; I^2= 35% **CRNMB** Treated with dalteparin: 107/1453 Treated with DOACs: 161/1451 RR 0.68; 95% CI 0.54-0.86; p=0.001; I^2= 43%	
[Desai 2020]	Literature search using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) data bases from June 1, 2014-April 31, 2020.	10 studies, 4193 patients [Agnelli 2015] [Bauersachs 2010] [Buller 2012] [Schulman 2009] [Schulman 2014] [Buller 2013] [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Incidence of recurrent VTE	Major bleeding (MB) Clinically relevant non-major bleeding (CRNMB) All bleeding events (composite MB and CRNMB)	Cochrane Collaboration's risk of bias tool to assess risk for bias. RR determined using Mantel-Haenszel method (random-effect model). I^2 statistic to assess heterogeneity between studies. GRADE approach was applied to assess quality of evidence for each outcome.	**Recurrent VTE** **DOACs vs. LMWHs:** Treated with DOACs: 86/1446 Treated with LMWHs: 143/1448 RR 0.57; 95% CI 0.40-0.83; p=0.003; I^2= 40% **DOACs vs. VKAs:** Treated with DOACs: 33/679 Treated with VKAs: 44/620 RR 0.69; 95% CI 0.44-1.06; p=0.09; I^2= 0% **Major bleeding** **DOACs vs. LMWHs:** Treated with DOACs: 69/1446 Treated with LMWHs: 53/1448 RR 1.31; 95% CI 0.78-2.18; p=0.31; I^2= 38% **DOACs vs. VKAs:** Treated with DOACs: 17/562 Treated with VKAs: 25/510 RR 0.62; 95% CI 0.34-1.14; p=0.12; I^2= 0% **CRNMB** **DOACs vs. LMWHs:** Treated with DOACs: 162/1446 Treated with LMWHs: 106/1448 RR 1.60; 95% CI 1.13-2.26; p=0.008; I^2= 40% **DOACs vs. VKAs:** Treated with DOACs: 73/562	DOACs are more effective than LMWH for prevention of recurrent VTE with CAT though carry an increased risk for non-major bleeding compared to standard of care, LMWH.

						Treated with VKAs: 68/510 RR 0.95; 95% CI 0.63-1.41; p=0.79; I^2= 36% **All bleeding** **DOACs vs. LMWHs:** Treated with DOACs: 231/1446 Treated with LMWHs: 159/1448 RR 1.49; 95% CI 1.10-2.01; p=0.010; I^2= 48% **DOACs vs. VKAs:** Treated with DOACs: 110/671 Treated with VKAs: 118/609 RR 0.84; 95% CI 0.65-1.08; p=0.18; I^2= 12%	
[Yan 2020]	Literature search using MEDLINE, EMBASE, CENTRAL from inception to May 15, 2020	4 studies, 2894 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020]	Recurrent VTE Major Bleeding CRNMB		RR determined using Mantel-Haenszel method (random-effect model). Quality of the included RCTs evaluated using the Cochrane Collaboration Risk of Bias Tool I^2 statistic to assess heterogeneity between studies. Surface under the cumulative ranking curves (SUCRA) values to rank treatments with respect to different outcomes.	**Recurrent VTE** Treated with DOACs: 82/1446 (5.67%) Treated with LMWHs: 132/1448 (9.12%) RR 0.62; 95% CI 0.44–0.87 I^2=24.9% Edoxaban vs. dalteparin RR 0.70; 95% CI 0.08-5.94 Rivaroxaban vs. dalteparin RR 0.44; 95% CI 0.05-4.25 Apixaban vs. dalteparin RR 0.37; 95% CI 0.05-2.46 Edoxaban vs. rivaroxaban RR 1.57; 95% CI 0.07-35.30 Edoxaban vs. apixaban RR 1.91; 95% CI 0.11-33.55 Rivaroxaban vs. apixaban RR 1.22; 95% CI 0.06-23.34 **Major bleeding** Treated with DOACs: 69/1446 (4.77%) Treated with LMWHs: 52/1448 (3.59%) RR 1.33; 95% CI 0.84–2.11; I^2=27% Edoxaban vs. dalteparin RR 1.72; 95% CI 0.92-3.21 Rivaroxaban vs. dalteparin RR 1.83; 95% CI 0.65-5.15	DOACs are a safe and effective alternative therapy to dalteparin in patients with CAT. Among them, edoxaban might provide a good risk-to-benefit balance. However, because of the lack of head-to-head studies, further investigations are needed to confirm our findings.

						Apixaban vs. dalteparin RR 0.89; 95% CI 0.11-7.35 Edoxaban vs. rivaroxaban RR 0.94; 95% CI 0.28-3.14 Edoxaban vs. apixaban RR 1.92; 95% CI 0.21-17.31 Rivaroxaban vs. apixaban RR 2.05; 95% CI 0.20-21.40 **CRNMB** Treated with DOACs: 212/1446 (14.66%) Treated with LMWHs: 151/1448 (10.43%) RR 1.45; 95% CI 1.05–1.99; I^2=50.3% Edoxaban vs. dalteparin RR 1.33; 95% CI 1.01-1.76 Rivaroxaban vs. dalteparin RR 2.77; 95% CI 1.51-5.06 Apixaban vs. dalteparin RR 1.22; 95% CI 0.89-1.66 Edoxaban vs. rivaroxaban RR 0.48; 95% CI 0.25-0.94 Edoxaban vs. apixaban RR 1.09; 95% CI 0.72-1.66 Rivaroxaban vs. apixaban RR 1 2.27; 95% CI 1.15- 4.48	
[Frere 2021]	Literature search using MEDLINE, EMBASE, CENTRAL from inception to August 2, 2021	6 studies, 3690 patients [Raskob 2018] [Young 2018] [Mc Bane 2020] [Agnelli 2020] [Planquette2021] [Schrag 2021]	Recurrent VTE Major Bleeding	CRNMB Overall mortality	RR determined using Mantel-Haenszel method (random-effect model). Quality of the included RCTs evaluated using the Cochrane Collaboration Risk of Bias Tool I^2 statistic to assess heterogeneity between studies.	**Recurrent VTE** Treated with DOACs: 99/1850 (5.3%) Treated with LMWHs: 152/1840 (8.3%) RR 0.67; 95% CI 0.52–0.85 **Major bleeding** Treated with DOACs: 80/1850 (4.3%) Treated with LMWHs: 68/1840 (3.7%) RR 1.17; 95% CI 0.82–1.67 **CRNMB** Treated with DOACs: 177/1850 (9.6%) Treated with LMWHs: 105/1840 (5.7%) RR 1.66; 95% CI 1.31–2.09	In this 2021 meta-analysis of 3,960 patients treated for CAT, DOAC significantly reduced the risk of recurrent VTE compared with LMWH, without increasing the risk of major bleeding. However, as previously highlighted, the use of DOAC was associated with an increased risk of CRNMB. Our results provide additional evidence for the use of DOAC as a safe and effective first-line option for the treatment of CAT in patients who are not at high risk of bleeding.

						Overall mortality Treated with DOACs: 436/1850 (23.6%) Treated with LMWHs: 428/1840 (23.3%) RR 1.02; 95% CI 1.02–1.16	

Table 7: Early maintenance and long-term treatment of established VTE – prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Wysokinski 2019]	750 patients	3 months	Consecutive cancer patients managed at the Thrombophilia Clinic, Gonda Vascular Center, Mayo Clinic Rochester between March 1, 2013 and January 30, 2018 with the diagnosis of acute Cancer-associated thrombosis receiving either rivaroxaban, apixaban, or LMWH within the first 14 days after diagnosis, and completed at least 3 months of anticoagulant therapy.	**Group A:** apixaban **Group B:** rivaroxaban **Group C:** enoxaparin	**Rate of recurrent VTE at 6 months** Group A: 10/224 Group B: 5/163 Group C: 12/363 p (group A vs group B) = 0.28 p (group A vs group C) = 0.32 p (group B vs group C) = 0.76	**Rate of major bleeding at 6 months** Group A: 9/224 Group B: 9/163 Group C: 18/363 p (group A vs group B) = 0.79 p (group A vs group C) = 0.80 p (group B vs group C) = 0.96 **Rate of CRNM bleeding at 6 months** Group A: 1/224 Group B: 12/163 Group C: 6/363 p (group A vs group B) <0.001 p (group A vs group C) = 0.23 p (group B vs group C) = 0.002	**Rate of death VTE at 6 months** Group A: 41/224 Group B: 20/163 Group C: 78/363 p (group A vs group B) =0.01 p (group A vs group C) =0.75 p (group B vs group C) =0.003
[Mahé 2020] Retrospective non-interventional multicenter cohort study	348/422	From 6 to 12 months following an index VTE	Adult patients with cancer and objectively diagnosed acute VTE previously included in both prospective observational cohort studies, aXa and PREDICARE, and who were still alive at the end of the initial 6-month treatment period with tinzaparin, and	Continuation of anticoagulation beyond 6 months	**Cumulative incidence of recurrent VTE at 12months following the index VTE** 8.0% (95% CI 4.2-15.1%) PE alone in 12 patients, PE and DVT in 2 patients and DVT alone in 10 patients	**Cumulative incidence of major bleeding at 12 months following the index VTE** 2.6% (95% CI 1.3-5.1%) **Cumulative incidence of clinically relevant bleeding at 12 months following the index VTE** 4.9% (95% CI 3.2-7.4%)	**Cumulative probability of death between the 6th and 12th months following the index VTE** 30.7% (95% CI:22.8-38.6%)

			having given their consent for the use of their data				

Table 8: Early maintenance and long-term treatment of established VTE – Systematic reviews with or without Meta-analysis

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[Moik 2021]	Literature search using MEDLINE, EMBASE, CENTRAL from inception to August 2, 2021	11 studies, 3019 patients [Marshall 2019] [Di Nisio 2019] [Napolitan 2014] [Jara-Palomares 2017] [Francis 2015] [Poudel 2019) [Prandoni 2002] [Mahé 2020] [Schmidt 2020] [Yim 2013] [Sakamoto 2019]	Recurrent VTE Major bleeding	CRNMB All cause mortality	Individual risk of recurrent VTE and MB presented in Forrest plots computing individual 95% CI by the score method. I^2 statistic to assess heterogeneity between studies.	**Rates of recurrent VTE between 6-12 months after index VTE** 1.1% to 12.0% I^2= 88% **Rates of MB between 6-12 months after index VTE** 1.7% to 4.8% I^2= 30%	VTE recurrence remains common beyond 6 months and continuation of different anticoagulation strategies has an acceptable safety profile indicated by lower bleeding rates. These findings support guideline recommendations to continue anticoagulation treatment beyond 6 months in patients with active cancer

Table 9: Prophylaxis of VTE in surgical cancer patients- RCT

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Hata 2019] multicenter, open-label, phase III randomized controlled trial	302/303 patients	16 days post surgery	Patients ≥ 20 years undergoing laparoscopic colorectal surgery who had an additional risk factor for VTE (thrombotic disorder, history of VTE, malignant disease, cancer chemotherapy, serious infection, central venous catheterization, long term bed rest (more than 24 hours after surgery), leg paralysis, leg cast fixation, hormone therapy, obesity (BMI ≥25 kg/m2) and varicose veins of the lower extremities	**Arm A:** IPC alone **Arm B:** IPC + fondaparinux (2.5 mg) given once daily for 4-8 days, or enoxaparin (2000 IU) given twice daily for 7-14 days.	**VTE** Arm A: 8/157 (5.1%) Arm B: 4/145 (2.76%) p=0.382 **PE** Arm A: 3/157 Arm B: 1/145 **DVT** Arm A: 5/157 Arm B: 13/145	**Major bleeding** Arm A: 2/157 (2.27%) Arm B: 2/145 (1.38%) p=0.936 **Minor bleeding** Arm A: 3/157 (1.91%) Arm B: 17/145 (11.7%) p=0.001	-
[Tanaka 2019]	72/72patients	15 days post surgery	Patients >18 years who had histologically or cytologically confirmed Stage IB-IV esophageal squamous cell carcinoma and Eastern Cooperative Oncology Group performance status of 0-1; life expectancy of >12 weeks; and adequate liver, bone marrow, renal, and cardiovascular functions (serum bilirubin ≤1.5 mg/dl; neutrophil count ≥1,500/mm^3; serum aspartate aminotransferase and alanine aminotransferase levels ≤ twice the upper limit of normal range; platelet count ≥10×104/mm^3; hemoglobin ≥8.0 g/dl; creatinine ≤1.2 mg/dl [or creatinine clearance ≥30 ml/min] and platelet count >10×104 /l).	**Arm A:** IPC alone **Arm B:** IPC until first ambulation then enoxaparin (2000 IU) given twice daily for 14 days.	**VTE** Arm A: 7/31 (22.6%) Arm B: 0/41 (0%) p=0.02	**Minor bleeding** Arm A: unspecified Arm B: 1/42	-
[Nagawaka 2020]	116/121	28 days	Patients ≥ 20 years of age undergoing curative laparoscopic surgery for colorectal cancer without signs of metastasis on preoperative diagnostic imaging and without DVT on screening lower extremity venous ultrasonography within 28 days before registration	**Arm A**: IPC + enoxaparin 20 mg, twice daily until discharge **Arm B**: IPC alone *IPC treatment started in the operating room and continued until the morning after surgery in both groups*	**Arm A:** 7/57 (12.3%) **Arm B:** 7/59 (11.9% p=1.00 (*All events were asymptomatic DVT*)	**Major bleeding** **Arm A:** 0/57 (0%) **Arm B:** 0/59 (0%) **Minor bleeding** **Arm A:** 1/57 (1.8%) **Arm B:** 0/59 (0%)	-

[Guntupalli 2020] multicenter, open-label, blinded, end point, randomized clinical trial	400/400	90 days	Patients with suspected or confirmed diagnosis of gynecologic cancer undergoing surgery, either by laparotomy or laparoscopy	**Arm A**: Apixaban 2.5 mg twice daily **Arm B**: enoxaparin 40 mg sc once daily	**Arm A:** 2/204 (1%) **Arm B:** 3/196 (1.5%) OR 1.57; 95% CI 0.26-9.50	**Major bleeding** **Arm A:** 1/204 (0.5%) **Arm B:** 1/196 (0.5%) OR 1.04; 95% CI 0.07-16.76 **CRNMB** **Arm A:** 12/204 (5.4%) **Arm B:** 19/196 (9.7%) OR 1.88; 95% CI 0.87-4.1 **Change in QOL (SF-8 score)** Physical **Arm A:** −5.9(−35.4 to 30.5) **Arm B:** −6.2(−36.1 to 28.7) p=0.75 Mental **Arm A:** 0.8(−30.3 to 30.8) **Arm B:** 0.0(−30.7 to 41.1) p=0.52 **Adherence** **Arm A:** 173 days (84.8) **Arm B:** 164 days (83.7) P=0.76	-
[Obitsu 2020] Multicenter, prospective randomized controlled trial from February 2013 to January 2017	347/400	7 days	Patients aged 40 years old or older, with good performance status scheduled for laparoscopic surgery for gastric and colorectal cancer	**Arm A**: IPC alone **Arm B**: IPC + enoxaparin 20 mg, twice daily until day 7	**Overall VTE** Arm A: 7/176 (4.0%) Arm B: 2/171 (1.2%) OR 0.3; 95% CI 0.03-1.53 **PE** Arm A: 3/176 (1.7%) Arm B: 0/171 (0%) OR 0.0; 95% CI 0.00-1.76 **DVT** Arm A: 6/176 (3.4%) Arm B: 2/171 (1.2%) OR 0.3;95% CI 0.03-1.91 **Proximal DVT** Arm A: 2/176 (1.1%) Arm B: 0/171 (0%) **Distal DVT** Arm A: 5/176 (2.8%)	**Major bleeding** Arm A: 0/200 (0%) Arm B: 0/195 (0%) **Minor bleeding** Arm A: 2/200 (1%) Arm B: 11/195 (5.6%) OR 5.6; 95% CI 1.27-25.1	-

					Arm B: 2/171 (1.2%)		
[Patel 2020] Prospective, phase 4, single-center, RCT (July 2017–November 2018).	500/501	30 days	Male patients aged 18 years or older, with a histologically confirmed diagnosis of clinically localized prostate cancer of any stage or grade scheduled to undergo radical prostatectomy by an open or robotic-assisted laparoscopic approach.	**Arm A**: IPC alone **Arm B**: IPC + UFH (5000 IU) given within 2 h prior to surgery and every 8 h after surgery until discharge from the hospital	**Symptomatic VTE** Arm A: 2.0% (95% CI 0.7–4.6) Arm B: 0.8% (95% CI 0.1–2.9) p=0.3 **Overall VTE** Arm A: 2.9% (95% CI 0.1–7.3) Arm B: 2.8% (95% CI 0.1–7.1) p=1.0	**Symptomatic lymphocele** Arm A: 2.4% (95% CI 0.9–5.2) Arm B: 3.2% (95% CI 1.4–6.2) p=0.8 **Symptomatic hematoma** Arm A: 1.2% (95% CI 0.3–3.5) Arm B: 1.6% (95% CI 0.4–4.0) p=1.0 **Bleeding** Arm A: 0.8% (95% CI 0.1–2.9) Arm B: 1.6% (95% CI 0.4–4.0) p=0.7	-

Table 10: Prophylaxis of VTE in surgical cancer patients- Systematic reviews with or without meta-analysis

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[Bisch 2021]	Literature search using PubMed, EMBASE, and The Cochrane Central Register of Clinical Trials	12 studies (14 273 patients) [Ailawadi 2001] [Bouchard-Fortier 2014] [Clarke-Pearson 1983] [Corr 2015] [Einstein 2008] [Freeman 2016] [Hansen 2008] [Hopp 2018] [Maxwell 2001] [Pelkofski 2014] [Ugaki 2008] [Whitworth 2011]	Rates of VTE	Rates of peri-operative bleeding complications (peri-operative blood transfusion, intra-operative blood loss greater than 1000 milliliters, post-operative vaginal vault bleed, post-operative pelvic hematoma)	Study quality evaluated using the the Newcastle–Ottawa Scale and the Agency for Healthcare Research and Quality Tool. Odds ratio (OR) and 95% CI estimated using random effects models. Heterogeneity among included articles assessed by the Q-	**Rates of VTE** Intervention group: 67/6736 Control group: 125 /7537 OR 0.59; 95 % CI 0.39-0.89 **Rates of peri-operative bleeding complications** Intervention vs. control group: OR 1.26; 95% CI 0.98-1.62	Pre-operative pharmacologic thromboprophylaxis decreases the odds of VTE in the peri-operative period for major gynecologic oncology surgery by approximately 40%. It remains unclear whether this benefit is present in benign and minor procedures.

					statistic and the I^2 statistic. Publication bias assessed by funnel plot.		Adequately powered studies are needed.
[Insin 2021]	Literature search using MEDLINE and Scopus databases through November 25, 2020	20 RCT (4970 patients) in gynecological cancer patients [Clarke-Pearson 1983] [Clarke-Pearson 1984] [Clarke-Pearson 1984B] [Turner 1984] [Fricker 1988] [Samama 1988] [Clarke-Pearson 1990] [Dindelli 1990] [Ferrari 1990] [Fontanelli 1992] [Clarke-Pearson 1993] [Urlep-Sallinovic 1993] [Von Tempelhoff 1997] [Ward 1998] [Di Carlo 1999] [Baykal 2001] [Maxwell 2001] [Bergqvist 2002] [Zheng 2014] [Nagata 2015]	VTE (DVT or PE) Major bleeding		Risk ratios (RR) and 95% CI estimated using the fixed-effects or random-effects models. Heterogeneity among included articles assessed by the Q-statistic and the I^2 statistic. Network map was constructed to display head-to-head comparisons in all included RCTs. Kappa statistics to estimate disagreements in study selections and data extractions between reviewers.	**Rate of VTE** LMWH vs. UFH RR 1.16; 95% CI 0.85-1.56; I^2 = 0% Antithrombin vs. UFH RR 0.69; 95% CI 0.48-0.99; I^2 = 0% **Rate of Major bleeding** LMWH vs. UFH RR 0.62; 95% CI 0.32-1.23; I^2 = 16.78% Antithrombin vs. UFH RR 0.88; 95% CI 0.56-1.38; I^2 = 6.21%	Sequential compression devices and LMWH represented the preferred strategy in terms of efficacy and safety. However, not one prophylactic strategy could be considered superior in all aspects.
[Knoll 2021]	Literature search using MEDLINE, EMBASE and CENTRAL databases through September 10, 2020	18 studies (7495 patients) included in the quantitative analysis [Rasmussen 2006] [Vedovati 2014] [Bergqvist 2002] [Kakkar 2021] [Kukreja 2015] [Kim 2017A] [Schmeler 2013] [Wang 2016] [Carbajal-Mamani 2020] [Chen 2016] [Ibrahim 2014] [Bateni 2020] [Melancon 2016]	Clinical VTE reported within the 30-day postoperative period Clinically-relevant bleeding complications and clinically-relevant non-major bleeding)		Study quality evaluated utilizing the Cochrane Collaboration Risk of Bias Tool for randomized controlled trials (RCT) and the Newcastle-Ottawa Scale for observational studies Risk ratios (RR) and 95% CI estimated using the random effects model of	**Clinical VTE reported within the 30-day postoperative period** Extended duration thromboprophylaxis group: 26-2597 (1.0%) Control group: 105/4898 (2.1%) RR 0.48; 95% CI 0.31-0.74; I^2=0 Clinically-relevant bleeding Extended duration thromboprophylaxis group: 45/1119 (4.0%)	The overall risk of symptomatic VTE within 30 days of surgery was relatively low. Extended LMWH thromboprophylaxis following major abdominopelvic cancer surgery was associated with a reduced incidence of clinical VTE without an increase in clinically-relevant bleeding.

		[Balavage 2018] [Freeman 2016] [Marques de Marino 2018] [Oo 2020] [Kim 2017B]			DerSimonian and Laird Heterogeneity among included articles assessed by the I^2 statistic. Publication bias assessed by funnel plot.	Control group: 97/1994 (4.9%) RR 1.0; 95% CI 0.66-1.5; I^2=0	

Table 11. Prophylaxis of VTE in medical cancer patients - Randomized Controlled Trials

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Zwicker 2020] randomized, double-blinded, phase 2 trial	47/50	14 days Scheduled ultrasound examination performed between days 17 to 25 in arm A	Hospitalized patients with active cancer (solid tumor, myeloma, lymphoma) at high risk of developing VTE based on Padua risk score	**Arm A:** fixed-dose enoxaparin (40 mg daily) during hospitalization and up to 14 days **Arm B:** weight-adjusted enoxaparin (1 mg/kg daily) during hospitalization and up to 14 days	**Symptomatic VTE during blinded assessment period (14 days)** Arm A: 0/23 (0%) Arm B: 0/24 (0%) 1 incidentally identified filling defect within segmental branch of left pulmonary artery (asymptomatic) in arm B **Symptomatic VTE at the end of the study** Arm A: 0/23 (0%) Arm B: 0/24 (0%) **Asymptomatic VTE at the end of the study (17 days)** Arm A: 2/23 (8.7%) Arm B: not assessed	**Major bleeding** Arm A: 0/23 (0%) Arm B: 0/24 (0%) **CRNM** Arm A: 1/23 (4.3%) Arm B: 0/24 (0%)	-

Table 12: Prophylaxis of VTE in medical cancer patients – Systematic reviews with or without Meta-analyses

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[Li 2019]	Literature search using EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from all languages up to February 2019; hand-searched American Society of Hematology, American Society of Medical Oncology, and International Society on Thrombosis and Haemostasis annual meeting abstracts; reviewed clinicaltrials.gov for unpublished studies. This systematic review was registered on PROSPERO (CRD42019123612).	2 RCTs (AVERT and CASSINI), 1415 ambulatory cancer patients. [Carrier 2019] [Khorana 2019]	Incidence rates of VTE	Incidence rates of Bleeding	Risk ratio (RR), absolute risk, difference (ARD), and 95% CI estimated using the Mantel-Haenszel random effects model (DerSimonian-Laird analysis). Heterogeneity among included articles assessed by visual inspection and by the I^2 statistic.	**Overall VTE (ITT 6-months study period)** DOAC group: 37/711 (5.20%) Control group : 65/704 (9.23%) RR 0.56; 95% CI 0.35-0.89; I^2=26% Sub-group of patients with Khorana score≥ 3 DOAC group: 13/239 (5.44%) Control group : 25/216 (11.57%) RR 0.47; 95% CI 0.25-0.89 **Symptomatic VTE (ITT 6-months study period)** DOAC group: 24/711 (3.38%) Control group : 41/704 (5.82%) RR 0.58; 95% CI 0.29-1.13; I^2=44% **Major bleeding (modified ITT on-treat study period)** DOAC group: 14/693 (2.02%) Control group : 7/679 (1.03%) RR 1.96; 95% CI 0.80- 4.82; I^2=0% Sub-group of patients with Khorana score≥ 3 DOAC group: 6/233 (2.58%) Control group : 3/211 (1.42%) RR 1.60; 95% CI 0.42-6.01 **CRNMB (modified ITT on-treat study period)** DOAC group: 29/693 (4.18%) Control group : 22/679 (3.24%) RR 1.28; 95% CI 0.74-2.20; I^2=0%	Low-dose DOAC prophylaxis reduces the rate of overall VTE in high-risk cancer patients starting systemic chemotherapy but may increase the likelihood of bleeding. A Khorana score risk-stratified strategy should be considered for decisions regarding thromboprophylaxis to ensure the largest absolute risk reduction in the highest risk patient population.

[Barbarawi 2019]	Literature search using Pubmed/MEDLINE, Cochrane Library, and Embase up to December 2018. This systematic review was registered on PROSPERO (CRD42019120799).	24 RCTs, 13,338 patients (7197 received anticoagulation and 6141 received placebo) [Lebeau 1994] [Levine 1994] [Altinbas 2004] [Kakkar 2004] [Klerk 2005] [Sideras 2006] [Agnelli 2009] [Perry 2010] [Palumbo 2011] [vanDoormaal 2011] [Elit 2012] [Larocca 2012] [Levine 2012] [Maraveyas 2012] [Agnelli 2012] [Haas 2012] [Vadhan-Raj 2013] [Lecumberri 2013] [Zwicker 2013] [Pelzer2015] [McBeth 2015] [Khorana 2017] [Carrier 2019] [Khorana 2019]	Incidence rates of VTE	Incidence rates of Bleeding	Risk ratio (RR) and 95% CI estimated using the Mantel-Haenszel random effects model. Heterogeneity among included articles assessed by the I^2 statistic.	**LMWH vs placebo** **VTE** LMWH group: 180/5100 (3.5%) Control group : 314/5109 (6.1%) RR 0.58; 95% CI 0.48-0.69; I^2=0% **DVT** LMWH group: 89/4849 (1.8%) Control group : 156/4381 (3.5%) RR 0.54; 95% CI 0.41-0.70; I^2=2% **PE** LMWH group: 77/4651(1.7%) Control group : 131/4177 (3.1%) RR 0.57; 95% CI 0.43-0.75; I^2=0% **VTE-related mortality** LMWH group: 10/3630 (0.2%) Control group : 19/3239 (0.5%) RR 0.62; 95% CI 0.28-1.34; I^2=0% **All-cause mortality** LMWH group: 2029/4813 (42.6%) Control group : 1924/4359 (44.1%) RR 0.95; 95% CI 0.91-0.99; I^2=7% **Major bleeding** LMWH group: 94/5077 (1.9%) Control group : 66/4616 ((1.4%) RR 1.26; 95% CI 0.92-1.74; I^2=0% **Direct Xa inhibitors vs placebo** **VTE** Direct Xa inhibitors group: 23/806 (2.8%) Control group : 58/734 (7.9%) RR 0.39; 95% CI 0.24-0.63; I^2=5% **DVT** Direct Xa inhibitors group: 26/806 (3.2%) Control group : 45/734 (6.1%) RR 0.53; 95% CI 0.26-1.07; I^2=33%	Anticoagulation therapy with both LMWH and direct Xa inhibitors of various classes are associated with lower VTE events when compared with placebo, with comparable safety profiles of both LMWH and direct Xa inhibitors.

						PE Direct Xa inhibitors group: 16/806 (2.0%) Control group : 32/734 (4.4%) RR 0.46; 95% CI 0.21-1.02; I^2=30% **All-cause mortality** Direct Xa inhibitors group: 120/806 (14.9%) Control group : 129/734 (17.6%) RR 0.93; 95% CI 0.58-1.48; I^2=53% **Major bleeding** Direct Xa inhibitors group: 20/806 (2.5%) Control group : 10/734 (1.4%) RR 1.76; 95% CI 0.83-3.73; I^2=0%	
[Beccattini 2020]	Literature search using MEDLINE and Scopus through December 2018. This systematic review was registered on PROSPERO (CRD42019120799).	11953 cancer patients receiving chemotherapy 22 studies with VTE (14 studies, 8226 patient) or death (8 studies, 3727 patients) as primary outcome [Agnelli 2009] [Agnelli 2012] [Altinbas 2004] [Carrier 2019] [Elit 2012] [Haas 2012] [Kakkar 2004] [Khorana 2017] [Khorana 2019] [Klerk 2005] [Lebeau1994] [Larocca 2012] [Lecumberri 2013] [Levine 1994] [Levine 2012] [McBeth 2015] [Maraveyas 2012]	Incidence rates of VTE	Incidence rates of major bleeding	Study quality evaluated using the Jadad score and the Cochrane risk assessment tool. Data pooled by the Mantel–Haenszel method; results reported according to fixed effects model in absence of significant heterogeneity and to random-effects model in presence of significant heterogeneity. Cochran's Chi2 test and I-squared test for heterogeneity to assess between-study heterogeneity	**In studies in studies having VTE as primary outcome** **VTE** Anticoagulant prophylaxis group: 122/4331 (2%) Control group: 252/3895 (6%) OR 0.45; 95% CI 0.36-0.56 Parenteral anticoagulant prophylaxis group: 84/3530 (2.4%) Control group: 183/3170 '5.8%) OR 0.43; 95% CI 0.33-0.56 Oral anticoagulant prophylaxis group: 38/801 (4.7%) Control group: 69/725 (9.5%) OR 0.49; 95% CI 0.33-0.74 **Symptomatic VTE** Anticoagulant prophylaxis vs control OR 0.485; 95% CI 0.391-0.601 **Fatal VTE**	Prophylaxis with oral or parenteral anticoagulants reduces the risk of venous thromboembolism in ambulatory cancer patients with acceptable increase in major bleeding.

		[MitchelL 2003] [Pelzer2015] [Perry 2010] [Sideras 2006] [van Doormaal 2011] [Zwicker 2015]				Anticoagulant prophylaxis vs control OR 0.52; 95% CI 0.25-1.08 **Major bleeding** Anticoagulant prophylaxis vs control OR 1.334; 95% CI 1.002-1.777 **In studies in studies having death as primary outcome** **VTE** Anticoagulant prophylaxis group: 87/1890 (4.6%) Control group: 137/1837 (7.4%) OR 0.62; 95% CI 0.47-0.82	
[Thein 2020]	Literature search using MEDLINE and EMBASE databases and the American Society of Clinical Oncology meeting through August 2019.	9 studies, 5443 ambulatory patients with lung cancer [Altinbas 2004] [Ek 2018] [Meyer 2018] [Groen 2019] [Lemcuberri 2013] [Macbeth 2016] [Agnelli 2009] [Agnelli 2012] [Haas 2012]	Overall Survival Progression free survival	VTE Events	Generic inverse variance method used to calculate the estimated pooled hazard ratio (HR). Random effect model Heterogeneity among included articles assessed by the I^2 statistic. Publication bias assessed by funnel plot.	**Overall Survival in patients receiving thromboprophylaxis *vs.* control** HR 1.02; 95% CI 0.83-1.26; p=0.83; I^2=65% *SCLC patients (n = 891)* HR 1.03; 95% CI 0.72-1.48; p=0.85 *Patients with limited stage SCLC* HR 1.70; 95% CI 0.70–4.15; p=0.24 *NSCLC (n = 2560)* HR 1.00; 95% CI 0.79- 1.26; p=0.98 **Progression or metastasis-free survival in patients receiving thromboprophylaxis *vs.* control** HR 1.03; 95% CI 0.86-1.24; p=0.74; I^2=58% **VTE incidence** LMWH: 4.18% Controls: 7.87% RR 0.54; 95% CI 0.43- 0.69: p<0.00001; NNT= 27	This analysis showed no survival advantage with the addition of primary thromboprophylaxis with LMWHs to standard chemotherapy in patients with LC, regardless of histology or stages of small cell LC.

[Frere 2020]	Literature search using PubMed and EMBASE from inception to July 2020	5 studies, 1003 pancreatic cancer patients [Agnelli 2009] [Agnelli 2012] [Marayevas 2012] [Pelzer 2015] [Vadhan-Raj 2020]	Incidence rates of symptomatic VTE	Incidence rates of major bleeding	Study quality evaluated by the Jadad score and the Cochrane Risk of Bias Tool for RCTs Risk ratio (RR) and 95% CI estimated using the Mantel-Haenszel random effect model. Heterogeneity among included articles assessed by the I^2 statistic. Publication bias assessed by funnel plot	**Rates of VTE:** Thromboprophylaxis: 20/516 (3.9%) Placebo or no treatment: 61/497 (12.3%) RR 0.31; 95% CI 0.19-0.51; p<0.00001; I^2=8% ***Sensitivity analyses*** Parenteral anticoagulants (4 studies, 740 patients) RR 0.30; 95% CI 0.17-0.53; p<0.0001; I^2=31% Oral anticoagulants (1 study, 273 patients) RR 0.37; 95% CI 0.14-0.99; p=0.05 Prophylactic doses of anticoagulants (3 studies, 580 patients) RR 0.34; 95% CI 0.17-0.70; p=0.003; I^2=7% Supra-prophylactic or therapeutic doses of anticoagulants (2 studies, 433 patients) RR 0.27; 95% CI 0.08-0.90; p=0.03; I^2=55% **Rates of Major bleeding:** Thromboprophylaxis: 11/354 (3.1%) Placebo or no treatment: 10/352 (2.8%) RR 1.08; 95% CI 0.47-2.52; p=0.85; I^2=0% ***Sensitivity analyses*** Parenteral anticoagulants (2 studies, 433 patients) RR 1.25; 95% CI 0.47-3.31; p=0.65; I^2=0% Oral anticoagulants (1 study, 273 patients) RR 0.68; 95% CI 0.12-4.01; p=0.67	Evidence support a net clinical benefit of thromboprophylaxis in ambulatory PC patients receiving chemotherapy. Adequately powered randomized phase III studies assessing the most effective anticoagulant and the optimal dose, schedule and duration of thromboprophylaxis to be used are warranted.

						Prophylactic doses of anticoagulants (1 study, 273 patients) RR 0.68; 95% CI 0.12-4.01; p=0.67 Supra-prophylactic or therapeutic doses of anticoagulants (2 studies, 433 patients) RR 1.25; 95% CI 0.47-3.31; p=0.65; I^2=0%	
[Xin 2020]	Literature search using PubMed, EMBASE and COCHRANE from inception to 26 April 2019	19 studies, 11430 ambulatory cancer patients [Khorana 2019] [Carrier 2019] [Levine 2012] [Kakkar 2004] [Agnelli 2009] [Perry 2010] [Haas 2012] [Maraveyas 2012] [Lecumberri 2013] [Pelzer 2015] [Macbeth 2016] [Khorana 2017] [Agnelli 2012] [Palumbo 2011] [Larocca 2016] [Levine 1994] [Chahinian 1989] [Zacharski 1984] [Maurer 1997]	Rates of VTE including DVT and PE	Rates of major bleeding Rates of CRNMB All-cause mortality	Odds ratio (OR) and 95% CI estimated using the Mantel-Haenszel random effects models Heterogeneity among included articles assessed by the I^2 statistic. Publication bias assessed by funnel plot.	**Rates of VTE** Apixaban 5mg: 12/320 (3.7%) Placebo: 31/304 (10.2%) OR 0.36; 95% CI 0.18-0.71; p=0.003; I^2=0% LMWH: 131/2220 (5.9%) Placebo: 222/1805 (12.3%) OR 0.50; 95% CI 0.40-0.64; p<0.00001; I^2=0% Semuloparin: 20/1608 (1.2%) Placebo : 55/1604 (3.4%) OR 0.35; 95% CI 0.21-0.59; p<0.0001 Rivaroxaban: 25/420 (6.0%) Placebo: 37/421 (8.8%) OR 0.66; 95% CI 0.39-1.11; p=0.12 Warfarin: 18/220 (8.2%) LMWH: 11/219 (5.0%) OR 1.68; 95% CI 0.78-3.66; p=0.19 Apixaban 20 mg: 0/32 (0%) Placebo: 3/29 (10.3%) OR 0.12; 95% CI 0.01-2.36; p=0.16 Aspirin: 18/396 (4.5%) LMWH: 13/385 (3.4%) OR 1.38; 95% CI 0.66-2.88; p=0.39; I^2=0%	Anticoagulation therapies in ambulatory cancer patients can significantly reduce the risk of VTE. However, this protective effect was associated with a significantly increased risk of major bleeding. Apixaban at the appropriate dose can decrease the risk of VTE without increasing the bleeding risk. These findings require validation in larger study cohorts

						Apixaban 10 mg: 0/29 (0%) Placebo: 3/29 (10.3%) OR 0.13; 95% CI 0.01-2.60; p=0.18 Warfarin: 18/220 (8.2%) Aspirin: 14/220 (6.4%) OR 1.31; 95% CI 0.64-2.71; p=0.46 Warfarin: 0/152 (0%) Placebo: 6/159 (3.8%) OR 0.08; 95% CI 0.00-1.39; p=0.08 Apixaban 10 mg: 0/29 (0%) Apixaban 20 mg: 0/32 (0%) Apixaban 5 mg: 0/32 (0%) Apixaban 20 mg: 0/32 (0%) Apixaban 5 mg: 0/32 (0%) Apixaban 10 mg: 0/29 (0%) **Rates of Major bleeding** LMWH: 49/1397 (3.5%) Placebo: 26/1374 (1.9%) OR 1.74; 95% CI 1.07-2.84; p=0.03; I^2=0% Apixaban 5mg: 10/320 (3.1%) Placebo: 6/304 (2.0%) OR 1.43; 95% CI 0.36-5.64; p=0.61; I^2=16% Semuloparin: 19/1589 (1.2%) Placebo : 18/1583 (1.1%) OR 1.05; 95% CI 0.55-2.01; p=0.88 Apixaban 10 mg: 0/29 (0%) Placebo: 1/29 (3.4%) OR 0.32; 95% CI 0.01-8.24; p=0.49 Apixaban 20 mg: 2/32 (6.2%)	

						Placebo: 1/29 (3.4%) OR 1.87; 95% CI 0.16-21.74; p=0.62 Apixaban 5 mg: 0/32 (0%) Apixaban 20 mg: 2/32 (6.2%) OR 0.19; 95% CI 0.01-4.07; p=0.29 Apixaban 10 mg: 0/29 (0%) Apixaban 20 mg: 2/32 (6.2%) OR 0.21; 95% CI 0.01-4.49; p=0.32 Warfarin: 108/638 (16.9%) Placebo: 25/619 (4.0%) OR 4.66; 95% CI 1.92-11.31; p=0.0007; I^2=38% Warfarin: 0/220 (0%) Aspirine: 3/220 (1.3%) OR 0.14; 95% CI 0.01-2.74; p=0.20 Aspirin: 3/396 (0.7%) LMWH: 0/385 (0%) OR 7.06; 95% CI 0.36-137.58; p=0.20 Rivaroxaban: 8/405 (2.0%) Placebo: 4/404 (0.9%) OR 2.02; 95% CI 0.60-6.75; p=0.26 Warfarin: 0/220 (0%) LMWH: 0/219 (0%) Apixaban 5 mg: 0/32 (0%) Apixaban 10 mg: 0/29 (0%)	
[Schünemann 2020]	Literature search using MEDLINE, Embase, and The Cochrane Library from inception to May 14, 2020	14 studies, 8278 ambulatory cancer patients [Agnelli 2012a] [Agnelli 2012b] [Altinbas 2004]	Mortality Overall VTE Symptomatic VTE	Major bleeding Minor bleeding, Thrombocytopenia Health-related quality of life	Meta-Analyses of Individual Participant Data. Multivariable hierarchical models with patient-level variables as fixed effects and a categorical trial variable as a random effect,	**Mortality at 1 year (primary endpoint, n=6898)** LMWH: 1971/3427 (57.5%) Control: 2021/3471 (58.2%) Adjusted RR 0.99; 95% CI 0.93–1.06	Low-molecular-weight heparin reduces risk of venous thromboembolism without increasing risk of major bleeding compared with placebo or standard care in

		[Haas 2012] [Klerk 2005] [Lebeau 1994] [Lecumberri 2010] [Macbeth 2016] [Maraveyas 2012] [Pelzer 2015] [Perry 2010] [Sideras 2006] [Van Doormaal 2011] [Weber 2008]			adjusting for age, cancer type, and metastatic status. Calculation of adjusted RR to anticipate absolute effects.	**Mortality at 2 years (n=5676)** LMWH: 2514 /2811 (89.4%) Control: 2560/2865 (89.4%) Adjusted RR 1.00; 95% CI 0.95–1.06 **Mortality during the study (n=8278)** LMWH: 2690/4139 (65.0%) Control: 2749/4139 (66.4%) Adjusted RR 0.98; 95% CI 0.93–1.04 **Any VTE (n=7915)** LMWH: 158/3958 (4.0%) Control: 279/3957 (7.1%) Adjusted RR 0.58; 95% CI 0.47–0.71 **Symptomatic VTE (n=7474)** LMWH: 114/3742 (3.0%) Control: 220/3732 (5.9%) Adjusted RR 0.58; 95% CI 0.48–0.70 **Symptomatic DVT (n=7476)** LMWH: 69/3743 (1.8%) Control: 130/3733 (3.5%) Adjusted RR 0.58; 95% CI 0.44–0.76 **Symptomatic PE (n=7472)** LMWH: 54 /3741 (1.4%) Control: 99/3731(2.7%) Adjusted RR 0.59; 95% CI 0.44–0.78 **Major bleeding (n=8274)** LMWH: 88 /4137(2.1%) Control: 71/4137 (1.7%) Adjusted RR 1.27; 95% CI 0.92–1.74 **Minor bleeding (n=7882)** LMWH: 652/3937 (16.6%) Control: 478/3945 (12.1%) Adjusted RR 1.34; 95% CI 1.19–1.51 **Thrombocytopenia (n=5614)** LMWH: 244/2818 (8.7%)	patients with solid tumours, but it does not improve survival.

						Control: 251/2823 (8.9%) Adjusted RR 0.95; 95% CI 0.80–1.14	
[Rank 2020]	Literature search using MEDLINE, EMBASE, SCOPUS and CENTRAL through April 2020	13 non-randomized studies [Al Rabadi 2017] [Chen 2019] [Farrell 2016] [Freixo 2017] [George 2020] [Grace 2018] [Grose 2018] [Orvain 2020] [Rank 2018] [Sibai 2020] [Umakanthan 2016] [Bigliardi 2015] [Elliott 2004]	First-time symptomatic VTE during ALL treatment with asparaginase until four weeks after the last asparaginase dose All-cause mortality Major bleeding during treatment with primary systemic prophylactic treatment for the prevention of	VTE-related mortality Asymptomatic VTE Adverse events (CRNMB and HIT) Quality of life	RR determined using Mantel-Haenszel method (random effect). Risk of bias assessed by using standardised tools (RoB 2.0 tool for RCTs and ROBINS-I tool for non-randomised studies) and certainty of evidence for each outcome assessed by using the GRADE approach.	**AT thrombin vs. no antithrombin** **First-time symptomatic VTE** *Not assessed* All-cause mortality - Intention-to-treat analysis follow up≥1 year RR 0.55; 95% CI 0.26-1.19 **Major bleeding** *Not reported* **VTE-related mortality** RR 0.10; 95% CI 0.01-1.94 **Asymptomatic VTE** *Not assessed* **Enoxaparin vs. no enoxaparin** *No result*	We do not know from the currently available evidence, if thromboprophylaxis used for adults with ALL treated according to asparaginase based regimens is associated with clinically appreciable benefits and acceptable harms. The existing research on this question is solely of non-randomised design, seriously to critically confounded, and underpowered with substantial imprecision.
[Rutjes 2020]	Literature search using Cochrane Vascular, CENTRAL, MEDLINE, Embase, CINAHL and AMED databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 3 August 2020.	**32 RCT** comparing any oral or parenteral anticoagulant or mechanical intervention to no thromboprophylaxis or placebo, or comparing two different anticoagulants Inpatients with cancer receiving chemotherapy, **15678 patients** **[**Agnelli 2012] [Agnelli 2009] [Altinbas 2004] [Campos-Cabrera 2018] [Carrier 2019] [Chahinian 1989] [Ek 2018] [Elit 2012]	Symptomatic VTE Major bleeding	Symptomatic PE Symptomatic DVT Any VTE One-year overall mortality Clinically relevant bleeding Incidental VTE. Minor bleeding Arterial thromboembolic events Superficial venous thrombosis. Quality of life. Any serious adverse event	Risk ratios for dichotomous variables determining a 95% confidence interval (CI) for each estimate. Inverse-variance random effects model used to combine trials (DerSimonian and Laird method) In the case of statistically significant overall estimates, number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). Assessed heterogeneity between trials through Tau^2 statistic (low heterogeneity >0.04; moderate >0.09; high >0.16). Assessed bias using funnel plots.	**DOACs *vs.*placebo** **Symptomatic VTE** RR 0.43; 95% CI 0.18-1.06; 3 studies, 1526 participants; high heterogeneity; Tau^2=0.35 **Major bleeding** RR 1.74; 95% CI 0.82-3.68; 3 studies, 1494 participants; no heterogeneity; Tau^2=0 **Symptomatic PE** RR 0.38; 95% CI 0.10-1.47; 3 studies, 1526 participants; high heterogeneity, Tau^2 0.65 **Symptomatic DVT** RR 0.51; 95% CI 0.21-1.22; 3 studies, 1526 participants; high heterogeneity, Tau^2=0.30 **Any VTE**	In ambulatory cancer patients, primary thromboprophylaxis with direct factor Xa inhibitors may reduce the incidence of symptomatic VTE (low-certainty evidence) and probably increases the risk of major bleeding (moderate-certainty evidence) when compared with placebo. LMWH decreases the incidence of symptomatic VTE (high-certainty evidence), but increases the risk of major bleeding (moderate-certainty evidence) when compared with placebo or no thromboprophylaxis. Evidence for the use of

		[Greiner 2019] [Haas 2012] [Kakkar 2004] [Khorana 2017] [Khorana 2019] [Klerk 2005] [Larocca 2012] [Lebeau 1994] [Lecumberri 2013] [Levine 1994] [Levine 2012] [Macbeth 2016] [Maraveyas 2012] [Maurer 1997] [Meyer 2018] [Mitchell 2003] [Palumbo 2011] [Pelzer 2015] [Perry 2010] [Sideras 2006] [Vadhan-Raj 2013] [van Doormaal 2011] [Zacharski 1981] [Zwicker 2013]				RR 0.55; 95% CI 0.34-0.90; 2 studies, 1404 participants **Clinically relevant bleeding** RR 1.61; 95% CI 0.82-3.15; 2 studies, 931 participants **LMWH *vs.* no thromboprophylaxis** **Symptomatic VTE** RR 0.62; 95% CI 0.46-0.83; 11 studies; 3931 participants; Tau^2=0.00 **Major bleeding** RR 1.63; 95% CI 1.12-2.35; 15 studies, 7282 participants; Tau^2=0.00 **Symptomatic PE** RR 0.60; 95% CI 0.42-0.88; 8 studies, 5324 participants; Tau^2=0.00 **Symptomatic DVT** RR 0.48; 95% CI 0.35-0.67; 9 studies, 5408 participants; Tau^2=0.00 **Any VTE** RR 0.57; 95% CI 0.46-0.71; 10 studies, 5743 participants; Tau^2=0.00 **Clinically relevant bleeding** RR 3.40; 95% CI 1.20-9.63; 4 studies, 3105 participants; Tau^2=0.73 **Overall mortality** RR 0.94; 95% CI 0.83-1.07; 9 studies, 2681 participants; Tau^2=0.02 **Subgroup analysis (LMWH *vs.* active control in participants with multiple myeloma)** **LMWH *vs.* warfarin** **Symptomatic VTE** RR 0.33; 95% CI 0.14 to 0.83; 439 participants **LMWH *vs.* aspirin** **Symptomatic VTE**	thromboprophylaxis with anticoagulants other than direct factor Xa inhibitors and LMWH is limited. More studies are warranted to evaluate the efficacy and safety of primary prophylaxis in specific types of chemotherapeutic agents and types of cancer, such as gastrointestinal or genitourinary cancer.

						RR 0.51; 95% CI 0.22-1.17; 2 studies, 781 participants; moderate-certainty evidence **Major bleeding** RR 0.14; 95% CI 0.01-2.76; 2 studies, 781 participants; low-certainty evidence **UFH *vs.* no thromboprophylaxis** Only one study, no report on VTE or major bleeding. **Warfarin *vs.*placebo or no thromboprophylaxis** **Symptomatic VTE** RR 0.15; 95% CI 0.02-1.2; 1 study; 311 participants **Major bleeding** RR 3.82; 95% CI 0.97-15.04; 4 studies, 994 participants **Antithrombin *vs.* no antithrombin (placebo or no thromboprophylaxis)** **Any VTE** RR 0.84; 95% CI 0.41-1.73; 85 participants; very low-certainty evidence **Major bleeding** RR 0.78; 95% CI 0.03-18.57; 85 participants; very low-certainty evidence **Minor bleeding** RR 11.73; 95% CI 0.58- 235.96; 85 participants; very low-certainty evidence	
[Bosch 2020]	Literature search using Embase, MEDLINE, and the Cochrane Central Register of Trials	**6 RCTS,** 4626 patients [Khorana 2019] [Carrier 2019] [Agnelli 2012] [Pelzer 2015] [Lecumberri 2013] [Macbeth 2016]	Rate of VTE Rate of major bleeding	Rate of all-cause-ortality	Summary relative risks (RRs) with 95% confidence intervals (CIs) calculated in a profile-likelihood random-effects model with inverse variance weighting. I^2 and tau^2 statistics to assess heterogeneity between studies.	**VTE** Khorana score ≥2 Prophylaxis: 80/2294 (3.5%) Control: 161/2332 (6.9%) RR 0.51; 95% CI 0.34-0.67; I^2=28% Khorana score 2 Prophylaxis: 46/1398 (3.3%) Control: 84/1439 (5.8%) RR 0.58; 95% CI 0.36-0.83; I^2=0% Khorana score ≥3	The results indicate thromboprophylaxis effectively reduces the risk of VTE in patients with an intermediate- to high-risk Khorana score, although the NNT is twice as high for intermediate-risk patients compared with high-risk patients.

						Prophylaxis: 34/891 (3.8%) Control: 77/890 (8.7%) RR 0.45; 95% CI 0.28-0.67; I^2=0% **Major bleeding** Khorana score ≥2 Prophylaxis: 45/2276 (2.0%) Control: 42/2307 (1.8%) RR 1.06; 95% CI 0.69-1.67; I^2=0% Khorana score 2 Prophylaxis: 18/1387 (1.3%) Control: 20/1419 (1.4%) RR 0.88; 95% CI 0.45-2.30; I^2=10% Khorana score ≥3 Prophylaxis: 27/885 (3.0%) Control: 22/885 (2.5%) RR 1.11; 95% CI 0.64-1.92; I^2=0% **Mortality** Khorana score ≥2 Prophylaxis: 585/2294 (25.5%) Control: 662/2332 (28.4%) RR 0.90; 95% CI 0.82-1.01; I^2=0% Khorana score 2 Prophylaxis: 243/940 (25.9%) Control: 275/954 (28.8%) RR 0.90; 95% CI 0.74-1.04; I^2=0% Khorana score ≥3 Prophylaxis: 223/652 (34.2%) Control: 260/674 (38.6%) RR 0.91; 95% CI 0.68-1.24; I^2=51%	

Table 13: Prophylaxis of VTE in medical cancer patients Comparative/observational – prospective/retrospective studies

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Pegourie 2019] Myelaxat (anti-Xa anticoagulant in myeloma) study	104/108 patients	7 months	Patients with myeloma, who were asymptomatic for VTE at inclusion, and requiring melphalan-thalidomide-prednisone (patients in first line)	Apixaban, 2.5 mg x 2/day for 6 months	**VTE**: 2/104 (1.9%) (1 event in the context of apixaban stopped 14 days before, due to lenalidomide-induced thrombocytopenia)	**Major bleeding**: 1/104 (0.96%) **CRNM bleeding**: 10/104 (9.6%)	-
[Sibai 2020] Single-centre retrospective cohort study	224/224 patients	From 2001 to 2017	Adult patients with Philadelphia chromosome negative ALL who received Asparaginase-based intensification from 2001 to 2017, with prophylaxis given from 2011 to 2017	Daily injections of enoxaparin at variable doses ranging depending on weight 0.39-1.2 mg/kg, starting on day 1, cycle 1, of the intensification phase until its completion	**VTE** Prophylaxis: 17/125 (13.6%) Controls: 27/99 (27.3%) P=0.01 OR 0.42; 95% CI 0.21–0.83	**Major bleeding** Prophylaxis: 0/125 (0%) Controls: 0/99 (0%)	-
[Cornell 2020] Phase IV, single-arm pilot study of patients with MM on IMiDs receiving apixaban 2·5 mg orally twice daily for primary prevention of VTE	50/50 patients	6 months	Patients with myeloma defined according to IMWG guidelines and receiving IMiD-based therapy for a planned minimum duration of six months	Apixaban, 2.5 mg x 2/day for 6 months	**VTE**: 0/50 (0%) **Stroke, myocardial infarction:** 0/50 (0%)	**Major bleeding**: 0/50 (0%) **CRNM bleeding**: 3/50 (6%)	1 death due to influenza A while on the study
[Vadhan-Raj 2020] Prespecified subgroup analysis of the CASSINI study	273/362	6 months	Adult ambulatory patients with pancreatic cancer included in the CASSINI trial	**Arm A:** placebo up to day 180 **Arm B:** rivaroxaban 10 mg once daily up to day 180	**Primary efficacy endpoint during the observation period** **Arm A:** 18/138 (13.0%) **Arm B:** 13/135 (9.6 %) HR 0.70; 95% CI 0.34-1.43; p=0.328 **Symptomatic VTE during the observation period** **Arm A:** 9/138 (6.5%) **Arm B:** 5/135 (3.7%) **Asymptomatic VTE during the observation period** **Arm A:** 10/138 (7.2%) **Arm B:** 8/135 (5.9%)	**Major bleeding** **Arm A:** 3/131 (2.3%) **Arm B:** 2/130 (1.5%) HR 0.67; 95% CI 0.11-3.99; p=0.654 **Clinically relevant, non-major bleeding** **Arm A:** 2/131 (1.5%) **Arm B:** 5/130 (3.9%) HR 2.47; 95% CI 0.48-12.72; p=0.264 **Any bleeding** **Arm A:** 11/131 (8.4%)	-

					VTE-related death during the observation period **Arm A:** 1/138 (0.7%) **Arm B:** 0/135 (0.0%) **Primary efficacy endpoint during the intervention period** **Arm A:** 14/138 (10.1%) **Arm B:** 5/135 (3.7%) HR 0.35; 95% CI 0.13-0.97; p=0.034 **Symptomatic VTE during the intervention period** **Arm A:** 6/138 (4.3%) **Arm B:** 1/135 (0.7%) **Asymptomatic VTE during the intervention period** **Arm A:** 9/138 (6.5%) **Arm B:** 4/135 (3.0%) **VTE-related death during the intervention period** **Arm A:** 0/138 (0.0%) **Arm B:** 0/135 (0.0%)	**Arm B:** 18/130 (13.8%) HR 1.61; 95% CI 0.76-3.41; p=0.21	

Table 14: Prophylaxis of catheter-related deep vein thrombosis - Comparative/observational – - Randomized Controlled Trials

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Picardi 2019] From April 1, 2015 to October 31, 2017	93/100	30 days	Adult patients with newly diagnosed AML scheduled for intent-to-cure via PICC or CICC insertion	**Group 1**: PICC **Group 2**: CICC	**Catheter-related DVT** Group 1: 4/46 (8.7%) Group 2: 12/47 (25%) RR 0.34; 95% CI 0.12-0.98; p=0.03 **Symptomatic CRT-related DVT** Group 1: 1/46 (2.2%) Group 2: 5/47 (10.6%) RR 0.20; 95% CI 0.02-1.68	**Catheter-related infection** Group 1: 2/46 (4.3%) Group 2: 11/47 (23.4%) RR 0.18; 95% CI 0.04-0.79 **Catheter malfunction** Group 1: 4/46 (8.7%) Group 2: 5/47 (10.6%) RR 0.82; 95% CI 0.23-2.85	Group 1: 4/46 (8.7%) Group 2: 10/47 (21.3%) RR 0.418; 95% CI 0.14-1.21
[Taxbro 2019] From March 13, 2013 to February 16, 2007	399/399	12 months	Patients ≥18 yr old with a life expectancy longer than 4 weeks and requiring chemotherapy through a CVC	**Group 1**: PICC **Group 2**: CICC	**Catheter-related DVT** Group 1: 16/201 (8%) Group 2: 2/198 (1%) HR 10.2; 95% CI 2.3-44.6; p=0.0002	**Catheter-related infection** Group 1: 4/201 (2%) Group 2: 16/198 (8%) HR 0.3; 95% CI 0.1-1.0; p=0.054 **Catheter occlusion** Group 1: 16/201 (8%) Group 2: 1/198 (0.5%) HR 26.1; 95% CI 3.4-203.9; p=0.002	Group 1: 12/201 (6%) Group 2: 37/198 (18.7%) HR 0.6; 95%CI 0.3-1.2; p=0.18
[Ikesaka 2021]	105/105	90 days	Adult patients with active cancer who had a CVC inserted within 72 hours of enrollment and	**Arm 1:** Rivaroxaban 10 md daily for 90 days **Arm 2:** standard of care	**VTE** Arm 1: 3/52 (5.8%) Arm 2: 5/53 (9.4%) HR 0.58; 95%CI 0.14-2.5 **Major VTE** Arm 1: 2/52 (3.9%) Arm 2: 3/53 (5.7%) HR 0.66; 95%CI 0.11-3.9	**Major bleeding** Arm 1: 1/52 (1.9%) Arm 2: 0/53 (0%) **CRNMB** Arm 1: 2/52 (3.9%) Arm 2: 2/53 (3.7%) HR 1.02; 95%CI 0.14-7.24	-

Table 15: Prophylaxis of catheter-related deep vein thrombosis –Systematic reviews with or without meta-analysis

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[**Liu 2020]**	Literature search using PubMed, Embase, Cochrane library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang until October, 2019.	22 studies, 4131 cases and 5272 controls [Marcy 2005] [Peynircioglu 2007] [Dong 2016] [Tippit 2018 [Yang 2018] [Wang 2019] [Xu 2017] [Decousus 2018] [Awan 2019] [Pardo 2011] [Teichgraber 2013] [Piran 2014] [Song 2015] [Liu 2017] [Mao 2017] [Mo 2017] [LeVasseur 2018] [Song 2018] [Makary 2018] [Erhancil 2019] [Isom 2019] [Zhang 2019]	Rates of complication	Rates of infection Rates of Thrombosis	Study quality evaluated by the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies Risk ratio (RR) and 95% CI estimated using the DerSimonian and Laird random effects model (REM). Heterogeneity among included articles assessed by the I^2 statistic. Publication bias assessed by funnel plot.	**Rates of complications (arm port vs chest port):** RR 1.01; 95% CI 0.77–1.34; I^2=48.6%; p=0.928 **Rates of infections (arm port vs chest port):** Comparative studies (n=4) RR 0.58; 95% CI 0.32-1.06; p=0.074; I^2=0% All studies RR 1.63; 95% CI 0.97-2.75; p=0.064 **Rates of thrombosis (arm port vs chest port):** Comparative studies (n=4) RR 2.23; 95% CI 1.04-4.79; p=0.041; I^2=46.1% All studies RR 1.21; 95% CI 01.02-1.43; p=0.0.29	This study indicated that the arm port might increase the risk of overall complication risks as well as the risk of catheter-related thrombosis compared with the chest port. However, these reported findings still need to be verified by large randomized clinical trials.

Table 16: Prophylaxis of catheter-related deep vein thrombosis - Comparative/observational – prospective/retrospective studies

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Lv 2019] From January 2014 to June 2015	394/423 patients	Unspecified	Adult patients with gastric, lung, esophageal, breast, colorectal, or ovarian cancer scheduled for treatment via PICC insertion	**Group 1**: rivaroxaban **Group 2**: LMWH **Group 3** control	**PICC-related VTE** **Group 1**: 5/138 (3.76%) **Group 2**: 4/144 (3.03%) **Group 3**: 16/141 (12.40%) p=0.003 Rivaroxaban vs. control, p=0.01 LMWH vs. control, p=0.04 Rivaroxaban vs. LMWH, p=0.743 **PE (no systematic screening)** **Group 1**: 1/138 (0,7%) **Group 2**: 0/144 (0%) **Group 3**: 2/141 (1.4%)	**Hemoptysis** **Group 1**: not reported **Group 2**: 1/144 (0,7%) **Group 3**: not reported **Myocardial infarction** **Group 1**: not reported **Group 2**: not reported **Group 3**: 2/141 (1.4%) **PICC-related infection and catheter removal** **Group 1**: not reported **Group 2**: not reported **Group 3**: 1/141 (0.76%)	-

Table 17: Specific populations and specific clinical situations: Patients with brain cancer –Systematic reviews with or without Meta-Analysis

References	Bibliographic search	Included studies	Primary endpoint	Secondary endpoint	Statistical tests	Results	Authors' conclusions
[Porfidia 2020]	Literature using PubMed, Scopus, and EMBASE databases from January 1980 to January 2019	**7 studies,** 1291 glioma patients **[**Al Megren 2017] [Choucair 1987] [Khoury 2016] [Mantia 2017] [Norden 2012] [Pan 2009] [Ruff 1983]	Rate of intracerebral hemorrhage (ICH)	-	Random effect model using inverse variance weighting to summarize the data. Heterogeneity of pooled data estimated by calculating the Q and I^2 statistics, considered as significant when $p < 0.05$ or $I^2 \geq 50\%$.	**Rate of IHC** **Glioma patients treated with full-dose anticoagulants for acute VTE (UFH, LMWH, VKA, UFH, Fondaparinux):** 52/431 (12%) **Glioma patients without VTE not receiving anticoagulant therapy:** 28/860 (3.2%) OR 3.66; 95% CI 1.84-7.29; I^2=31%	Anticoagulation for VTE increases the risk of ICH in subjects with glioma tumors. Future studies are warranted to fully understand the best medical treatment of VTE in glioma patients.

Table 18: Specific populations and specific clinical situations: Patients with brain cancer - prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Carney 2019] Retrospective cohort	172 patients with brain tumors were evaluated (42 DOAC and 131 LMWH).	From 2011 to 2018	Patients with brain tumors who developed ICH on anticoagulation for VTE	-	-	**Cumulative incidence of any ICH at 12 months** **Primary brain tumor cohort (n = 67)** DOACs: 0/20 (0%); no major ICH event LMWHs: 8/47 major ICH event; 36.8% (95% CI 22.3–51.3%) **Brain metastases cohort (n = 105)** DOACs: 27.8% (95% CI 5.5–56.7%); major ICH event 11.1% (95% C, 0.5–40.6%) LMWHs: 52.9% (95% CI 37.4–66.2%); major ICH event 17.8% (95% CI 10.2–27.2%).	-
[Carney 2020] Retrospective cohort	79 patients	From 2011 to 2019	Patients with brain tumors who developed ICH on anticoagulation for VTE	Patients who restarted systemic anticoagulation	**Recurrent VTE at 1 year** Patients restarting systemic anticoagulation (n=54): 8.1% Patients not restarting systemic anticoagulation (n=25): 35.3% P=0.003	**Cumulative incidence of ICH at 1 year** Patients restarting systemic anticoagulation(n=54): 6.1%; 95% CI 1.5-15.3% Patients not restarting systemic anticoagulation (n=25): 4.2%; 95% CI 0.3-18.3% Median time from anticoagulation restart to recurrent ICH: 36 days (range, 20-119 days)	**Median survival:** Patients restarting systemic anticoagulation: 185 days Patients not restarting systemic anticoagulation: 79 days p=0.15 Recurrent ICH was associated with a 30-day mortality of 67%.
[Swartz 2021] Retrospective cohort	125 patients	From 2015 to 2018	Patients with primary or metastatic brain tumors treated with anticoagulants	**DOAC**: 52 patients, **LMWH:** 57 patients **Warfarin:** 16 patients	**Recurrent VTE** DOAC: 1.9% LMWH: 5.3% Warfarin: 0% p=0.35	**Major bleeding** DOAC: 9.6% LMWH: 26% Warfarin**:** 12.5% p=0.03 **Intracranial hemorrhage** DOAC: 5.8% LMWH: 16% Warfarin: 12.5%	

						p=0.09 **Minor bleeding** DOAC: 19% LMWH: 21% Warfarin: 6.2% p=0.79	
[Wood 2021] Matched, retrospective cohort study	291 patients (100 receiving therapeutic anticoagulation vs 191 controls)	From 1998 to 2015.	Patients with brain metastases treated with anticoagulants vs controls	**Therapeutic anticoagulation**: 100 patients **Controls**: 191 patients	-	**Any ICH at 6 months** Patients with therapeutic anticoagulation: 51% Controls: 40% HR 1.31, 95% CI 0.96-1.79, p=0.09 **ICH as identified by gradient echo/susceptibility-weighted imaging** Patients with therapeutic anticoagulation: 53% Controls: 38% HR 1.46, 95% CI 1.06-2.01, p=0.02 **Symptomatic ICH** Patients with therapeutic anticoagulation: 13% Controls: 3% HR 1.80, 95% CI 1.01-3.22, p=0.05 HR in patients with melanoma 6.46, 95% CI 2.23-18.8, p<0.001 HR in patients with other primary malignancies 1.36, 95%CI 0.66-2.80, p=0.41 **Extra-lesional ICH** Patients with therapeutic anticoagulation: 6% Controls: 1% HR 5.82, 95% CI 1.56-21.7, p=0.009 **Fatal ICH** Patients with therapeutic anticoagulation: 3% Controls: 0.5% HR 5.68, 95% CI 0.60-54.2, p=0.13	-

[Jo 2021] retrospective matched cohort study of high-grade glioma patients	220 high-grade glioma patients	From January 2005 to August 2016	High-grade glioma patients	**Patients with VTE treated with LMWH:** 88 (40%) **Patients with VTE with LMWH out anticoagulation:** 22 (10%) **Patients without VTE:** 110 (50%)	-	**1-year Cumulative Incidence of Intracranial Hemorrhage** Patients with VTE treated with LMWH: 17%; 95% CI, 0.10-0.26 Patients with VTE with LMWH out anticoagulation: 9%; 95% CI 0.01-0.26 Gray's test, p= 0.36 Patients without VTE: 13% 95% CI, 0.07-0.20)	Median survival was similar among all 3 cohorts.
[Lee 2021] Multicenter, retrospective cohort study of patients with primary brain tumor or secondary brain metastasis	111 patients	From January 2012 to October 2019	Patients with primary brain tumor or secondary brain metastasis	**DOAC group:** 55 **LMWH group:** 56	**6-month cumulative incidence of recurrent VTE** DOAC : 5.6% ; 95% CI 1.5-14.2% LMWH : 6.6% ; 95% CI 1.7-16.5% p=1.0	**6-month cumulative incidence of ICH** DOAC: 4.3%; 95% CI 0.74-13.2% LMWH: 5.9%; 95% CI 1.5-14.9% p=1.0 **6-month cumulative incidence of bleeding** DOAC : 14.3% ; 95% CI 6.2-25.8% LMWH : 27.8% ; 95% CI 15.5-41.6% p=0.22	

Table 19: Specific populations and specific clinical situations: Patients with thrombocytopenia - prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	VTE incidence	Toxicity	Death
[**Lecumberri 2020**] From 2001 to December 2018	15,337 patients (8 patients with a platelet count < 20 G/L) 166 patients had severe thrombocytopenia (<50 G/L) 711 patients had mild thrombocytopenia (50–99 G/L) 14,460 had normal count platelet count (>100 G/L).	30 days	Active cancer patients with VTE included in the RIETE registry	**Recurrent VTE at 10 days** Severe thrombocytopenia: 0/166 (0%) Mild thrombocytopenia: 9/711(1.2%) Normal pl. count: 89/14460 (0.6%) p=ns **Recurrent VTE at 30 days** Severe thrombocytopenia:4/166 (2.4%) Mild thrombocytopenia:15/711 (2.1%) Normal pl. count: 239/14460 (1.6%) p=ns	**Major bleeding at 10 days** Severe thrombocytopenia:2/166 (1.2%) Mild thrombocytopenia:18/711 (2.5%) Normal pl. count: 192/14460 (1.3%) Severe vs normal: OR 0.83; 95%CI 0.20–3.41 Mild vs normal: OR 2.07; 95%CI 1.25–3.40 **Major bleeding at 30 days** Severe thrombocytopenia:4/166 (2.4%) Mild thrombocytopenia:31/711 (4.4%) Normal pl. count:322/14460 (2.2%) Severe vs normal: OR 1.07; 95%CI 0.39–2.94 Mild vs normal: OR 2.12; 95%CI 1.44–3.12	**At 10 days** Severe thrombocytopenia:20/166 (12%) Mild thrombocytopenia:67/711 (9.4%) Normal pl. count:479/14460 (3.3%) **At 30 days** Severe thrombocytopenia:45/166 (27%) Mild thrombocytopenia:127/711 (18%) Normal pl. count:1360/14460 (9.4%)
[**Carney 2021**]	121 patients	60 days	Patients with active malignancy, acute VTE, and concurrent thrombocytopenia (<100 G/L)	**Recurrent VTE at 60 days** **Full dose:** 4/75 (5%) **Modified-dose:** 0/33 (0%) **No anticoagulation:** 1/13 (8%)	**Total bleeding at 60 days** **Full dose:** 18/75 (24%) **Modified-dose:** 5/33 (15%) **No anticoagulation:** 0/13 (0%)	

Table 20: Specific populations and specific clinical situation: Children – RCT –randomized controlled trials

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Greiner 2019] **THROMBOTECT trial**	929/949	6 months	Patients with ALL treated on the ALL-BFM 2000 or AIEOP-BFM ALL 2009 protocol, having a CVC inserted by day 8 of induction which remained in place until at least day 33.	**Arm A:** UFH at a dose of 2 IU/kg body weight/h as long as an infusion drip was running. **Arm B:** enoxaparin at a dose of 80-100 IU/kg once daily subcutaneously. **Arm C:** antithrombin infusion for a target 100% in patients with AT levels <80%.	**ITT** **Arm A:** 25/312 (8.0%) **Arm B:** 11/317 (3.5%) **Arm C:** 6/320 (1.9%) UFH vs. LMWH OR 0.41; 95% CI 0.20-0.85; p=0.011 UFH vs. antithrombin OR 0.22; 95% CI 0.09-0.54; p<0.001	**Treated bleeding** **Arm A:** 4/312 (1.3%) **Arm B:** 1/317 (0.03%) **Arm C:** 3/320 (0.09%)	-

Table 21: Specific populations and specific clinical situations: Children– systematic review with or without Meta-Analysis

References	Bibliographic search	Included studies	Primary endpoint	Safety endpoint	Statistical tests	Results	Authors' conclusions
[Pelland-Marcotte 2019]	Literature search using MEDLINE, Medline-in-Process,Medline Epubs Ahead of Print, Embase ClassicþEmbase databases (OvidSP), and Cochrane database (Wiley) on November 14, 2018	6 studies, 1318 children and adolescent from 0 to 21 years [Elhasid 2001] [Mitchell 2003] [Ruud 2006] [Meister 2008] [Mitchell 2010] [Greiner 2019]	VTE	MB CRNMB Mortality	Random effect network meta-analysis. Risk of bias assessed by using the checklist for the assessment of the methodological quality of studies by Downs and Black. I^2 and Tau^2 statistics to assess heterogeneity between studies.	**VTE** Treated with antithrombin: 22/416 (5.3%) Treated with LMWH: 12/407 (2.9%) Treated with VKA: 6/29 (20.7%) Standard of care: 65/466 (13.9%) AT vs. LMWH All studies: RR 1.74; 95% CI 0.42-7.13 RCT: RR 0.80; 95% CI 0.33-1.94	Current evidence suggests that low-dose LMWH is effective and safe to prevent TE in children with cancer compared with standard of care but is insufficient to conclude if AT replacement or VKA are effective thromboprophylaxis options.

						AT vs. VKA All studies: RR 0.49; 95% CI.0.05–4.99 RCT: RR 0.45; 95% CI 0.12–1.74 AT vs. standard of care All studies: RR 0.40; 95% CI 0.12–1.37 RCT: RR 0.37; 95% CI 0.19–0.72 LMWH vs. VKA All studies: RR 0.28; 95% CI 0.03–2.91 RCT: RR 0.56; 95% CI 0.14–2.21 LMWH vs. standard of care All studies: RR 0.23; 95% CI 0.06–0.81 RCT: RR 0.46; 95% CI 0.22–0.94 VKA vs. standard of care All studies: RR 0.81; 95% CI 0.11–5.82 RCT: RR 1.23; 95% CI 0.38–3.95 **MB** AT vs. LMWH All studies: RR 1.49; 95% CI 0.26-8.55 AT vs. VKA All studies: RR 3.2; 95% CI.0.10-91.07 AT vs. standard of care All studies: RR 0.81; 95% CI 0.21-3.03 LMWH vs. VKA All studies: RR 2.02; 95% CI 0.06-0.81	

						LMWH vs. standard of care All studies: RR 0.54; 95% CI 0.11-2.76 VKA vs. standard of care All studies: RR 0.27; 95% CI 0.01-6.17 **CRNMB** No difference between groups **Mortality** Overall survival was comparable between all groups	

Table 22: Specific populations and specific clinical situation: Children – prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Jaffrey 2020] From October 2013 to June 2018	1967/2006 including 802 (41%) patients with cancer	6 months	Children aged 6 months to less than 18 years with a newly placed PICC or tunneled lines (TLs)	**Group 1**: PICC **Group 2**: TL	**Overall incidence rate of catheter-related VTE** Group 1: 9.0% ± 1.4% Group 2: 2.9% ± 0.64% HR 8.5; 95% CI 3.1-23.0; p<0.001	-	-
[Thom 2020] **Predefined analysis of the CVC-VTE cohort of EINSTEIN-Jr RCT** From 3 March 2015 through 18 January 2019	126/126 Including 31 (25%) children with active cancer	1-month (children < 2 years) or 3-month (all other children)	Children with CVC-VTE (age, birth to 17 years) included in the EINSTEIN-Jr RCT. CVC-VTE was defined as occlusive or nonocclusive venous Thrombosis, symptomatic or asymptomatic that occurred in the	**Arm A:** body weight–adjusted 20-mg equivalent doses of rivaroxaban after 5 to 9 days of anticoagulation by UFH or LMWH or Fondaparinux **Arm B:** standard anticoagulation for the	**Recurrent VTE** Arm A: 0/90 (0%) Arm B: 0/36 (0%) Absolute risk difference 0; 95% CI -11 to 4.2 **Other clinically relevant venous thrombosis** Arm A: 1/90 (1.1%) Arm B: 1/36 (2.8%) Absolute risk difference -1.7; 95% CI -14 to 3.6	**Major bleeding** Arm A: 0/90 (0%) Arm B: 0/36 (0%) Absolute risk difference 0; 95% CI -11 to 4.2 **Clinically relevant nonmajor bleeding** Arm A: 3/90 (3.3%) Arm B: 0/36 (0%) Absolute risk difference 3.3; 95% CI -6.4 to 9.7	No child died during the study

			proximity of a (recent) indwelling CVC or associated embolism.	treatment of VTE in children.			

Table 23: Prophylaxis of venous thromboembolism in COVID-19 - Randomized Controlled Trials

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Safety	Death
[REMAP-CAP, ACTIV-4a, and ATTACC Investigators 2021] Open label adaptative RCT Critically ill patients	1098/1207	21 days or hospital discharge	Adult Critically ill patients hospitalized for COVID-19 (rate of cancer patients not documented)	**Arm A:** Therapeutic LMWH or UFH as defined as per hospital policy for treatment of venous thrombotic events **Arm B:** Usual care pharmacological thromboprophylaxis as per hospital policy	**Major thrombotic events (composite of MI, PE, stroke, systemic arterial embolism)** Arm A: 34/530 (6.4%) Arm B: 58/559 (10.4%) **Venous thromboembolism (PE)** Arm A: 19/530 (3.6%) Arm B: 48/559 (8.6%)	**Major bleeding** Arm A: 20/529 (3.8%) Arm B: 13/562 (2.3%) OR 1.48; 95% CI 0.75-3.04%)	**Mortality** Arm A: 199/534 (37.3%) Arm B: 200/564 (35.5%)
[ATTACC, ACTIV-4a, and REMAP-CAP Investigators 2021] Open label adaptative RCT Moderate state	2219/2244	21 days or hospital discharge	Adult moderately ill patients hospitalized for COVID-19 (rate of cancer patients not documented)	**Arm A:** Therapeutic LMWH or UFH as defined as per hospital policy for treatment of venous thrombotic events **Arm B:** Usual care pharmacological thromboprophylaxis as per hospital policy	**Major thrombotic events or death** Arm A: 94/1180 (8.0%) Arm B: 104/1046 (9.9%) OR 0.72; 95% CI 0.53-0.98 **Venous thromboembolism** Arm A: 16/1180 (1.4%) Arm B: 26/1046 (2.5%)	**Major bleeding** Arm A: 22/1180 (1.9%) Arm B: 9/1047 (0.9%) OR 1.80; 95% CI 0.90-3.74	**Mortality** Arm A: 86/1171 (7.3%) Arm B: 86/1048 (8.2%)
[Sadeghipour 2021] INSPIRATION	562/600	30-days	Adult patients hospitalized for COVID-19 requiring critical care at time of admission (rate of cancer patients not documented)	**Arm A:** Intermediate dose (Enoxaparin 1 mg/kg once daily) **Arm B:** Standard dose (Enoxaparin, 40 mg daily)	**Venous thromboembolism** Arm A: 9/276 (3.3%) Arm B: 10/286 (3.5%) OR 0.93; 95%CI 0.37-2.32	**Major bleeding** Arm A: 7/276 (2.5%) Arm B: 4/286 (1.4%) OR 1.83; 95%CI 0.0-5.93	**Mortality** Arm A: 119/276 (43.1%) Arm B: 117/286 (40.9%) OR 1.09; 95%CI 0.78-1.53 -
[Lopes 2021] ACTION Trial	614/615	30 days in the therapeutic group and during the in-hospital period in the prophylaxis group	Adult patients hospitalized for COVID-19 not requiring critical care at time of admission (16 cancers patients/615 patients included)	**Arm A:** Rivaroxaban (20 mg once daily) for patients with a stable condition or enoxaparin (1 mg/kg twice daily) for patients with an unstable condition **Arm B:** Standard in-hospital prophylactic anticoagulation	**Venous thromboembolism** Arm A: 11/311 (4%) Arm B: 18/304 (6%) RR 0.60; 95% CI 0.29-1.25	**Major bleeding** Arm A: 10/310 (3%) Arm B: 4/304 (1%) RR 2.45; 95% CI 0.78-7.73	**Mortality** Arm A: 35/310 (11%) Arm B: 23/304 (8%) RR 1.49; 95%CI 0.90-2.46

[Sholzberg 2021] RAPID Trial	465/465	hospital discharge, day 28, study withdrawal or death	Adult patients hospitalized for COVID-19 and elevated D-dimer levels (>ULN) not requiring critical care at time of admission (32 cancers patients/465 patients included)	**Arm A:** Therapeutic doses of LMWH or unfractionated heparin UFH **Arm B:** Dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance	**Venous thromboembolism** Arm A: 2/228 (0.9%) Arm B: 7/237 (3.0%) OR 0.29; 95% CI 0.06-1.42	**Major bleeding** Arm A: 2/228 (0.9%) Arm B: 4/237 (1.7%) OR 0.52; 95% CI 0.09-1.27	**Mortality** Arm A: 4/228 (1.8%) Arm B: 18/237 (7.6%) OR 0.22; 95% CI 0.07-0.65
[Perepu 2021]	169/176	30-days	Adult patients hospitalized for COVID-19 requiring critical care at time of admission and/or having a modified ISTH Overt DIC score ≥3 (20 cancers patients/176 patients included)	**Arm A:** intermediate weight-adjusted dose enoxaparin **Arm B:** standard prophylactic dose enoxaparin	**Venous thromboembolism** Arm A: 7/87(8%) Arm B: 6/86 (7%) OR 1.79; 95% CI 0.51-6.25	**Major bleeding** Arm A: 2/87(2%) Arm B: 2/86 (2%) OR 0.99; 95% CI 0.17-7.14	**Mortality** Arm A: 13/87(15%) Arm B: 18/86 (21%) OR 0.66; 95% CI 0.30-1.45
[Connors 2021] ACTIV-4B Trial	558/657	45-days	Ambulatory patients between the ages of 40 and 80 years with newly diagnosed symptomatic SARS-CoV-2 infection.	**Arm A:** aspirin 81 mg once daily for 45 days **Arm B:** apixaban 2.5 mg twice daily for 45 days **Arm C:** apixaban 5 mg twice daily for 45 days **Arm D:** placebo for 45 days	**Venous thromboembolism** Arm A: 0/144 (0%) Arm B: 0/135 (0%) Arm C: 0/143 (0%) Arm D: 0/136 (0%)	**Major bleeding** Arm A: 0/144 (0%) Arm B: 0/135 (0%) Arm C: 0/143 (0%) Arm D: 0/136 (0%) **CRNMB** Arm A: 0/144 (0%) Arm B: 1/135 (0.7%) Arm C: 1/143 (0.7%) Arm D: 0/136 (0%)	-
[Ramacciotti 2022] MICHELLE Trial	318/320	35-days	Patients hospitalized with COVID-19 at increased risk for venous thromboembolism (IMPROVE score of ≥4 or 2–3 with a D-dimer >500 ng/mL)	**Arm A:** rivaroxaban 10 mg once daily for 35 days **Arm B:** no anticoagulation	**Symptomatic and fatal Venous thromboembolism** Arm A: 1/159 (0.63%) Arm B: 8/159 (5.03%) RR 0.13; 95% CI 0.02-0.99	**Major bleeding** Arm A: 0/159 (0%) Arm B: 0/159 (0%) **CRNMB** Arm A: 2/159 (1.26%) Arm B: 2/159 (1.26%) RR 1.00; 95% CI 0.14-7.01	**Cardiovascular death** Arm A: 0/159 (0%) Arm B: 1/159 (0.63%) RR 0.33; 95% CI 0.01-8.12

Table 24: Prophylaxis of venous thromboembolism in COVID-19 – prospective/retrospective

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[Eswaran 2020] March 15 to July 4, 2020	447/447	30 days of discharge	Patients hospitalized for COVID-19	**Group 1**: no anticoagulation at Discharge (57.5%) **Group 2**: anticoagulation at Discharge (42.5%)	**Vascular thromboembolic events** **Group 1**: 7/257 (2.7%) **Group 2**: 2/190 (1.1%) Adjusted OR 0.52; 95% CI 0.08-2.26; p=0.42	-	-
[Giannis 2021] March 1 to May 31, 2020	4906/4906	90 days after hospital discharge	Patients hospitalized for COVID-19 [644/4906 (13.1% cancer patients]	**Group 1**: no anticoagulation at Discharge (87.3%) **Group 2**: anticoagulation at Discharge (12.7%)	**Composite of VTE, ATE and all-cause mortality** OR 0.54; 95% CI 0.47-0.81;p=0.003 **VTE:** 76/4906, history of cancer associated with an increased risk of VTE in univariate analysis (OR, 1.57;95% CI 1.18-2.08**)**	-	-

Appendix 6: Conclusions Tables

Chapter 1

Q1 Initial treatment of established VTE– BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: UFH followed by VKA	**6 retrospective studies** [Moore 1981] [Clarke Pearson 1983] [Calligaro 1991] [Chan 1992] [Debourdeau 1996] [Elting 2004] **2 control arms of randomized studies** [Hull 2006] [van Doormaal 2009]
HTA 2: LMWH followed by VKA	**5 control arms of randomized studies** [Meyer 2002] [Lee 2003] [Deitcher 2006] [Romera 2009] [van Doormaal 2009]
HTA 3: LMWH vs. UFH	**9 meta-analyses not specific to cancer patients** (5%–22% cancer) [Lensing 1995] [Siragusa 1996] [Hettiaratchi 1998] [Gould 1999] [Dolovich 2000] [Rocha 2000] [Quilan 2004] [Mismetti 2005] [Robertson 2017] **6 cancer-specific meta-analyses** [Akl 2008] [Akl 2011] [Akl 2014] [Erkens 2010] [Hakoum 2018] [Kahale 2021]
HTA 4: LMWH vs. DOACs	**5 randomized controlled trials** [Young 2018] [McBane II 2019] [Agnelli 2020] [Planquette 2021] [Schrarg 2021 abstact]
HTA 5: Fondaparinux	**Analysis of the subgroup of cancer patients included in 2 randomized controlled trials** [van Doormaal 2009] [Akl 2008] [Akl 2011] [Akl 2014] [Hakoum 2018] [Kahale 2021]
HTA 6: Thrombolytics	**1 retrospective study of cancer patients included in a prospective trial** [Mikkola 1997] **1 retrospective study of cancer patients included in the National Inpatient Sample database** [Brailovsky 2019]
HTA 7: Vena cava filters	**25 retrospective studies – cancer population** [Cohen 1991] [Calligaro 1991] [Cohen 1992] [Levin 1993] [Hubbard 1994] [Schiff 1994] [Schwarz 1996] [Greenfield 1997] [Ihnat 1998] [Schleich 2001] [Jarrett 2002] [Wallace 2004] [Zerati 2005] [Schunn 2006] [Stein 2013] [Muriel 2014] [Narayan 2016] [Brunson 2016] [Casanegra 2016] [Brunson 2017] [Coombs 2017] [Stein 2018] [Kang 2018] [Balabhadra 2020] [Quezada 2020]] [Takase 2020] **2 randomized studies** [Barginear 2012] [Mismetti 2015]

Q1 Initial treatment of established VTE– CONCLUSIONS

Q1.1: UFH followed by VKA

Studies	**6 retrospective studies** [Moore 1981] [Clarke Pearson 1983] [Calligaro 1991] [Chan 1992] [Debourdeau 1996] [Elting 2004] **2 control arms of randomized studies** [Hull 2006] [Vandoormaal 2009]
Agreement	Yes
Quality of evidence	Moderate (retrospective + large effect)
Results	**Retrospective studies**: high complication rate with 11%–38% relapse and 8%–35% major bleeding **Control arm of randomized studies** (UFH + VKA): 10%–17.2% relapses and 6.3%–7% major bleeding at 3 months under treatment

Conclusion

Treatment of VTE in cancer patients with UFH followed by VKA is associated with a high rate of relapse and bleeding.

Q1.2: LMWH followed by VKA

Studies	**5 control arms of randomized studies** [Meyer 2002] [Lee 2003] [Deitcher 2006] [Romera 2009] [van Doormaal 2009]
Agreement	Yes
Quality of evidence	High (randomized + consistency)
Results	**In the "cancer" population**: at 6 months' high rate of relapse (2%–16.9%) and major bleeding (2.7%–16%) in patients with cancer vs. patients without cancer **In the control arm of prospective studies** (LMWH + VKA): 6.7%–16.9% relapses and 2.9%–16% major bleeding at 6 months

Conclusion

Treatment of VTE in cancer patients with LMWH followed by VKA is associated with a high rate of relapse and bleeding. Using indirect comparison, the rate of major bleeding and relapse of VTE in cancer patients treated with LMWH and VKA appears lower than the rate with UFH + VKA and is increased in cancer patients compared to non-cancer patients.

Q1.3: **LMWH vs. UFH**

Studies	**9 meta-analyses not specific to cancer patients** (5%–22% cancer) [Lensing 1995] [Siragusa 1996] [Hettiaratchi 1998] [Gould 1999] [Dolovich 2000] [Rocha 2000] [Quilan 2004] [Mismetti 2005] [Robertson 2017] **6 cancer-specific meta-analyses** [Akl 2008] [Akl 2011] [Akl 2014] [Erkens 2010] [Hakoum 2018] [Kahale 2021]
Agreement	Yes
Quality of evidence	Moderate (indirectness)
Results	**Meta-analyses in the general population** • Decrease of relapse rate (4/9 meta-analyses) for LMWH • Decrease of major bleeding (6/8 meta-analyses) for LMWH • Few specific data except for survival in patients treated by LMWH [Siragusa 1996] [Gould 1999] • Reduction in overall mortality in participants with cancer who were treated with LMWH [Siragusa 1996] [Robertson 2017] **Meta-analysis in cancer patients**: Reduced mortality at 3 months or at the end of follow-up. The rates of recurrence were not statistically different between LMWH and UFH.

Conclusion

There is moderate evidence to demonstrate the superiority of LMWH over UFH in the initial treatment of VTE in cancer patients. LMWH appears superior in reducing the rate of mortality and the incidence of recurrent VTE at 3 months compared to UFH in the initial treatment of VTE in cancer patients.

Q1.4: **LMWH vs. DOACS**

Studies	**5 randomized controlled trials** [Young 2018] [McBane II 2019] [Agnelli 2020] [Planquette 2021] [Schrarg 2021 abstact]
Agreement	Yes
Quality of evidence	High
Results	**2 specific RCT comparing rivaroxaban vs LMWH in cancer patients** [Young 2018] [Planquette 2021] • In Select-D trial [Young 2018], rivaroxaban was non-inferior to dalteparin regarding the rates of VTE recurrence and overall survival at 6 months but was associated with higher rates of CRNM bleeding. • The CASTA-DIVA trial [Planquette 2021] did not fulfill the predefined criteria of non-inferiority regarding the rates of VTE but results were consistent with previous RCT comparing DOACs with LMWHs. There was no difference in major bleeding or CRNMB between the two arms. **2 specific RCT comparing apixaban vs LMWH in cancer patients** [McBane II 2019] [Agnelli 2020] • Apixaban decreased the rates of VTE recurrence in 1 study (0.7% vs. 6.3% in the LMWH arm) [McBane II 2019]; Apixaban was non inferior to LMWH regarding the rates of VTE recurrence (HR 0.63, 95% CI 0.37-1.07, p<0.001) without increase in major bleeding (HR 0.82, 95% CI 0.40-1.69, p=0.60) [Agnelli 2020] • No difference in major bleeding or CRNM bleeding between Apixaban and LMWH **1 specific RCT comparing DOACs vs LMWH in cancer patients** [Schrag 2021]

Conclusion

In 5 RCTs, DOACs were non-inferior or superior to LMWH to prevent recurrent VTE but rivaroxaban was associated with a trend toward more CRNB (1 study [Young 2018]).

Q1.5: **Fondaparinux**

Studies	**Analysis of the subgroup of cancer patients included in 2 randomized controlled trials** [van Doormaal 2009] [Akl 2008] [Akl 2011] [Akl 2014] [Hakoum 2018] [Kahale 2021]
Agreement	Impossible to determine
Quality of evidence	Low

Results	**Analysis of cancer patients in randomized controlled trials** For the initial treatment, the rate of recurrence is lower with fondaparinux than with UFH, but higher than enoxaparin with the same rate of bleeding.

Conclusion

There are insufficient data to adequately compare the efficacy and safety of fondaparinux, UFH and LMWH for the initial treatment of thrombosis in cancer patients.

Q1.6: Thrombolytics

Studies	**1 retrospective study of cancer patients included in a prospective trial** [Mikkola 1997] **1 retrospective study of cancer patients included in the National Inpatient Sample database** [Brailovsky 2019]
Agreement	Impossible to determine
Quality of evidence	Very low (observational, serious limitations, serious imprecision)
Results	In cancer patients, thrombolysis was associated with a 6% relapse rate [Mikkola 1997] and a significant increase in the rate of major bleeding [Brailovsky 2019], including intracranial hemorrage.

Conclusion

Due to paucity of data, the indications for thrombolytics should be considered on a case-by-case basis in cancer patients.

Q1.7: Vena cava filters

Studies	**1 randomized controlled study – not specific to cancer** [Mismetti 2015] **1 randomized study – cancer population** [Barginear 2012] **25 retrospective studies – general or cancer population** [Cohen 1991] [Calligaro 1991] [Cohen 1992] [Levin 1993] [Hubbard 1994] [Schiff 1994] [Schwarz 1996] [Greenfield 1997] [Ihnat 1998] [Schleich 2001] [Jarrett 2002] [Wallace 2004] [Zerati 2005] [Schunn 2006] [Stein 2013] [Muriel 2014] [Narayan 2016] [Brunson 2016] [Casanegra 2016] [Brunson 2017] [Coombs 2017] [Stein 2018] [Kang 2018] [Balabhadra 2020] [Quezada 2020] [Takase 2020] **1 meta-analysis** [Young 2020]
Agreement	Heterogeneity across retrospective studies
Quality of evidence	**General population** Randomized – indirectness (moderate) **Cancer population** Randomized – serious limitations (very low) Observational - Low or moderate (serious imprecision, serious indirectness, very large effect)
Results	**General population** **[Mismetti 2015] - randomized study (n=199)** At 3- and 6-month follow-up, the rate of recurrent PE doubled with vena cava filters, although this effect was not significant. No differences in other endpoints, including rates of symptomatic DVT, major bleeding, 3- and 6-month mortality, and filter complications. **Cancer population** **23 previous observational studies –** heterogeneity/inconsistency. **2 new observational studies** 1 retrospective cohort study [Balabhadra 2020] found a significant improvement in PE-free survival and in recurrent-DVT free survival in patients with IVC filters. 1 propensity-matched cohort study of cancer patients included in RIETE [Quezada 2020] found a significant decrease in PE-related death in patients with IVC filters. 1 retrospective study of patients with CAT from COMMAND VTE registry found a significant increased risk of DVT, major bleeding and death in patients with IVC filters compared to those without IVC filter [Takase 2020] The efficacy of vena cava filters is not proven in cancer patients

Conclusion

Recurrent VTE (non-fatal DVT, non-fatal PE) are increased after IVC placement with no significant improvement in overall survival. Active bleeding within 3 months of discharge or less appeared to be increased when anticoagulation is resumed.

Evidence is lacking to recommend the use of IVC filters in cancer patients. Cancer is neither a specific indication nor a special contraindication to vena cava filter placement.

Chapter 2

Q2 Early maintenance and long-term (beyond 6 months) treatment of established VTE – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Early maintenance and long-term use of LMWH (includes dose comparison for LMWH, and LMWH vs. fondaparinux)	**8 randomized controlled trials** [Lopez-Beret 2001] [Meyer 2002] [Lee 2003] [Deitcher 2006] [Hull 2006] [Romera 2009] [Lee 2015–CATCH] [Amato 2016] **5 control arms of RCT** for LMWH *versus* DOAC [Raskob 2018] [Young 2018] [McBane II 2020] [Agnelli 2020] [Planquette 2021] **11 meta-analyses** [Ioro 2003] [Ferretti 2006] [Louzada 2009] [Akl 2008B] [Akl 2008C] [Noble 2008] [Laporte 2012] [Akl 2014] [Romera-Villegas 2010] [Rojas-Henandez 2017] [Kahale 2018a] **1 prospective study** [Pesavento 2015]
HTA 2: Duration of treatment	**1 specific randomized controlled trial** [Napolitano 2014] **4 control arms of RCT for LMWH versus DOAC** [Raskob 2018] [Young 2018] [McBane II 2020] [Agnelli 2020] **2 prospective studies** [Francis 2015] [Jara-Palomares 2018] **1 retrospective study** [Mahé 2020] **1 systematic review** [Moik 2021]
HTA 3: The DOACs in the treatment of established VTE	**6 randomized studies (4 cancer subgroup analyses)** [Bauersachs 2010/Buller 2012–Prins 2013] [Schulman 2009/2014–Schulman 2015] [Agnelli 2013–Agnelli 2015] [Buller 2013–Raskob 2013] **6 specific randomized controlled trials** [Raskob 2018] [Young 2018] [McBane II 2019] [Agnelli 2020] [Planquette 2021] [Shrag 2021] **1 post-hoc analysis in patients with different type of cancers** [Mudler 2019] **1 subgroup analysis in patients with bleeding** [Ageno 2020] **8 meta-analyses of the cancer subgroup included in RCTs in the general population** [Vedovati 2015] [Vanes 2014] [Vanderhulle 2014] [Larsen 2014] [Carrier 2014] [Posch 2015] [Gomez-Outes 2014] [Brunetti 2017] **17 meta-analyses of studies comparing DOACs vs LMWH in cancer patients** [Li 2018] [Kahale 2018 A] [Ay Ayami 2018] [Xing 2018] [Verdovati 2018] [Moik 2020] [Giustozzi 2020] [Samanayake 2020] [Haykal 2020] [Dong 2021] [Elbadawi 2020] [Camilli 2020] [Mudler 2020] [Sabatino 2020][Desai 2020B] [Yan 2020] [Frere 2021] **1 non-randomized studies** [Wysokinski 2019]

Q2 Early maintenance and long-term (beyond 6 months) treatment of established VTE – CONCLUSIONS

Q2.1: Early maintenance treatment and long-term treatment by use of LMWH

Studies	**8 randomized controlled trials** [Lopez-Beret 2001] [Meyer 2002] [Lee 2003] [Deitcher 2006] [Hull 2006] [Romera 2009] [Lee 2015–CATCH] [Amato 2016] **5 control arms of RCT** for LMWH *versus* DOAC [Raskob 2018] [Young 2018] [McBane II 2020] [Agnelli 2020] [Planquette 2021] **11 meta-analyses**

	[Ioro 2003] [Ferretti 2006] [Louzada 2009] [Akl 2008B] [Akl 2008C] [Noble 2008] [Laporte 2012] [Akl 2014] [Romera-Villegas 2010] [Rojas-Henandez 2017] [Kahale 2018a] **1 prospective study** [Pesavento 2015]
Agreement	Yes, except studies with low number of patients [Deitcher 2006] [Romera 2009] Coherent data for cancer patients (3/5 good-quality trials and meta-analyses)
Quality of evidence	High (randomized, meta-analysis, consistency)
Results	**Meta-analyses** Early maintenance treatment (10 days to 3 months) and long-term treatment by LMWH alone (up to 6 months) *vs.* heparins (UFH/LMWH) with early VKA in cancer patients with VTE decreases the recurrence rate by 50% with no increase in bleeding risk or any effect on the mortality rate. [Kahale 2018a] metanalysis showed that the long-term treatment of VTE by LMWHs in people with cancer compared to VKAs probably produce an important reduction in VTE with no beneficial or harmful effect on major or minor bleeding (including ICH) nor on thrombocytopenia. [Romera-Villegas 2010] Studies using full and moderate doses of LMWH (3-month treatment) showed significantly reduced rates of VTE at 1-year follow-up compared to VKA, whereas low doses did not. Full LMWH treatment doses had similar rates of bleeds as low and moderate doses.

Conclusion

LMWH should be used for a minimum of 6 months to treat established VTE in cancer patients. Four large studies in this setting treated patients for 6 months, the strength of the evidence for treatment up to 6 months is high.

Q2.2: Duration of anticoagulation

Studies	**1 specific randomized controlled trial** [Napolitano 2014] **4 control arms of RCT for LMWH versus DOAC** [Raskob 2018] [Young 2018] [McBane II 2020] [Agnelli 2020] **2 prospective studies** [Francis 2015] [Jara-Palomares 2018] **1 retrospective study** [Mahé 2020] **1 systematic review)** [Moik 2021]
Agreement	Impossible to determine
Quality of evidence	Moderate (one RCT with serious indirectness, 2 observational specific studies with large sample size)
Results	Patients with residual VTE are at higher risk of VTE recurrence compared to patients without residual VTE, regardless of whether they received extended prophylaxis with LMWH or not. LMWH did not significantly reduce the incidence of recurrent VTE during the 6 months of extended anticoagulation among patients with residual VTE at 6 months. [Napolitan 2014] There is no study comparing 3 and 6 months of treatment with LMWH, but four specific RCTs used a 6-month regimen for LMWH (CATCH, SELECT-D, ADAM-VTE, CARAVAGGIO); 1 prospective RCT (HOKUSAI VTE cancer) and 2 prospective observational single arm cohort studies used a 12-months regimen with no increase in major bleeding at 6 and 12 months. **2 prospective studies** [Francis 2015] [Jara-Palomares 2018], **1 retrospective study** [Mahé 2020] and **1 systematic review** [Moik 2021] found that long-term treatment (beyond 6 months up to 12 months) is validated in cancer patients

Conclusion

Early maintenance treatment (up to 6 months) and long-term treatment (beyond 6 months and up to 12 months) by LMWH alone are validated in cancer patients

Q2.3: Treatment and management of acute VTE with DOACs

Studies	**6 randomized studies in the general population (4 cancer subgroup analyses)** [*Bauersachs 2010/Buller 2012*–Prins 2013] [*Schulman 2009/2014*–Schulman 2015] [*Agnelli 2013*–Agnelli 2015] [*Buller 2013*–Raskob 2013] **6 specific randomized controlled trials** [Raskob 2018] [Young 2018] [McBane II 2019] [Agnelli 2020] [Planquette 2021] [Shrag 2021] **1 post-hoc analysis in patients with different type of cancers** [Mudler 2020] **1 subgroup analysis in patients with bleeding** [Ageno 2020] **8 meta-analyses of the cancer subgroup included in RCTs in the general population** [Vedovati 2015] [Vanes 2014] [Vanderhulle 2014] [Larsen 2014] [Carrier 2014] [Posch 2015] [Gomez-Outes 2014] [Brunetti 2017] **17 meta-analyses of studies comparing DOACs vs LMWH in cancer patients**

	[Li 2018] [Kahale 2018 A] [Ay Ayami 2018] [Xing 2018] [Verdovati 2018] [Moik 2020] [Giustozzi 2020] [Samanayake 2020] [Haykal 2020] [Dong 2021] [Elbadawi 2020] [Camilli 2020] [Mudler 2020] [Sabatino 2020][Desai 2020B] [Yan 2020] [Frere 2021] **1 non-randomized studies** [Wysokinski 2019]
Agreement	Yes
Quality of evidence	High
Results	**6 randomized studies in the general population (4 cancer subgroup analyses) + 8 Meta-analyses including+ 1 Network meta-analysis** [Posch 2015] found that DOACs are non-inferior to LMWH/VKA in terms of rate of VTE recurrence with comparable or reduced bleeding rates relative to VKA **6 specific RCT (n=3690 pts) + 16 meta-analyses comparing DOACs for at least 6 months (3 RCT) and up to 12 month (1 RCT) vs LMWH in cancer patients found that l**ong term treatment with DOACs as compared to LMWH up to 6 months is superior [Young 2018] [McBane 2019] or non-inferior [Raskob 2018] [Agnelli 2020] [Shrag 2021] in terms of VTE recurrence rates at 6 months and associated with similar [McBane 2019] [Agnelli 2020] or higher rates of major bleeding [Raskob 2018] or of CRNMB [Young 2018] The CASTA-DIVA study [Planquette 2021] assessed the efficacy of rivaroxaban in cancer patients with VTE compared to dalteparin at 3 months of follow-up. The study did not fulfill the predefined criteria of non-inferiority regarding the rates of VTE, but results were consistent with previous RCT comparing DOACs with LMWHs. There was no difference in major bleeding or CRNMB between the two arms.

Conclusion

In 6 RCTs, DOACs were non-inferior or superior to LMWH in preventing recurrent VTE. Pooled analysis of the 6 RCTs showed no difference in major bleeding but a significant increase in CRNB, which was more evident in subgroup of cancer patients with gastro-intestinal and genitourinary malignancies.

Chapter 3

Q3 Treatment of VTE recurrence in cancer patients under anticoagulation – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Recurrence in patients treated with LMWH VKA or DOAC	**3 specific retrospective studies** [Carrier 2009] [Ihaddadene 2014] [Schulman 2015]
HTA 2: Vena cava filters	**17 retrospective studies** [Cohen 1991] [Calligaro 1991] [Cohen 1992] [Levin 1993] [Hubbard 1994] [Schiff 1994] [Schwarz 1996] [Greenfield 1997] [Ihnat 1998] [Schleich 2001] [Jarrett 2002] [Wallace 2004] [Zerati 2005] [Schunn 2006] [Matsuo 2013] [Abtahian 2014] [Mellado 2016] **2 systematic reviews** [Angel 2011] [Rojas-Hernandez 2018]

The results of the bibliographic search for vena cava filters (VCFs) are also shown in a previous chapter. In these studies, the main indications of insertion of VCFs were recurrence of VTE and contraindication to anticoagulation. In some cases, VCFs were inserted as a primary treatment of VTE.

Treatment of VTE recurrence in cancer patients under anticoagulation – CONCLUSIONS

Q3.1: Patients treated with LMWH, VKA or DOAC

Studies	**3 specific retrospective studies** [Carrier 2009] [Ihaddadene 2014] [Schulman 2015]
Agreement	Not applicable
Quality of evidence	Very low (observational study + very serious indirectness)

Results	In the case of recurrence of VTE, there is only retrospectives studies with three therapeutic options: • in patients treated with VKA: switch from VKA to LMWH • in patients treated with LMWH: increase LMWH The results appear to be similar to those obtained in cancer patients without VTE recurrence

Q3.2: Vena cava filters

Studies	**17 retrospective studies** [Cohen 1991] [Calligaro 1991] [Cohen 1992] [Levin 1993] [Hubbard 1994] [Schiff 1994] [Schwarz 1996] [Greenfield 1997] [Ihnat 1998] [Schleich 2001] [Jarrett 2002] [Wallace 2004] [Zerati 2005] [Schunn 2006] [Matsuo 2013] [Abtahian 2014] [Mellado 2016] **2 systematic reviews** [Angel 2011] [Rojas-Hernandez 2018]
Agreement	Impossible to determine heterogeneity
Quality of evidence	Very low (observational, serious limitations, serious imprecision)
Results	The efficacy of vena cava filters is not proven in cancer patients. Cancer is neither a specific indication nor a special contraindication to vena cava filters

Conclusion

In the case of recurrence of VTE or PE in cancer patients, three therapeutic options have been studied:

1. Increased dose of LMWH in patients treated with LMWH
2. Switch from VKA to LMWH or DOACS in patients treated with VKA
3. Switch from DOACS to LMWH in patients treated with DOACs
4. Vena cava filter insertion

There is no relevant study concerning the use of DOACS in this setting. There is insufficient evidence to determine if one option is superior to the others.

Chapter 4

Q4 Prophylaxis of VTE in surgical cancer patients – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: LMWH or Fondaparinux or UFH vs. placebo or no treatment	**1 randomized controlled study** [Shukla 2008] **3 meta-analyses** [Mismetti 2001] [Einstein 2007] [Guo 2017] **1 systematic review** [Rahn 2011]
HTA 2: LMWH vs. UFH	**2 randomized controlled trials** [Haas 2005] [Kakkar 1997] **5 meta-analyses** [Mismetti 2001] [Akl 2008] [Akl 2014] [Guo 2017] [Insin 2021]
HTA 3: Comparison of drugs	**2 randomized controlled trials** **Fondaparinux vs. dalteparin** [Agnelli 2005] **Nadroparin vs. enoxaparin** [Simonneau 2006] **1 open-label RCT comparing apixaban vs. enoxaparin** [Guntupalli 2020] **1 meta-analysis** [Insin 2021]
HTA 4: Dose of LMWH	**1 randomized controlled trial Dalteparin 2500 IU vs. 5000 IU** [Bergqvist 1995]
HTA 5: Pre-operative thromboprophylaxis	**1 meta-analyses** [Bisch 2021]
HTA 6: Extended duration	**1 retrospective study** [Pariser 2017] **1 prospective study** [Schomburg 2017] **3 randomized controlled trials – not specific to cancer** [Lausen 1998] [Rasmussen 2006] [Bergqvist 2002] **2 randomized controlled trials – cancer patient population** [Kakkar 2010] [Vedovati 2014] **5 meta-analyses**

	[Akl 2008E] [Faragasanu 2016] [Guo 2017] [Felder 2020] [Knoll 2021] **1 systematic review without metanalysis** [Carrier 2018]
HTA 7: Vena cava filters	**1 prospective study** [Matsuo 2013]
HTA 8: External compression devices	**12 randomized controlled trials** [Turpie 1989] [Dickinson 1998] [Maxwell 2001] [Song 2014] [Nagata 2015] [Dong 2018] [Jung 2018] [Hata 2019] [Tanaka2019] [Nagawaka 2020] [Obitsu 2020] [Patel 2020] **1 meta-analysis in neurosurgical patients** [Collen 2008] **1 meta-analysis in gynecological cancer patients undergoing major abdominopelvic surgery** [Insin 2021]

Q4 Prophylaxis of VTE in surgical cancer patients – CONCLUSIONS

Q4.1: LMWH or UFH compared to placebo or no treatment

Studies	**1 randomized controlled study** [Shukla 2008] **3 meta-analyses** [Mismetti 2001] [Einstein 2007] [Guo 2017] **1 systematic review** [Rahn 2011]
Agreement	Yes
Quality of evidence	High (randomized trials, meta-analysis)
Results	In 1 RCT Shukla 2008], there was no difference between LMWH and placebo in the rates of recurrence and bleeding. In meta-analyses (1 conducted in general surgery patients with <10% of cancer patients [Mismetti 2001], and two focusing on patients undergoing gynecologic surgery), LMWH and UFH were superior to placebo or no prophylaxis in preventing postoperative VTE in cancer patients. However, in 2 meta-analyses the rate of any bleeding was higher with LMWH than with placebo or no treatment.

Q4.2: LMWH vs. UFH

Studies	**2 randomized controlled trials** [Haas 2005] [Kakkar 1997] **5 meta-analyses** [Mismetti 2001] [Akl 2008] [Akl 2014] [Guo 2017] [Insin 2021]
Agreement	Yes
Quality of evidence	High (randomized trials, meta-analysis)
Results	In clinical studies, LMWH and UFH showed the same efficacy with a trend towards less bleeding with LMWH. In meta-analyses, UFH given three times a day was as effective as LMWH [Akl 2008D], but LMWH once a day appeared to be superior to UFH twice a day. The rate of bleeding was the same with UFH and LMWH. [Akl 2014] metanalysis was consistent with [Akl 2008] meta-analysis. [Insin 2021] metanalysis in gynecological cancer patients (20 RCTs, 4970 pts) found no difference between LMWH and UFH regarding the rate of VTE and major bleeding

Conclusion

LMWH and UFH are superior to placebo or no prophylaxis in the prevention of postoperative VTE in cancer patients.

- UFH x3/day is as effective as LMWH x1/day
- LMWH x1/day seems superior to UFH x2/day

There are no data to conclude on the superiority of one type of LMWH over another one.

Q4.3: Comparison of drugs

Studies	**2 randomized controlled trials** **Fondaparinux vs. dalteparin** [Agnelli 2005] **Nadroparin vs. enoxaparin** [Simonneau 2006] **1 open-label RCT comparing apixaban vs. enoxaparin** [Guntupalli 2020] **1 meta-analysis**

	[Insin 2021]
Agreement	Not applicable
Quality of evidence	Low (randomized, indirectness for one study, imprecision because of a non-inferiority study with a secondary endpoint)
Results	In one study including two-thirds of cancer patients, fondaparinux compared to dalteparin was associated with less VTE recurrence and with a trend towards an increase in bleeding [Agnelli 2005]. Nadroparin (2850 IU) was at least as effective as enoxaparin (4000 IU) with less major bleeding [Simmoneau 2006] In one RCT [Guntupalli 2020] comparing apixaban to enoxaparin for postoperative thromboprophylaxis in 400 patients with gynecologic cancer (19.3% of benign tumors) there was no statistically significant differences between the apixaban and enoxaparin groups regarding the rates of major bleeding events, clinically relevant nonmajor bleeding events, venous thromboembolic events, and adverse events or quality of life.

Conclusion

There is insufficient evidence to conclude on

- the superiority of fondaparinux over dalteparin (1 study with two-thirds of cancer patients) or of nadroparin over enoxaparin (1 study showing the same rate of venous thromboembolic events but with a difference in the rate of bleeding events),
- the safety of DOACs for postoperative thromboprophylaxis in women undergoing surgery for gynecologic cancer

Q4.4: Dose of LMWH

Studies	**1 randomized controlled trial Dalteparin 2500 IU vs. 5000 IU** [Bergqvist 1995]
Agreement	Not applicable
Quality of evidence	High (one randomized study but with a large effect size)
Results	For prophylaxis a high dose of LMWH is superior to a low dose

Conclusion

One study (1957 patients) with a large effect size showed that a high dosage of LMWH is superior to a low dosage of LMWH in the prevention of VTE in surgical cancer patients.

Q4.5: pre-operative pharmacologic thromboprophylaxis

Studies	**1 meta-analyses** [Bisch 2021]
Agreement	Moderate
Quality of evidence	Low (1 meta-analysis mainly including retrospective studies- serious study limitations)
Results	In one meta-analysis, OR for incidence of post-operative venous thromboembolism was 0.59 (95% CI 0.39-0.89), favoring pre-operative pharmacologic thromboembolism prophylaxis compared with no pre-operative pharmacologic prophylaxis (Q=13.80, I2=20.30).

Conclusion

Preoperative pharmacologic thromboprophylaxis for major gynecologic oncology surgery decreases the risk of VTE by approximately 40% in the peri-operative period.

Q4.6: Extended duration of prophylaxis

Studies	**1 retrospective study** [Pariser 2017] **1 prospective study** [Schomburg 2017] **3 randomized controlled trials – not specific to cancer** [Lausen 1998] [Rasmussen 2006] [Bergqvist 2002]

	2 randomized controlled trials – cancer patient population [Kakkar 2010] [Vedovati 2014] **5 meta-analyses** [Akl 2008E] [Faragasanu 2016] [Guo 2017] [Felder 2020] [Knoll 2021] **1 systematic review without metanalysis** [Carrier 2018]
Agreement	Yes-Despite 2 negative studies (but one was stopped before the calculated number of patients was achieved), 3 RCTS, 1 retrospective study [Pariser 2017], 1 prospective study [Schomburg 2017] and 4 meta-analyses [Faragasanu 2016] [Guo 2017] [Felder 2019] [Knoll 2021] and 1 systematic review without meta-analysis [Carrier 2018] showed a significant decreased in all VTE with extended duration of prophylaxis.
Quality of evidence	Moderate (randomized trials+ meta-analysis)
Results	A trend toward a higher risk of bleeding was reported in one study [Bergqvist 2002]. Two RCTs in cancer patients showed that extended LMWH treatment (28 days *vs.* 8 days) in patients undergoing major abdominal surgery [Kakkar 2010, 1251 patients] or laparoscopic surgery [Vedovati 2014, 225 patients] was associated with a decreased rate of proximal DVT, without increase in the rate of major or minor bleeding. 1 retrospective study [Pariser 2017] reported a significantly lower rate of VTE at 90 days with extended duration of prophylaxis (5% *vs.* 12% p=0.024). 1 prospective study /Schomburg 2017] reported a significantly lower rate of VTE at 90 days with extended duration of prophylaxis (5.06% vs. 17.6%, p=0.021). 4 recent meta-analyses [Faragasanu 2016] [Guo 2017] [Felder 2020] [Knoll 2021]and 1systematic review without meta-analysis [Carrier 2018] showed a significant decreased in all VTE with extended duration of prophylaxis.

Conclusion

- Four weeks of LMWH reduced the rate of postoperative VTE after major laparotomy/laparoscopic surgery in cancer patients.
- The superiority of extended duration of LMWH (4 weeks) can be generalized to all cancer patients undergoing major abdominal or laporoscopy surgery for cancer
- Extended duration of LMWH (4 weeks) should be considered in selected patients without a high risk of bleeding.

Q4.7: Vena cava filters

Studies	**1 prospective study** [Matsuo 2013]
Agreement	Impossible to determine
Quality of evidence	Very low (observational/prospective, one study with limitations)
Results	In 1 prospective study including 274 patients with ovarian cancer undergoing primary cytoreductive surgery, the cumulative risk of metastasis or disease progression was 45.2% in patients with inferior vena cava filter versus 13.6% in patients without filter placement. Median survival in the two groups was 5.7 months in patients with filters and 15.3 months in patients without filters (p<0.001).

Conclusion

Inferior vena cava filter placement in patients with ovarian cancer undergoing primary cytoreductive surgery may be associated with increased risk of distant metastasis and decreased survival.

Q4.8: External compression devices

Studies	**12 randomized controlled trials** [Turpie 1989] [Dickinson 1998] [Maxwell 2001] [Song 2014] [Nagata 2015] [Dong 2018] [Jung 2018] [Hata 2019] [Tanaka2019] [Nagawaka 2020] [Obitsu 2020] [Patel 2020] **1 meta-analysis in neurosurgical patients** [Collen 2008] **1 meta-analysis in gynecological cancer patients undergoing major abdominopelvic surgery** [Insin 2021]
Agreement	Not applicable (different external compression devices were used)
Quality of evidence	Low (randomized but serious study limitations due to the differences in study design, study population and the external compression device used, inconsistency and imprecisions, so move down two grades)
Results	To prevent VTE in major abdominal or pelvic surgery for gynecologic malignancies, ECD and LMWH appeared equivalent. [Song 2014] In 217 patients with confirmed adenocarcinoma undergoing gastrectomy, there was no significant difference in the rate of VTE between IPC alone versus

	IPC+enoxaparin. However, a significant increase in the risk of bleeding was reported for the IPC with enoxaparin treatment arm For prophylaxis after surgery for brain tumors, GCS + IPC had the same efficacy as GCS alone, and both were superior to no prophylaxis In neurosurgical patients, LMWH were superior to ECD despite an increase of minor bleeding but with no increase in intracranial bleeding or in major bleeding 1 RCT in 30 chinese women undergoing major abdominal or pelvic surgery [Nagata 2015] found no significant difference in the rate of VTE between IPC alone *vs.* IPC + enoxaparin 1 RCT in 90 japanese patients undergoing thoracotomy [Dong 2018] found no significant difference in the rate of VTE between IPC alone *vs.* IPC +nadroparin 2850 IU od for 7 days 1 RCT in 682 korean patients with histologically confirmed gastric adenocarcinoma [Jung 2018] found a significant difference in the rate of VTE between IPC alone *vs.* IPC +LMWH 40 mg od 1 RCT [Hata 2019] conducted in 302 japanese patients undergoing laparoscopic surgery for colorectal cancer found no significant difference in the rate of VTE at day 16 with IPC alone *vs.* IPC + Fondaparinux (2.5 mg) given once daily for 4-8 days, or enoxaparin (20 000 IU) given twice daily for 7-14 days. 1 RCT [Tanaka 2019] conducted in 73 japanese patients undergoing esophagectomy found a significant higher rate of VTE at day 14 with IPC alone *vs.* IPC + enoxaparin (20 000 IU) given twice daily 14 days. 1 RCT [Nagawaka 2020] conducted in 116 japanese patients undergoing laparoscopic surgery for colorectal cancer found no significant difference in the rate of VTE at day 28 between IPC alone *vs.* IPC + enoxaparin 20 mg twice daily for 7 days. 1 RCT [Obitsu 2020] conducted in 347 japanese patients undergoing laparoscopic surgery for gastric or colorectal malignancies found no significant difference in the rate of VTE between IPC alone *vs.* IPC + enoxaparin 20 mg twice daily for 7 days. However, an increase in the risk of bleeding was reported for the IPC with enoxaparin treatment arm. 1 RCT [Patell 2020] found no significant difference in the rate of VTE between IPC alone *vs.* IPC + UFH (5000 IU every 8 hours) for 7 days in 500 patients undergoing radical prostatectomy. In 1 network meta-analysis (SUCRA) [Insin 2021], graduated compression stockings LMWH was top-ranked for prevention of composite VTE in gynecological cancer patients undergoing major abdominopelvic surgery.

Conclusion

External compression devices (ECDs) are superior to no prophylaxis, but whether or not they are superior to LMWH may depend on the malignancy and/or type of surgery. There are insufficient data to conclude on the superiority of one type of ECD or one ECD regimen over others.

Chapter 5

Q5 Prophylaxis of VTE in medical cancer patients – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Hospitalized patients	**4 prospective randomized studies – general population (safety and efficacy LMWH, UFH)** [Bergmann 1996] [Harenberg 1996] [Lechler 1996] [Kleber 2003] [Haas 2011] **4 randomized double-blind studies – general population (compared to placebo)** [Dahan 1986] [Samama 1999] [Leizorovicz 2004] [Cohen 2006] [Cohen 2013-MAGELLAN] **1 RCT comparing fixed- to weight-adjusted enoxaparin dose-cancer patients** [Zwicker 2020] **1 meta-analysis (cancer patient subgroups)** [Carrier 2014]
HTA 2: Ambulatory patients treated with chemotherapy	**15 randomized double-blind trials** [Haas 2012] [Agnelli 2009] [Perry 2010-PRODIGE] [Barni 2011-PROTECHT] [Agnelli 2012- SAVE ONCO] [Macbeth 2015-FRAGMATIC] [Haas 2012-TOPIC] [Maraveyas 2012-FRAGEM] [Levine 2012-ADVOCATE] [Pelzer 2015- CONKO 004] [Khorana 2017-PHACS] [Ek 2018-RASTEN] [Meyer 2018-TILT] [Khorana 2019-CASSINI] [Carrier 2019-AVERT] **1 subgroup analyses of a RCT** [Vadhan-Raj 2020] **25 meta-analyses** [Ben-Aharon 2014] [DiNisio 2014] [Phan 2014] [Che 2013] [Akl 2014] [Akl 2014-VKA] [Sanford 2014] [Zhang 2013] [Dinisio 2016] [Tun 2016] [Yu 2016] [Fuentes 2017] [Thein 2017] [Akl 2017] [Kahale 2017] [Li 2019] [Barbarawi 2019] [Becattini 2020] [Thein 2020] [Frere 2020] [Xin 2020] [Schünemann 2020] [Rank 2020] [Rutjes 2020] [Bosch 2020]
HTA 3: Patients treated with Immunomodulatory imide drugs	**2 randomized studies** [Larocca 2012] [Palumbo 2011] **2 retrospective studies** [Zangari 2004] [Ikhlaque 2006]

	1 systematic review [Al-Ani 2016] **3 meta-analyses** [Elaccaoui 2007] [Hicks 2008] [Carrier 2011] **2 prospective studies** [Pegourie 2019] [Cornell 2020]

Q5 Prophylaxis of VTE in medical cancer patients – CONCLUSIONS

Q5.1: Hospitalized cancer patients

Studies	**4 prospective randomized studies – general population (safety and efficacy LMWH, UFH)** [Bergmann 1996] [Harenberg 1996] [Lechler 1996] [Kleber 2003] [Haas 2011] **4 randomized double-blind studies – general population (compared to placebo)** [Dahan 1986] [Samama 1999] [Leizorovicz 2004] [Cohen 2006] [Cohen 2013-MAGELLAN] **1 RCT comparing fixed- to weight-adjusted enoxaparin dose-cancer patients** [Zwicker 2020] **1 meta-analysis (cancer patient subgroups)** [Carrier 2014]
Agreement	Yes
Quality of evidence	General population: moderate (randomized studies but indirectness) Cancer patients: low (only one meta-analysis, small sample size, n=307 and 1 phase 2 RCT, small sample size, n=50)
Results	For primary prophylaxis of VTE in hospitalized medical cancer patients – **general population**: • LMWH and UFH have a similar efficacy and safety • LMWH and fondaparinux are superior to placebo with a non-significant trend towards increased bleeding (except for enoxaparin 40 mg and fondaparinux) • the rate of cancer patients included in these studies varies from 5% to 15% • no study reports a difference of efficacy between cancer and non-cancer patients For primary prophylaxis of VTE in hospitalized medical cancer patients – **cancer patient subgroup analysis (n-307)** • LMWH prophylaxis did not significantly reduce the relative risk of VTE recurrence relative to placebo in hospitalized cancer patients • the rates of major and minor bleeding were not reported according to cancer status in the studies analyzed • In a retrospective propensity-matched comparative-effectiveness cohort study of critically ill cancer patients, LMWH for VTE prophylaxis was not associated with a reduction in the incidence of in-hospital VTE as compared with UFH, but was associated with significant reductions in PE, clinically important bleeding events, and incidence of HIT • In a randomized, double-blinded, phase 2 trial including 50 hospitalized patients with active cancer at high risk of developing VTE based on Padua risk score [Zwicker 2020], no VTE occur in either arm (fixed-dose enoxaparin or weight-adjusted-dose enoxaparin). For primary prophylaxis of VTE in hospitalized medical cancer patients **– with the DOACs specifically, in cancer patient subgroup analysis** • [Cohen 2013-MAGELLAN, 125 patients] Thromboprophylaxis with rivaroxaban tended to be less effective than enoxaparin in cancer patients, but this did not reach significance. Rivaroxaban increased the risk of bleeds in patients with active cancer.

Conclusions

Primary prophylaxis with UFH, LMWH, fondaparinux has been shown to be effective in studies, including hospitalized cancer patients (5% to 15% cancer patients) with reduced mobility. Meta-analysis of cancer patient subgroups suggests that effects may be different in cancer patients overall; no significant difference in VTE recurrence relative to placebo.

Q5.2: Ambulatory patients treated with chemotherapy

Studies	**15 randomized double-blind trials** [Haas 2012] [Agnelli 2009] [Perry 2010-PRODIGE] [Barni 2011-PROTECHT] [Agnelli 2012- SAVE ONCO] [Macbeth 2015-FRAGMATIC] [Haas 2012-TOPIC] [Maraveyas 2012-FRAGEM] [Levine 2012-ADVOCATE] [Pelzer 2015- CONKO 004] [Khorana 2017-PHACS] [Ek 2018-RASTEN] [Meyer 2018-TILT] [Khorana 2019-CASSINI] [Carrier 2019-AVERT] **1 subgroup analyses of a RCT** [Vadhan-Raj 2020]

	25 meta-analyses [Ben-Aharon 2014] [DiNisio 2014] [Phan 2014] [Che 2013] [Akl 2014] [Akl 2014-VKA] [Sanford 2014] [Zhang 2013] [Dinisio 2016] [Tun 2016] [Yu 2016] [Fuentes 2017] [Thein 2017] [Akl 2017] [Kahale 2017] [Li 2019] [Barbarawi 2019] [Becattini 2020] [Thein 2020] [Frere 2020] [Xin 2020] [Schünemann 2020] [Rank 2020] [Rutjes 2020] [Bosch 2020]
Agreement	Results depend on the type of cancer
Quality of evidence	Moderate in unselected cancer patients; Strong in pancreatic and lung cancer patient studies
Results	• VKA: [Kahale 2017] updated meta-analysis from the previous [Akl 2014]–compared safety and efficacy of VKA *vs.* placebo which showed no effect on mortality at 6 months, 1, 2 and 5 years. One study (n=315 participants) showed low certainty evidence for a decrease in symptomatic VTE and very low certainty evidence for a decrease in PE with VKA, but VKA produced significant increase in the rate of major bleeding and minor bleeding • Primary prophylaxis with anticoagulants in cancer patients treated with chemotherapy decreased the risk of VTE by ~35% without excess of bleeding [Beccatini 2020] • Primary prophylaxis with LMWH in cancer patients treated with chemotherapy did not decrease the rate of mortality [Schünemann 2020] • Patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy: primary prophylaxis with LMWH [Marayevas 2012] [Pelzer 2015] or rivaroxaban [Vadhan-Raj 2020] decreases the rate of VTE without an excess of bleeding. [Frere 2020] meta-analysis of 5 RCTs found a crude VTE incidence of 3.8% and 11.2% in LMWH and in control groups, respectively (risk ratio, 0.18; 95% CI, 0.083-0.39; P < 0.0001) with no significant difference in the rate of major bleedings across groups. • Patients with lung cancer treated with chemotherapy: In the RASTEN trial [Ek 2018], LMWH did not increase overall survival in patients with SCLC. Risk of VTE was decreased from 8.4% to 2.7% with LMWH with an increase in pulmonary bleeding and other sites in the LMWH treatment arm. In the TILT trial [Meyer 2018], LMWH did not increase overall survival in patients with NSCLC. Risk of VTE was not decreased with LMWH compared to control arm (no treatment). Four recent meta-analysis [Fuentes 2017] [Thein 2017] [Thein 2020] [Schünemann 2020] found no significant improvement in overall survival in lung cancer patients receiving LMWH. Primary VTE prophylaxis with LMWH reduced the occurrence of VTE (small but significant improvement) among ambulatory patients with lung cancer without increased bleeding in two meta-analysis [Fuentes 2017] [Schünemann 2020] and with an increase in bleeding in one meta-analysis [Thein 2017] • Patients with metastatic breast cancer: primary prophylaxis with LMWH has no effect on VTE in patients with metastatic breast cancer [Haas 2012-TOPIC] • Patients with brain cancer (see special situations): [Perry 2010-PRODIGE] did not report a significant reduction in VTE occurrence, or improvement in mortality rate. LMWH was not associated with an increase in major bleeding, but the 95% CI was very wide (HR 4.2, 95% CI 0.48 -36; p=0.22). • [Khorana 2019-CASSINI] randomized 841 ambulatory cancer patients initiating a systematic chemotherapy and at intermediate-high risk of VTE (defined as Khorana score ≥2) to rivaroxaban 10 mg once daily or placebo for 6 months. Rivaroxaban reduced the rate of VTE during the on-treatment period (2.63% *vs*. 6.41%; p=0.007) without further increase in major and clinically relevant non-major bleeding (p=0.265 and p=0.53, respectively). • [Carrier 2019-AVERT] randomized 574 ambulatory cancer patients initiating a systematic chemotherapy and at intermediate-high risk of VTE (defined as Khorana score ≥2) to apixaban 2.5 mg twice daily or placebo for 6 months. Apixaban reduced the rate of VTE (4.3% *vs*. 10.2%, p<0.001) with a further increase in major bleeding (3.5% *vs*. 1.8%, p=0.046) • 5 meta-analyses compared the safety and efficacy of DOACs *vs.* placebo and found that DOACs reduced the rate of VTE without excess of major bleeding in intermediate to high-risk patients (defined as Khorana score ≥2) [Li 2019] [Barbarawi 2019] [Beccatini 2020] [Xin 2020] [Bosch 2020]

Conclusions

- VKA prophylaxis in ambulatory cancer patients receiving chemotherapy does not appear to reduce the risk of VTE, but significantly increases the risk of bleeding.
- LMWH prophylaxis (at subtherapeutic dosages) have a benefit in patients with locally advanced or metastatic pancreatic or locally advanced or metastatic lung cancers, has no effect on VTE in patients with metastatic breast cancer and may increase the risk of bleeding particularly in the presence of thrombocytopenia and in patients with brain tumor.
- Parenteral prophylaxis in ambulatory cancer patients receiving chemotherapy has robust effects on the risk of VTE. Broad confidence intervals are observed around these estimates, suggesting considerable variability in bleeding risk among the study populations (various cancer types, cancer treatments, and patient characteristics).

- New DOACs RCTs and meta-analyses of DOACs *vs* placebo: the CASSINI [Khorana 2019] and AVERT [Carrier 2019] trials and meta-analyses of DOACs *vs* placebo 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 (Khorana score≥ 2) initiating chemotherapy.
- Patients undergoing chemotherapy regimens with gemcitabine, platinum analogues, or their combination are at higher risk of VTE. The clinical benefits of LMWH thromboprophylaxis in these patients may outweigh the risk.

Q5.3: Patients treated with Immunomodulatory imide drugs

Studies	**2 randomized studies** [Larocca 2012] [Palumbo 2011] **2 retrospective studies** [Zangari 2004] [Ikhlaque 2006] **1 systematic review** [Al-Ani 2016] **3 meta-analyses** [Elaccaoui 2007] [Hicks 2008] [Carrier 2011] **2 prospective studies** [Pegourie 2019] [Cornell 2020]
Agreement	Yes
Quality of evidence	Low (one randomized study with serious limitations and imprecision; meta-analyses did not take into account this study)
Results	Prophylactic doses of LMWH or aspirin (100 mg/day) or warfarin to maintain INR within the therapeutic range reduced the risk of thromboembolic events among multiple myeloma patients treated with lenalidomide or thalidomide with no increase in bleeding risk Prophylactic doses of apixaban (2.5 mg twice daily) prevent thromboembolic events among multiple myeloma patients treated with lenalidomide or thalidomide with no increase in bleeding risk [Pegourie 2020] [Cornell 2020].

Conclusions

2 retrospective studies investigating the risks and benefits of VTE prophylaxis in cancer patients treated with thalidomide [Zangari 2004] [Ikhlaque 2006], 2 prospective randomized studies comparing aspirin, LMWH and warfarin for VTE prophylaxis in patients with myeloma [Larocca 2012] [Palumbo 2011], 1 systematic review comparing the efficacy of aspirin or LMWH prophylaxis in myeloma patients using lenalidomide based therapy [Al Ani 2016], 3 meta-analyses of anticoagulation prophylaxis in myeloma patients [Elaccaoui 2007] [Hicks 2008] [Carrier 2011] and 2 prospective non-randomized studies comparing the safety and efficacy of apixaban for VTE prophylaxis in myeloma patients receiving thalidomide/lenalidomide [Pegourie 2020] [Cornell 2020] found that :

- The rate of VTE occurrence is very high in patients treated with IMiDs (thalidomide and lenalidomide) combined with steroids and/or chemotherapy (doxorubicin).
- Prophylactic doses of LMWH, aspirin (100 mg/day), warfarin or apixaban (2.5 mg twice daily) decreases the risk of VTE in multiple myeloma patients treated with lenalidomide or thalidomide, without increasing the incidence of bleeding complications.
- Notably, none of the studies included a placebo group.

Chapter 6

Q6 Treatment of established catheter-related thrombosis – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Treatment of CVC thrombosis: LMWH, VKA (*includes drug comparison*), DOACs	**3 prospective non-randomized studies** [Savage 1999] [Kovacs 2007] [Davies 2018] **3 retrospective studies** [Tran 2010] [Delluc 2015] [Oliver 2015] **1 meta-analysis** [Akl 2014]
HTA 3: Treatment of CVC thrombosis: thrombolytic therapy	**2 retrospective studies** [Pucheu 1996] [Schindler 1999]
HTA 2: Treatment of CVC thrombosis: CVC removal	**1 retrospective study** [Frank 2000]

Q6 Treatment of established catheter-related thrombosis – CONCLUSIONS

Q6.1: LMWH, VKA, DOACs

Studies	**3 prospective non-randomized studies** [Savage 1999] [Kovacs 2007] [Davies 2018] **3 retrospective studies** [Tran 2010] [Delluc 2015] [Oliver 2015] **2 prospective non-randomized studies** [Savage 1999] [Kovacs 2007] **3 retrospective study** [Tran 2010] [Delluc 2015] [Oliver 2015] **1 meta-analysis** [Akl 2014]
Agreement	Not applicable, poor quality (39, 46, 64 patients; new studies 99 and 21 patients)
Quality of evidence	Very low (observational studies, serious limitations, serious imprecision)
Results	[Delluc 2015] (99 patients) The majority of patients (73%) were treated with full-dose LMWH for 1 month, followed by an intermediate dose. The rate of VTE recurrence was 0% in this treatment group; 11% of patients received a preventative dose of LMWH. In this group, the rate of VTE recurrence was 15.4% [Oliver 2015] (21 patients) No difference in the rate of VTE resolution between no anticoagulation, high-, low-dose enoxaparin. The rate of morality was 33% in the anticoagulant treatment group, compared to 71% in the no anticoagulant treatment group. HR remained <1 after adjustments for leukemia type and cytogenetics [Akl 2014] Heparin associated with reduction in symptomatic DVT. No differences in major bleeding, minor bleeding, mortality, or thrombocytopenia. Same profile reported for VKA, but quality of evidence was ranked as low [Davies 2018] assessed rivaroxaban monotherapy for preservation of line function and safety outcomes of VTE recurrence, bleeding risk and death in 47 women with cancer who develop upper extremity deep vein thrombosis (UEDVT) due to CVC. Preservation of line function was 100% at 12 weeks. The risk of recurrent VTE at 12 weeks was 1.43%, with one episode of fatal PE. 9 patients (12.9%) experienced 11 total bleeding episodes.

Conclusion

There are insufficient data to determine the efficacy and tolerance of LMWH, VKA and DOACS for treating CVC-VTE.

Q6.2: Catheter removal

Studies	**1 retrospective study** [Frank 2000]
Agreement	Not applicable
Quality of evidence	Very low (observational study, serious limitations)

Results	There are insufficient data to conclude on the efficacy and tolerance of CVC withdrawal for treating CVC-VTE. There are no data on the optimal timing between withdrawal and the initiation of anticoagulant therapy

Q6.3: Thrombolytics

Studies	**2 retrospective studies** [Pucheu 1996] [Schindler 1999]
Agreement	Yes
Quality of evidence	Very low (observational studies, serious limitations, very serious imprecision)
Results	There are insufficient data to determine the efficacy and tolerance of systemic or localized thrombolytic therapy for treatment of CVC-VTE. Nonetheless, thrombolysis can be used even with intensive chemotherapy.

Conclusions

There is no evidence in cancer patients with catheter-related thrombosis to support:

- the withdrawal of a non-infected, functioning, well-positioned CVC
- the use of LMWH + VKA or long-term LMWH or DOACs
- thrombolytic therapy via the catheter or systemic thrombolysis

Chapter 7

Q7 Prophylaxis of catheter-related thrombosis – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
Safety and efficacy of different anticoagulants in CVC-related VTE treatment:	
HTA 1: VKA	**6 randomized controlled trials** [Bern 1990] [Couban 2005] [Heaton 2002] [Ruud 2006] [Young 2009] [Decicco 2009] **7 meta-analyses** [Carrier 2007] [Akl 2007] [Rawson 2007] [Kirkpatrick 2007] [Chaukiyal 2008] [Akl 2008f] [Kahale 2018b]
HTA 2: UFH	**1 randomized study** [Abdelkefi 2004]
HTA 3: LMWH	**6 randomized trials** [Monreal 1996] [Mismetti 2003] [Verso 2005] [Karthaus 2006] [Niers 2007] [Decicco 2009] **8 meta-analyses** [Carrier 2007] [Akl 2007] [Rawson 2007] [Kirkpatrick 2007] [Chaukiyal 2008] [Schoot 2013] [Kahale 2018b]
HTA 4: DOAC	**1 randomized trial** **[Ikesaka 2021]**
HTA 5: Drug comparison	**1 randomized study** [Lavau-Denes 2013] **1 meta-analyses** [Kahale 2018b] **1 prospective non-randomized trial** [Lv 2019]
HTA 6: Thrombolytics	**1 non-randomized prospective study** [Kalmanti 2002] **1 randomized double-blind study** [van Rooden 2008]
HTA 7: Type of CVC and insertion techniques	**4 meta-analysis** [Saber 2010] [Chopra 2013] [Lv 2018] [Liu 2020] **5 randomized trials** [Biffi 2001] [Carlo 2004] [Biffi 2009] [Picardi 2019] [Taxbro 2019] **4 prospective non-randomized trials** [Labourey 2004] [Lee 2006] [Luciani 2001] [Nightingale 1997] **6 retrospective studies** [Eastridge 1995] [Craft 1996] [Cadman 2004] [Caers 2005] [Morazin 2005] [Mclean 2005]

Q7 Prophylaxis of catheter-related thrombosis – CONCLUSIONS

Q7.1: VKA

Studies	**6 randomized controlled trials** [Bern 1990] [Couban 2005] [Heaton 2002] [Ruud 2006] [Young 2009] [Decicco 2009] **7 meta-analyses** [Carrier 2007] [Akl 2007] [Rawson 2007] [Kirkpatrick 2007] [Chaukiyal 2008] [Akl 2008f] [Kahale 2018b]
Agreement	Yes 4 randomized trials in agreement 4 meta-analyses in agreement
Quality of evidence	High
Results	**VKA low dose** In the RCTs: similar CRT rate with and without VKA prevention (5% symptomatic CRT) One positive study on asymptomatic CRT with VKA started before CVC insertion [Decicco 2009] The most recent meta-analysis [Kahale 2018b] 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, premature catheter removal and catheter-related infection **Low-intensity VKA (INR 1.5 to 2)** One randomized study (1570 patients included and evaluated) showing a decrease of symptomatic CRT with an increased risk of bleeding [Young 2009]

Q7.2: UFH

Studies	**1 randomized study** [Abdelkefi 2004]
Agreement	Not applicable
Quality of evidence	Moderate (randomized, serious study limitation)
Results	Continuous intravenous infusion of UFH may decrease the incidence of symptomatic and asymptomatic CRT as diagnosed by Doppler US in bone marrow transplant recipients (adults and children)

Q7.3: LMWH

Studies	**6 randomized trials** [Monreal 1996] [Mismetti 2003] [Verso 2005] [Karthaus 2006] [Niers 2007] [Decicco 2009] **8 meta-analyses** [Carrier 2007] [Akl 2007] [Rawson 2007] [Kirkpatrick 2007] [Chaukiyal 2008] [Schoot 2013] [Kahale 2018b]
Agreement	Yes
Quality of evidence	High
Results	The randomized trials showed no excess in major bleeding, but no benefit in preventing symptomatic VTE in the superior vena cava. Meta-analyses indicated a trend towards reduction of asymptomatic CRT or all CRT (asymptomatic and symptomatic) using different comparisons (VKA + LMWH vs. no treatment) The most recent meta-analysis [Kahale 2018b] found moderate-certainty evidence that LMWH reduced catheter-related thrombosis compared to no LMWH (risk ratio 0.43, 95% CI 0.22-0.81) without increase in major or minor bleedings.

Q7.4: DOAC

Studies	**1 randomized trial** [Ikesaka 2021]
Agreement	Impossible to determine
Quality of evidence	Low
Results	[Ikesaka 2021] pilot study enrolled 105 patients with active cancer and a newly inserted CVC to receive rivaroxaban 10 mg daily for 90 days or standard of care. Overall, thrombotic complications occurred in 3 patients in the rivaroxaban group (5.8%) compared with 5 patients in the control group (9.4; HR, 0.58; 95% CI 0.14-2.5). Major VTE occurred in 2 (3.9%) and 3 (5.7%) patients in the rivaroxaban and control group, respectively (HR, 0.66; 95% CI, 0.11-3.9).

Q7.5: **Drug comparison**

Studies	**1 randomized study** [Lavau-Denes 2013] **1 meta-analysis** [Kahale 2018b] **1 prospective non-randomized trial** [Lv 2019]
Agreement	Yes
Quality of evidence	Low
Results	[Lavau-Denes 2013] (420 patients) 3-month anticoagulant treatment period in patients on chemotherapy. LMWH and warfarin produced comparable reductions in catheter-related and non-related DVT. No increase overall increase in bleeding rate, results pooled for all drug types. A recent meta-analysis [Kahale 2018b] did not confirm or exclude a beneficial or detrimental effect of LMWH relative to VKA on mortality, symptomatic catheter related VTE, PE, major bleeding, or minor bleeding. The meta-analyses showed that LMWH probably increased the risk of thrombocytopenia compared to VKA at three months of follow-up (RR 1.69, 95% CI 1.20- 2.39). [Lv 2019] compared prophylaxis with rivaroxaban or LMWH to no prophylaxis in 423 adult cancer patients with PICC. The rates of PICC-related upper extremity venous thrombosis were significantly lower in the rivaroxaban group (3.76%) and in the LMWH group (3.03%) compared to the no prophylaxis group (12.4%).

Q7.6: **Thrombolytics**

Studies	**1 non-randomized prospective study** [Kalmanti 2002] **1 randomized double-blind study** [van Rooden 2008]
Agreement	Yes
Quality of evidence	Low (only one randomized study, but limitations as one study included few patients and one study evaluated CRT as a secondary endpoint, inconsistency)
Results	Neither study supported the use of fibrinolysis to prevent CRT in cancer patients

Conclusions

For the prevention of CRT, when compared to no prophylaxis, there is no evidence to support:

- the routine use of low dose of VKA (warfarin 1 mg)
- the routine use of VKA to maintain an INR between 1.5 and 2
- the routine use of DOACs
- the use of continuous IV UFH or fibrinolytics

More studies are required to analyze the effect of routine use of LMWH or DOAC.

Q7.8: **Type of CVC and insertion techniques**

Studies	**4 meta-analysis** [Saber 2010] [Chopra 2013] [Lv 2018] [Liu 2020] **5 randomized trials** [Biffi 2001] [Carlo 2004] [Biffi 2009] [Picardi 2019] [Taxbro 2019] **4 prospective non-randomized trials** [Labourey 2004] [Lee 2006] [Luciani 2001] [Nightingale 1997] **6 retrospective studies** [Eastridge 1995] [Craft 1996] [Cadman 2004] [Caers 2005] [Morazin 2005] [Mclean 2005]
Agreement	Yes
Quality of evidence	High (meta-analysis + consistency except in 1 RCT [Picardi 2019] in AML)
Results	Independent risk factors for CRT include: • Catheter tip location: SVC-RA junction or RA • Insertion site: jugular vein better than subclavian, right side better than left side • Type of catheter: valved tips = open-ended tips, implanted ports better than external catheter • Past medical history of CVC • Doppler US guidance: no data [Chopra 2013] PICCs are associated with a higher risk of DVT than are central venous catheters, especially in critically ill patients or those with cancer.

	[Lv 2018] PICCs were associated with a higher risk of deep vein thrombosis, when compared with CICCs. In [Taxbro 2019] RCT, PICCs were associated with a higher risk of deep vein thrombosis, when compared with CICCs. In [Picardi 2019] RCT, PICCs were associated with a lower risk of deep vein thrombosis, when compared with CICCs, in AML patients In [Liu 2020] meta-analysis, arm port were associated with a higher risk of thrombosis rates compared with chest port according to the results of comparative studies (RR 2.23,95% CI 1.04-4.79, p=0.041) as well as pooled comparative and single-arm studies (RR 1.21, 95% CI 1.02-1.43, p=0.029).

Conclusion

The catheter should be located:

- at the SVC-RA junction
- in the jugular vein rather than the subclavian vein

Implanted ports are better than a SC catheter. There is no evidence to support the use of Doppler US guidance to prevent CRT.

Chapter 8

Q8 Special situations – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Treatment and prophylaxis of established VTE in patients with a brain tumor	**9 non-randomized studies** [Schmidt 2002] [Altschuler 1990] [Levin 1993] [Schiff 1994] [Chai-Adisaksopha 2017] [Carney 2019] [Carney 2020] [Swartz 2021] [Wood 2021] [Jo 2021] [Lee 2021] **3 meta-analyses** [Simonetti 2014] [Zwicker 2016] [Porfidia 2020] **1 double-blind randomized trial** [**Perry 2010**-PRODIGE]
HTA 2: Prophylaxis of VTE in cancer patients undergoing neurosurgery	**5 prospective randomized studies** [Turpie 1989] [Cerrato 1978] [Constantini 2001] [Dickinson 1998] [Macdonald 2003] **4 randomized double-blind studies** [Melon 1991] [Nurmohamed 1996] [Agnelli 1998] [Goldhaber 2002] **4 meta-analyses** [Ioro 2001] [Collen 2008] [Salmaggi 2013] [Alsheri 2016]
HTA 3: Treatment and prophylaxis of VTE in cancer patients with thrombocytopenia	**2 prospective studies** [Babilonia 2014] [Falvo 2011] [Carney 2021] **3 retrospective studies** [Kopolovic 2015] [Khanal 2016] [Lecumberri 2020] **1 systematic review** [Samuelson Bannow 2018]
HTA 4: Treatment and prophylaxis of VTE in cancer patients with renal failure	**1 prospective study** [Kooiman 2013] **Analysis of the subgroup of cancer patient with renal failure Included in 2 randomized studies** [Woodruf 2016] [Bauersachs 2018]
HTA 5: Gender differences	**2 prospective studies** [Martin-Martos 2015]
HTA 6: Children with acute lymphocytic leukemia (ALL)	**1 prospective non-randomized study during two periods** [Meister 2008] **2 RCT** [Mitchel 2003] [Greiner 2019] **1 meta-analysis** [Pelland-Marcotte 2019] **1 prospective non-randomized study comparing PICCs *vs* CICCs** [Jaffrey 2020] **1 retrospective predefined analysis of the CVC VTE cohort of the EINSTEIN Jr RCT** [Thom 2020]

Q8 Special situations – CONCLUSIONS

Q8.1: Treatment and prophylaxis of established VTE in patients with a brain tumor

Studies	**9 non-randomized studies** [Schmidt 2002] [Altschuler 1990] [Levin 1993] [Schiff 1994] [Chai-Adisaksopha 2017] [Carney 2019] [Carney 2020] [Swartz 2021] [Wood 2021] [Jo 2021] [Lee 2021] **3 meta-analyses** [Simonetti 2014] [Zwicker 2016] [Porfidia 2020] **1 double-blind randomized trial** [Perry 2010-PRODIGE]
Agreement	Yes
Quality of evidence	Low (1 RCT, observational, but consistent)
Results	Treatment: In patients with brain tumors, treatment of VTE with use of anticoagulation yield the same rate of VTE recurrence (0% to 12%) and bleeding (intracerebral bleeding 0% to 7%) as in other cancer patients without brain tumors. [Simonetti 2014] meta-analysis reported that the rate of VTE was not significantly different across cancer treatments (p=0.091). The incidence of severe central nervous system (CNS) bleeding increased considerably with anticoagulant administration (0.6% vs. 8.2%, p<0.001). [Chai-Adisaksopha 2017] compared the rates of recurrent VTE and major bleeding in patients with cancer-associated VTE in the setting of primary or metastatic brain tumours and those without known brain tumours. The rate of recurrent VTE was not significantly different in patients with primary or metastatic brain tumours (11 per 100 patient-years, 95 % CI; 6.7–17.9) and in those without (13.5 per 100 patient-years, 95 % CI; 9.3–19.7) with higher rates of intracranial bleeds in patients with brain tumours compared to those without known brain tumours (4.4 % vs 0 %, p=0.004).) [Zwicker 2016] meta-analysis in patients with brain tumors receiving or not receiving therapeutic anticoagulation reported a 2.13 (95% CI, 1.00–4.56) OR for intracranial hemorrhage (ICH). In studies evaluating anticoagulation in patients with brain metastases, there was no apparent increased risk of ICH (OR, 1.07; 95% CI, 0.61–1.88%). In patients with glioma there was an increase in risk of ICH associated with the administration of anticoagulation (OR, 3.75; 95% CI, 1.42–9.95). [Carney 2019] conducted a retrospective cohort in 172 patients with brain tumors and VTE. In the primary brain tumor cohort (n = 67), the cumulative incidence of any ICH was 0% in patients receiving DOACs *vs.* 36.8% (95% CI 22.3–51.3%) in those treated with LMWH. In the brain metastases cohort (n = 105), the cumulative incidence of any ICH was 27.8% (95% CI 5.5–56.7%) in patients receiving DOACs vs. 52.9% (95% CI 37.4–66.2%) in those treated with LMWH. [Carney 2020] conducted a retrospective cohort in 79 patients who developed ICH on anticoagulation for VTE. The cumulative incidence of recurrent VTE was significantly lower in the restart cohort compared to patients who did not restart anticoagulation (8.1% vs 35.3%; P = .003) [Swartz2021] conducted a retrospective cohort in 125 patients with primary or metastatic brain tumors treated with anticoagulants (52 DOAC, 57 LMWH). The rate of major bleeding was 26% in the LMWH group versus 9.6% in the DOAC group (p = 0.03). The rate of ICH was 15% in the LMWH group versus 5.8% in the DOAC group (p = 0.09). The rates of minor bleeding and recurrent thrombosis were low in both groups. [Wood 2021] performed a matched, retrospective cohort study of 291 patients (100 receiving therapeutic anticoagulation vs 191 controls) with brain metastases. Anticoagulation was associated with clinically significant ICH (HR 1.31, 95% CI 0.96-1.79, p=0.09) in patients with brain metastases, especially those with melanoma or prior ICH. [Jo 2021] et al. performed a retrospective matched, cohort study of 220 patients with high-grade glioma (88 receiving therapeutic anticoagulation for VTE, 22 receiving no anticoagulation for VTE and 110 controls). No significant difference was observed in the 1-year CI of ICH in the LMWH cohort and the no anticoagulation group (17% vs 9%; Gray's test, p =0 .36). [Lee 2021] et al. performed a retrospective cohort study of 111 patients with primary brain tumors or secondary brain metastases. There were no significant differences in bleeding or recurrent VTE events between DOACs and LMWH groups. Porfidia 2020] meta-analysis in patients with glioma receiving or not receiving therapeutic anticoagulation reported a 3.66 (95% CI, 1.84-7.29) OR for ICH. Prophylaxis: [Perry 2010-PRODIGE] did not report a significant reduction in VTE occurrence, or improvement in mortality rate. LMWH was not associated with an increase in major bleeding, but the 95% CI was very wide (HR 4.2, 95% CI 0.48 -36; p=0.22).

Conclusion

The efficacy of anticoagulation for established VTE is similar in patients with and without brain tumors, however patients with brain tumor receiving therapeutic anticoagulation have an increased risk of ICH. VTE prophylaxis in patients with brain tumors may increase the risk of severe central nervous system bleeding.

In retrospective studies, DOACs did not increase the risk of ICH compared to LMWHs.

Q8.2: Prophylaxis of VTE in cancer patients undergoing neurosurgery: heparins

Studies	**5 prospective randomized studies** [Turpie 1989] [Cerrato 1978] [Constantini 2001] [Dickinson 1998] [Macdonald 2003] **4 randomized double-blind studies** [Melon 1991] [Nurmohamed 1996] [Agnelli 1998] [Goldhaber 2002] **4 meta-analyses** [Ioro 2001] [Collen 2008] [Salmaggi 2013] [Alsheri 2016]
Agreement	Yes
Quality of evidence	High
Results	For VTE prophylaxis after surgery for brain or spinal tumors in cancer patients: • LMWH and UFH (5000 IU sc/12 h) are associated with the same rates of VTE and bleeding and lead to a 50% reduction in the risk of VTE without an excess of major bleeding but with a two-fold higher rate of minor bleeding • GCS + IPC have the same efficacy as GCS alone • The reduction of VTE with ECD is about 60% when compared to no prophylaxis • LMWH are superior to ECD with a reduction of VTE from 20% to 40%, and an increase of minor bleeding (relative risk: 2), with no increase in intracranial bleeding or major bleeding [Collen 2008] • Consistent with previous studies, [Salmaggi 2013] reported that mechanical prophylaxis reduced the rate of VTE without increasing risk of bleeding. Concomitant use of intermittent pneumatic compression devices and LMWH significantly further reduced the rate of VTE compared to the use mechanical compression. Addition of LMWH was associated with a non-significant increase in major bleeding • [Alsheri 2016] found a significant VTE risk reduction among brain tumor patients receiving prophylaxis 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 as compared to mechanical prophylaxis alone (0.61; 95 % CI: 0.46–0.82).

Conclusion

LMWH and UFH *have a similar efficacy and safety* (in terms of major bleeding and intracranial bleeding) and are superior to no treatment. In this setting, pharmacological prophylaxis should be started postoperatively. After surgery for brain or spinal tumors, adding LMWH to an intermittent compression device increases the risk of minor bleeding but not the risk of major or intracranial bleeding.

Q8.3: Treatment and prophylaxis of VTE in cancer patients with thrombocytopenia

Studies	**3 prospective studies** [Babilonia 2014] [Falvo 2011] [Carney 2021] **3 retrospective studies** [Kopolovic 2015] [Khanal 2016] [Lecumberri 2020] **1 systematic review** [Samuelson Bannow 2018]
Agreement	Impossible to determine (different study designs)
Quality of evidence	Low
Results	**[**Babilonia 2014] (93 cancer patients) assessed the safety and efficacy of LMWH administered at a lower dose (dalteparin 100 IU/Kg od for 6 months) for cancer patients with thrombocytopenia (platelet 20.10^9/L<count<50.10^9/L) compared to LMWH administered at the standard dose (dalteparin 200IU/Kg for 1 month followed by 150 U/kg for 5 months) in cancer patients with mild to no thrombocytopenia. The rate of failure to attain clot resolution or to prevent a new or recurrent VTE and the overall the rate of bleeding complications did not differ between the two groups. [Falvo 2011] assessed whether LMWH or UFH conferred a higher risk of developing thrombocytopenia (24 401 LMWH/25 153 UFH) 6 months after starting LMWH or UFH. The incidence of thrombocytopenia was significantly greater with LMWH vs. UFH. [Carney 2021] assessed the safety and efficacy of no anticoagulation, modified-dose anticoagulation an full-dose anticoagulation in cancer patients with CAT and thrombocytopenia (platelet count<100.10^9/L). modified-dose anticoagulation was associated with a lower rate of major hemorrhage and no recurrent VTE. [Kopolovic 2015] 74 patients with inoperable, advanced pancreatic cancer receiving first-line chemotherapy received either 1) no anticoagulant treatment (group A); 2) anticoagulation at standard doses (group B); or 3) partial anticoagulation (group C). Standard anticoagulant treatment at the full dose significantly reduced the rate of VTE. Treatment did not affect the rate of bleeding complications. [Khanal 2016] compared the outcomes of 47 patients with thrombocytopenia (platelets <50×10^9/L) and 81 patients without thrombocytopenia receiving anticoagulation for cancer-associated thrombosis. 14/47 patients with thrombocytopenia received therapeutic anticoagulation with LMWH and 22/47 received dose-modified LMWH (enoxaparin 40 mg daily during the period of significant thrombocytopenia). 4/14 patients receiving therapeutic anticoagulation and 3/22 patients receiving

	dose-modified LMWH had a recurrent VTE. 4/14 patients receiving therapeutic anticoagulation and 1/22 patients receiving dose-modified LMWH had a clinically significant bleeding. 1 systematic review [Samuelson Bannow 2018] highlighted a higher risk of recurrent VTE. in cancer patient with thrombocytopenia but available data do not support one management strategy over another to treat cancer-associated thrombosis in patients with thrombocytopenia. 1 retrospective analysis of 15337 cancer patients included in RIETE [Lecumberri 2020] found that patients with severe thrombocytopenia (n=166) had a similar risk for major bleeding at 10 days (OR 0.84; 95%CI 0.20–3.49) and at 30 days (OR 0.90; 95%CI 0.32–2.49) than patients with a normal platelet count.

Q8.4: Treatment and prophylaxis of VTE in cancer patients with renal failure

Studies	**1 prospective study** [Kooiman 2013] **Analysis of the subgroup of cancer patient with renal failure Included in 2 randomized studies** [Woodruf 2016] [Bauersachs 2018]
Agreement	Impossible to determine
Quality of evidence	Low
Results	[Woodruf 2016] conducted a post hoc analysis using data from the CLOT study to compare the efficacy and safety of dalteparin *vs*. VKA for prevention of recurrent VTE in patients with cancer and renal impairment (CrCl<60 ml/min, n=162/676). Compared to VKA, dalteparin significantly reduced the risk of recurrent VTE in patients with cancer and renal impairment (p = 0.01) with a comparable safety profile. [Bauersachs 2018] conducted a secondary analysis using data from the CATCH study to assess the impact of renal impairment (GFR-MDR<60 ml/min/1.73m², n=131/864) on the efficacy and the safety (with respect to bleeding and mortality) of anticoagulation. Patients with cancer-associated thrombosis and renal impairment had a statistically significant increase in recurrent VTE and major bleeding compared to patients with, but no significant increase in CRB or mortality. No differences were observed between long-term tinzaparin therapy and warfarin.

Q8.5: Gender differences

Studies	**2 prospective studies** [Martin-Martos 2015] [Martin-Martos 2017]
Agreement	Impossible to determine
Quality of evidence	Low
Results	In [Martin-Martos 2017], the RIETE database was used compare the rate of VTE recurrences, major bleeding and mortality in patients with lung, colorectal, pancreatic, hematologic or gastric cancer during the course of anticoagulation, according to gender (2005 female/3130 male). Women with VTE and lung, colorectal, pancreatic, haematological or gastric cancer experienced a similar rate of VTE recurrences, major bleeding or death during the course of anticoagulant therapy than men with similar cancers

Q8.6: Children

Studies	**1 prospective non-randomized study during two periods** [Meister 2008] **2 RCT** [Mitchel 2003] [Greiner 2019] **1 meta-analysis** [Pelland-Marcotte 2019] **1 prospective non-randomized study comparing PICCs *vs* CICCs** [Jaffrey 2020] **1 retrospective predefined analysis of the CVC VTE cohort of the EINSTEIN Jr RCT** [Thom 2020]
Agreement	Impossible to determine
Quality of evidence	Moderate
Results	**[Meister 2008]** conducted a non-randomized prospective cohort study during two periods, comparing antithrombin supplementation alone (1995–2000) with antithrombin supplementation + LMWH (2001–2006) [104] in children with ALL. The rates of thromboembolic events were 12.7% and 0% (P=0.02), respectively, with no reports of bleeding complications. **[Mitchel 2003]** conducted a randomized study (n=109) comparing antithrombin supplementation with no antithrombin supplementation in children with ALL. The incidence of thrombosis in patients treated with antithrombin was 28% (95% CI 10-46%), compared to 37% (95% CI 24-49%) in the non-treated arm. The difference between the two arms was not statistically significantly different (p=0.43).

	[Greiner 2019] conducted a randomized study (n=949) comparing UFH, LMWH and antithrombin supplementation in children with ALL. Patients assigned to UFH had a higher risk of VTE (8.0%) compared with those assigned to enoxaparin (3.5%; P=0.011) or antithrombin (1.9%; P<0.001). **[Pelland-Marcotte 2019]** network metanalysis aimed to determine the effectiveness and safety of primary pharmacological thromboprophylaxis in children with cancer. LMWH was the only agent associated with lower odds of VTE compared with standard of care (OR: 0.23, 95% CI: 0.06–0.81). No statistically significant difference was detected between other thromboprophylaxis modalities and standard of care. **[Jaffrey 2020]** multicenter, prospective, observational cohort study (41% of cancer patients) found that children with PICCs had a significantly higher incidence of catheter-related VTE than children with CICCs (HR 8.5; 95% CI3.1-23.0; p<0.001). **[Thom 2020]** predefined analysis of the CVC-VTE cohort of the EINSTEIN-Jr RCT compared rivaroxaban versus standard of care in children with CVC-VTE. There was neither recurrent VTE nor major bleeding. No child died during the study

Conclusion

Prophylaxis of VTE and CVC-VTE

- Current evidence suggests that prophylactic doses of LMWH are effective and safe to prevent VTE in children with ALL throughout induction therapy. Antithrombin infusion for levels below 50% to 60% should also be considered.
- Central ports are associated with a lower rate of CRT than PICCs-line.

Treatment of CVC-VTE

- There are insufficient data to determine the efficacy and tolerance of LMWH, VKA and DOACS for treating CVC-VTE in children.

Chapter 9

Q9 Treatment of VTE in cancer patients with COVID-19 – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Initial treatment of VTE cancer patients with COVID-19	**None**
HTA 2: Early maintenance and long-term treatment of VTE cancer patients with COVID-19	**None**

Chapter 10

Q10 Prophylaxis of VTE in cancer patients with COVID-19 – BIBLIOGRAPHIC TABLE

HTA questions	Studies included
HTA 1: Prophylaxis of VTE in ambulatory cancer patients with COVID-19	**1 RCT general population** [Connors 2021]-ACTIV 4b
HTA 2: Prophylaxis of VTE in hospitalized moderately ill cancer patients with COVID-19	**3 RCT- general population** [Lopes 2021] [Sholzberg 2021] [ATTACC, ACTIV-4a, and REMAP-CAP Investigators 2021]
HTA 3: Prophylaxis of VTE in hospitalized critically ill cancer patients with COVID-19	**3 RCT- general population** [Sadeghipour 2021] [REMAP-CAP, ACTIV-4a and ATTACC Investigators 2021] [Perepu 2021]

HTA 4: Prophylaxis of VTE in hospitalized cancer patients with COVID-19 following discharge	**1 retrospective study- general population** Eswaran 2021 **1 prospective registry- general population** [Giannis 2021] **1 RCT** [Ramacciotti 2022]

Q10 Prophylaxis of VTE in cancer patients with COVID-19 – CONCLUSIONS

Q10.1: Ambulatory patients with COVID-19

Studies	**1 RCT general population** [Connors 2021]-ACTIV 4b
Agreement	Impossible to determine
Quality of evidence	Very low (general population, few cancer patients)
Results	The ACTIV-4b trial randomized outpatients with mild COVID-19 to receive aspirin 81 mg once daily or apixaban 2.5 mg twice daily (prophylactic dose), or apixaban 5 mg twice daily (therapeutic dose), or placebo for 45-days. The rates of an adjudicated composite outcome (all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause) after 45 days were 0.0%, 0.7%, 1.4%, and 0.0%, respectively; there were no significant differences between the active groups and the placebo group.

Q10.2: Hospitalized moderately ill patients with COVID-19

Studies	**3 RCT- general population** [Lopes 2021] [Sholzberg 2021] [ATTACC, ACTIV-4a, and REMAP-CAP Investigators 2021]
Agreement	Yes, regarding the rate of VTE and major bleeding
Quality of evidence	Very low (general population, few cancer patients)
Results	The ACTION trial [Lopes 2021] randomized 615 patients with COVID-19 (moderate state) and elevated D-dimer to receive therapeutic dose anticoagulation (mostly rivaroxaban 20 mg once daily) or prophylactic dose anticoagulation (mostly prophylactic LMWH). There was no difference in the primary composite efficacy outcome of survival, duration of hospital-stay and duration of supplemental oxygen between the 2 groups. The risk of VTE was low (4 % in the intervention arm *versus* 6.0 % in the control arm; RR 0.60; 95% CI 0.29-1.25). The risk of all bleeding was higher in the therapeutic dosing arm (RR 3.64; 95% CI 1.61-8.27). The open-label, adaptive, multiplatform ATTACC, ACTIV-4a, and REMAP-CAP trial randomized 2244 critically ill patients with COVID-19 to receive either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. Therapeutic-dose heparin or LMWH appeared to increase the probability of survival until hospital discharge with a reduced need for organ support (OR 1.27; 95% CI 1.03-1.58). VTE occurred in 1.4% of patients in the therapeutic-dose anticoagulation arm *versus* 2.5 % in the usual-care pharmacologic thromboprophylaxis arm while major bleeding occurred in 1.9% of patients in the therapeutic-dose anticoagulation arm *versus* 0.9% in the usual-care pharmacologic thromboprophylaxis arm (OR 1.80; 95% CI 0.90-3.74). The RAPID trial [Sholzberg 2021] randomized 465 patients to receive either therapeutic dose of heparin or prophylactic dose of heparin. The primary composite efficacy outcome of death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission within 28 days occurred in 16.72 of patients in the therapeutic-dose arm *versus* 21.9% in the standard-dose arm (HR 0.69; 95% CI 0.43 to 1.10). The rate of VTE was low (0.9 % in the intervention arm *versus* 3.0 % in the control arm; OR 0.29; 95%CI 0.06 to 1.42). Major bleeding occurred in 2 (0.9%) patients in the therapeutic-dose arm *versus* 4 (1.7%) patients in the prophylactic-dose arm (OR, 0.52; 95%-CI, 0.09 to 2.85).

Q10.3: Hospitalized critically ill patients with COVID-19

Studies	**3 RCT- general population** [Sadeghipour 2021] [REMAP-CAP, ACTIV-4a and ATTACC Investigators 2021] [Perepu 2021]
Agreement	Yes, regarding the rate of VTE and major bleeding
Quality of evidence	Very low (general population, few cancer patients)
Results	The INSPIRATION trial [Sadeghipour 2021] randomized 600 patients to receive either 1 mg/kg enoxaparin daily or 40 mg enoxaparin daily. The primary composite efficacy outcome of adjudicated acute VTE, arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality within 30 days occurred in 45.7% of patients in the intermediate-dose arm *versus* 44.1% in the standard-dose arm (HR 1.06; 95% CI 0.83 to 1.36). The rates of adjudicated VTE were low (3.3 % in the intervention arm *versus* 3.5 % in the control arm; OR 0.93; 95%CI 0.37-2.32).

	The open-label, adaptive, multiplatform REMAP-CAP, ACTIV-4a and ATTACC trial randomized 1207 critically ill patients with COVID-19 to receive either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. The median value for organ support–free days (primary outcome) was 1 (interquartile range, −1 to 16) in the therapeutic-dose anticoagulation arm *versus* 4 (interquartile range, −1 to 16) in the usual-care pharmacologic thromboprophylaxis arm (adjusted proportional odds ratio, 0.83; 95% CI 0.67 to 1.03; posterior probability of futility 99.9%). VTE occurred in 2.8% of patients in the therapeutic-dose anticoagulation arm *versus* 6.7% in the usual-care pharmacologic thromboprophylaxis arm while major bleeding occurred in 3.8% of patients in the therapeutic-dose anticoagulation arm *versus* 2.3% in the usual-care pharmacologic thromboprophylaxis arm (OR 1.48; 95% CI 0.75-3.04). [Perepu2021] randomized 176 patients to receive either standard prophylactic dose enoxaparin or intermediate weight-adjusted dose enoxaparin. The rates of all-cause mortality at 30 days (primary outcome) did not differ between the 2 groups (HR 0.66, 95%CI 0.3-1.45, p=0.31). VTE occurred in 21% of patients in the standard prophylactic dose *versus* 15% in the intermediate weight-adjusted dose arm (HR 1.79, 95%CI 0.51-6.25). Major bleeding occurred in 2% of patients in the standard prophylactic dose *versus* 2% in the intermediate weight-adjusted dose arm (HR 0.99, 95%CI 0.14-7.14).

Q10.4: Hospitalized patients with COVID-19 following discharge

Studies	**1 retrospective study- general population** Eswaran 2021 **1 prospective registry- general population** [Giannis 2021] **1 RCT** [Ramacciotti 2022]
Agreement	Impossible to determine
Quality of evidence	Very low (observational/prospective, one study with limitations)
Results	One retrospective single-center study [Eswaran 2021] of 447 patients hospitalized for COVID-19 reported that vascular thromboembolic events (myocardial infarction, PE, stroke and splenic infarct) within 30 days occurred in 1.1% of patients receiving anticoagulation at discharge *versus* 2.7% of those not receiving anticoagulation at discharge (OR 0.52; 95% CI 0.08-2.26, p=0.42). One prospective registry [Giannis 2021] of 4906 patients hospitalized for COVID-19, VTE occurred in 1.55% of patients over 3 months. Post-discharge thromboprophylaxis was prescribed in 12.7% of patients and reduced the risk of a composite of VTE, ATE and all-cause mortality by 46%. One RCT [Ramacciotti 2022] found that rivaroxaban 10 mg once daily for 35 days improved clinical outcomes compared with no extended thromboprophylaxis in patients with COVID-19 at high-risk of VTE.

Conclusion

Ambulatory cancer patients with COVID-19

There is no specific data regarding the benefit and risk of thromboprophylaxis in ambulatory cancer patients with COVID-19. The ACTIV-4b double-blind RCT, which assessed the efficacy and safety of several anti-thrombotic strategies in COVID-19 adult patients not requiring hospitalization at time of diagnosis reported low rates of an adjudicated composite outcome (all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause) after 45 days; there were no significant differences between the active groups and the placebo group.

Cancer patients with moderate COVID-19

There is no specific data regarding the benefit and risk of thromboprophylaxis in hospitalized moderately ill cancer patients with COVID-19. Three RCT (ACTION, ATTACC/ACTIV-4a/REMAP-CAP and RAPID), which compared the benefit and risk of therapeutic dose of anticoagulant with standard-dose prophylaxis in ward patients with COVID-19 reported conflicting results regarding survival. In all studies, therapeutic dosing non significantly decreased the risk of VTE at the cost of an increase in major bleeding.

Critically ill cancer Patients with COVID-19

There is no specific data regarding the benefit and risk of thromboprophylaxis in hospitalized critically ill cancer patients with COVID-19. Three RCT compared the benefit and risk of intermediate doses of LMWH or therapeutic-dose of heparin/LMWH with standard-dose prophylaxis in hospitalized critically ill patients with COVID-19. In the INSPIRATION trial, intermediate dose of LMWH did not improve the primary composite efficacy outcome of adjudicated acute VTE, arterial thrombosis, treatment with ECMO or all-cause mortality within 30 days. The rate of VTE was low in both arms. In the international, multiplatform, randomized REMAP-CAP, ACTIV-4a and ATTACC trial, therapeutic dose of heparin/LMWH did not improve the primary outcome of organ support-free days but was associated with a decrease in VTE and an increase in major bleeding compared with usual-care prophylaxis.

Hospitalized cancer patients with COVID-19 at discharge

The risk of VTE following discharge in COVID-19 patients appears to be very similar to that of acutely ill hospitalized patients without COVID-19 following discharge. One RCT [Ramacciotti 2022] found that rivaroxaban 10 mg once daily for 35 days improved clinical outcomes compared with no extended thromboprophylaxis in patients with COVID-19 at high-risk of VTE.

Appendix 7: Randomized clinical trials assessing the efficacy and safety of direct oral anticoagulants for the treatment of symptomatic or incidental venous thromboembolism

Study		HOKUSAI-VTE CANCER[1]	SELECT-D[2]	ADAM-VTE[3]	CARAVAGGIO[4]	CASTA-DIVA[5]	CANVAS[6]
Trial design		Non inferiority	Pilot	Superiority	Non inferiority	Non inferiority	Non inferiority
Number of randomized patients		1050	406	300	1170	158	671
Types of Cancer at Baseline		Colorectal: 15% Lung: 15% Breast: 12% Genitourinary: 13% Gynecologic: 11% Pancreatic or hepatobiliary: 9% Upper gastrointestinal: 5% Hematological malignancies: 11% Other: 10%	Colorectal: 25% Lung: 12% Breast: 10% Genitourinary: 17% Gynecologic: 10% Pancreatic or hepatobiliary: 8% Upper gastrointestinal: 10% Hematological malignancies: 8% Other: 10%	Colorectal: 16% Lung: 17% Breast: 9% Genitourinary: 9% Gynecologic: 10% Pancreatic or hepatobiliary: 16% Upper gastrointestinal: 4% Hematological malignancies: 8% Other: 11%	Colorectal: 20% Lung: 17% Breast: 13% Genitourinary: 9% Gynecologic: 10% Pancreatic or hepatobiliary: 8% Upper gastrointestinal: 5% Hematological malignancies: 7% Other: 11%	Gastro-intestinal: 20% Lung: 18% Breast: 12% Genitourinary: 13% Gynecologic: 8% Hematological malignancies: 8% Other: 21%	Not reported
Metastatic disease		53%	58%	64%	68%	73%	Not reported
Treatment allocation	**DOAC**	Edoxaban	Rivaroxaban	Apixaban	Apixaban	Rivaroxaban	Any DOAC
	LMWH	Dalteparin	Dalteparin	Dalteparin	Dalteparin	Dalteparin	Any LMWH
Duration of follow-up		12 months	6 months	6 months	6 months	3 months	6 months
Primary outcome		Composite of recurrent VTE or major bleeding	Recurrent VTE	Major bleeding* including fatal bleeding	Efficacy: Recurrent VTE Safety: Major bleeding*	Efficacy: Recurrent VTE Safety: Major bleeding*	Recurrent VTE
Secondary outcomes		Recurrent VTE Major bleeding* CRNMB Mortality	Major bleeding* CRNMB Mortality	Recurrent VTE CRNMB Mortality	CRNMB Mortality	CRNMB Mortality	Major bleeding* CRNMB Mortality
Recurrent VTE*		• Edoxaban: 7.9% • Dalteparin: 11.3%	• Rivaroxaban: 4% (95% CI 2, 9)	• Apixaban: 0.7% • Dalteparin: 6.3%	• Apixaban: 5.6% • Dalteparin: 7.9%	• Rivaroxaban: 6.4% • Dalteparin: 10.1%	• Any DOAC: 6.1% • Any LMWH: 8.8%

	• HR 0.71 (95% CI 0.48, 1.06)	• Dalteparin: 11% (95% CI 7, 16) • HR 0.43 (95% CI 0.19, 0.99)	• HR 0.099 (95% CI 0.013, 0.780)	• HR 0.63 (95% CI 0.37, 1.07)	• HR 0.75 (95% CI 0.21, 2.66)	
Major bleeding*	• Edoxaban: 6.9% • Dalteparin: 4% • HR 1.77 (95% CI 1.03, 3.04)	• Rivaroxaban: 6% (95% CI 3, 11) • Dalteparin: 4% (95% CI 2, 8) • HR 1.83 (95% CI 0.68, 4.96)	• Apixaban: 0% • Dalteparin: 1.4% • HR Not estimable	• Apixaban: 3.8% • Dalteparin: 4% • HR 0.82 (95% CI 0.40, 1.69)	• Rivaroxaban: 1.4% • Dalteparin: 3.7% • HR 0.36 (95% CI 0.04, 3.43)	• Any DOAC: 5.2% • Any LMWH: 5.6%
CRNMB	• Edoxaban: 14.6% • Dalteparin: 11.1% • HR 1.38 (95% CI 0.98, 1.94)	• Rivaroxaban: 13% (95% CI 9, 19) • Dalteparin: 4% (95% CI 2, 9) • HR 3.76 (95% CI 1.63, 8.69)	• Apixaban: 6.2% • Dalteparin: 4.9%	• Apixaban: 9% • Dalteparin: 6% • HR 1.42 (95% CI 0.88, 2.30)	• Rivaroxaban: 10.8% • Dalteparin: 6.1%	• Any DOAC: 5.8% • Any LMWH: 2.6%
Mortality	• Edoxaban: 39.5% • Dalteparin: 36.6% • HR 1.12 (95% CI 0.92, 1.37)	• Rivaroxaban: 23.6% • Dalteparin: 27.6%	• Apixaban: 16% • Dalteparin: 11%	• Apixaban: 23.4% • Dalteparin: 26.4% • HR 0.82 (95% CI 0.62, 1.09)	• Rivaroxaban: 25.7% • Dalteparin: 23.8% • HR 1.05 (95% CI 0.56, 1.97)	• Any DOAC: 21.5% • Any LMWH: 18.4%

*Major bleeding was defined according to the ISTH criteria except in CANVAS where major bleeding was defined as Grade ≥3 bleeding on the Common terminology Criteria for adverse Events from the national Cancer Institute (NCI CTCAE) criteria.

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; PE; pulmonary embolism; VTE, venous thromboembolism.

From 2018 to 2022, six randomized controlled trials (RCTs)[1–6] compared DOACs with LMWHs for the acute and long-term treatment of cancer-associated thrombosis (CAT). Together, these RCTs enrolled a total of 3690 patients cancer patients with acute VTE (1850 patients randomized to the DOACs arms and 1840 patients randomized to the LMWHs arms). These 6 RCTs were heterogeneous in terms of study design, sample size, types of cancer included, primary outcomes, and treatment duration. Characteristics and main results from these RCTs are presented in the appendix 7. Four comparative effectiveness studies (HOKUSAI-VTE CANCER[1] **,** CARAVAGGIO[4], CASTA-DIVA[5], CANVAS[6]) assessed DOACs noninferiority *vs* LMWHs, 1 pilot study (SELECT-D[2]) was designed to obtain estimates of the rates of recurrent VTE in cancer patients treated with either DOACs or LMWHs[2], and 1 comparative safety study (ADAM-VTE[3]) assessed DOACs safety superiority *vs* LMWHs[3]. In HOKUSAI-VTE CANCER[1], the primary outcome was a composite of recurrent VTE or major bleeding during the 12 months after randomization, regardless of treatment duration, while the primary outcome was recurrent VTE in the CARAVAGGIO[4], CASTA-DIVA[5] and CANVAS[6] trials. All studies were open label and used a blinded central outcome adjudication (PROBE) design. The duration of the follow-up was 3 months in CASTA-DIVA[5], 6 months in SELECT-D[2]**,** ADAM-VTE[3]**,** CARAVAGGIO[4], and CANVAS[6], and 12 months in HOKUSAI-VTE CANCER[1].

In the 2 largest studies (HOKUSAI-VTE CANCER[1] and CARAVAGGIO[4]), DOACs were non-inferior to dalteparin for recurrent VTE. An increased risk of major bleeding with DOACs was observed in HOKUSAI-VTE CANCER[1], mainly attributable to patients with gastrointestinal (GI) cancer, of whom 12.7% experienced major bleeding in the edoxaban arm compared to 3.6% in the dalteparin arm. The site of bleeding was the upper GI tract in most patients developing major bleeding under edoxaban (16 of 21 patients). After a safety review of the first 220 patients, the data safety monitoring committee of the SELECT-D[2] observed a non-significant increase in major bleeding events in 19 patients with esophageal or gastroesophageal junction cancers, and these cancer patients were subsequently excluded from enrolment. The rates of major bleeding were similar in the DOACs and LMWHs arms in the CARAVAGGIO[4] and CASTA-DIVA[5] trials.

Regarding compliance to treatment, the proportion of patients discontinuing treatment was lower in patients receiving DOACs compared to those receiving LMWHs (4% *vs* 15% in HOKUSAI-VTE CANCER[1], 6% *vs* 10% in SELECT-D[2], 4% *vs* 15% in ADAM-VTE, 5.8% *vs* 16% in CARAVAGGIO[4]**)**.

Cross-study comparison is limited by differences in RCTs design and baseline characteristics of patients. In the absence of randomized head-to-head comparison between DOACs, no conclusion can be drawn on the superiority of one type DOAC over the others. Selection of an anticoagulant agent for the treatment of CAT should be based on the patient's bleeding risk, the type of cancer, and potential drug–drug interactions, as well as patient values and preferences. Anticoagulant therapy should be reassessed on a regular basis as the patient's cancer profile change over time.

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Appendix 8: Risk stratification schemes for prophylaxis of VTE in patients with cancer

Patients with cancer are at increased risk of Venous thromboembolism (VTE) compared to patients without cancer. Risk for VTE is multifactorial and depends on the clinical setting and the presence of various risk factors. 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, Tumor 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, protein kinase inhibitors, immune checkpoint inhibitors, 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

Established and emerging biomarkers

- **Blood-count parameters**: platelets and leukocytes count before starting prechemotherapy
- **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** (*e.g.,* citrullinated histone H3)
- **Tissue-factor-bearing microvesicles** (TF-MVs)
- **High podoplanin expression** (in brain tumors only)
- **Tumor genomic mutations**: *isocitrate dehydrogenase (IDH)* wild type (in brain tumors), *ALK* and *ROS1* rearrangement (lung cancer), *EGFR* mutation (lung cancer), *KRAS* mutation (lung and colon cancers), *JAK2V617F* mutation (myeloproliferative neoplasms)

Risk assessment models

The Khorana Score[1] was developed to stratify the risk of VTE in cancer patients initiating chemotherapy. This risk score was externally validated in the Vienna Cancer and Thrombosis Study (CATS)[2] more than ten years ago and is yet the only one to have undergone multiple validation studies. A Khorana score ≥2 has been used as eligibility criteria in randomized controlled trials of thromboprophylaxis. Several variations of the Khorana risk score have been

proposed to improve risk assessment, including the extended "Vienna CATS Score" [2], the PROTECHT score[3], and the CONKO score[4] (see Appendix 10 pp 119)

The COMPASS-CAT score[5] was developed for use in only breast, colorectal, lung, and ovarian cancer. It includes the following variables: anthracycline or anti-hormonal therapy, time since cancer diagnosis ≤ 6 months, central venous catheter, advanced cancer stage, cardiovascular risk factors ≥ 2, recent hospitalization for acute medical illness, personal history of VTE and prechemotherapy platelet count ≥350 × 10^9/L.

The TiC-Onco score[6] includes the following variables: very high-risk or high-risk tumors (by original Khorana score), genetic risk score (germline polymorphisms in *F5*, *F13* or *SERPINA10*), body mass index > 25 kg/m^2.

The ONKOTEV score[7] is based on a Khorana score of >2, then adds metastatic disease, personal history of VTE, and macroscopic vascular/lymphatic compression.

Pabinger et al.[8] developed and externally validated in a single prospective cohort (MICA) of 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; an online risk calculator (https://cemsiis.meduniwien.ac.at/en/kb/science-research/software/webtools/cancer-vte/) is provided for estimating an individual cancer patient VTE risk.

The ThroLy score[9] was developed for use in lymphoma patients. It includes the following variables: previous VTE event, reduced mobility, previous acute myocardial infarction or stroke, body mass index (BMI) > 30 kg/m^2, extranodal localization, mediastinal involvement, neutropenia, hemoglobin<100g/L. Two validation studies have been performed yet.

The IMPEDE score[10] was developed for use in only multiple myeloma. It includes the following variables: immunomodulatory agent, BMI ≥25 kg/m2, pelvic, hip or femur fracture, erythropoietin stimulating agent, dexamethasone/doxorubicin, Asian ethnicity, VTE history, tunneled line/central venous catheter, existing thromboprophylaxis.

The SAVED score[11] was developed for use in only multiple myeloma. It includes the following variables: prior surgery, Asian race, VTE history, age ≥80 years, and dexamethasone dose.

The CoVID-TE score[12] was developed in 2804 patients included in the CCC19 cohort study of patients with both cancer and COVID-19. It includes the following variables: high to very-high risk by original Khorana score, VTE history, intensive care unit admission, D-dimer elevation, recent systemic anti-cancer therapy, and non-Hispanic ethnicity.

The CAT-BLEED score[13] was developed in 1046 patients included in the Hokusai-VTE Cancer trial to assess the risk of bleeding in cancer patients treated with cancer-associated thrombosis. It includes the following variables: regionally advanced or metastatic cancer, genitourinary cancer, creatinine clearance, recent use of anticancer therapies associated with gastrointestinal toxicity, age of 75 years and older, gastrointestinal cancer and edoxaban treatment.

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Appendix 9: 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 10^9/L	+1	+1	+1	+1
BMI ≥35 kg/m^2	+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: stomach, pancreas; ‡high risk tumors: lung, lymphoma, gynecologic, bladder, testicular; # 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

Appendix 10: Pharmacokinetics and pharmacodynamics properties of anticoagulant drugs

Table A.7.1. Pharmacokinetics and pharmacodynamics properties of parenteral anticoagulants used for the treatment and prophylaxis of cancer-associated venous thromboembolism.

	Unfractionated Heparin	Tinzaparin (Not available in the US)	Dalteparin	Enoxaparin	Nadroparin (Not available in the US)	Fondaparinux
Ratio anti-Xa/anti-IIa	1	1.5-2	2.6	4	>4	Only Anti-Xa
Bioavailability	30%	90%	90%	100%	89%	100%
Activity onset	IV: immediate SC: 20 to 60 minutes	4-6 h	4-6 h	3-4h	3h	3-6h
Half-life	1.5h	1.5h	3-5h	4h	3.5-11h	17-21h
Volume of distribution	40-70 mL/min	4L	3L	4-5L	3-4L	7-11
Protein binding	Very high	Low	Low	Not available in the literature	Low	Specifically to Antithrombin
Elimination (% of administered dose)	Reticuloendothelial system small fraction (unchanged) excreted in urine	Renal	Renal	Renal	Renal	Renal
Interaction	-	-	-	-	-	-
Specific Antidote	Protamine	Protamine	Protamine	Protamine	Protamine	None
Dosing	**Treatment of VTE** • 80 IU/kg IV bolus, then continuous infusion of 18 IU/kg/h, • Or 5000 IU IV bolus, then continuous infusion of 1300 IU/h, • Or 250 IU/kg (alternatively, 17,500 IU) SC, then 250 IU/kg every 12h • For at least 6 months **Treatment of VTE** • 5000 IU SC every 8/12h • Or 7500 IU SC every 12h	**Treatment of VTE** • 175 IU/Kg • For at least 6 months **Prophylaxis of VTE** • 4500 IU SC daily or 75 IU/kg SC daily (for extremes of body weight)	**Treatment of VTE** • 200 IU/kg SC daily for 30 days, followed by 150 IU/Kg SC daily thereafter for at least 6 months **Prophylaxis of VTE** • 5000 IU SC daily or 75 IU/kg SC daily	**Treatment of VTE** • 1.5 mg/gk SC daily • 1 mg/kg SC every 12 hours • For at least 6 months **Prophylaxis of VTE** • 30-40 mg SC daily	**Treatment of VTE** • 171 IU/Kg • For at least 6 months **Prophylaxis of VTE** • 2800 or 3800 IU SC daily or 38 IU/kg SC daily (for extremes of body weight)	**Treatment of VTE** • <50 kg: 5 mg SC once daily • 50-100 kg: 7.5 mg SC once daily • >100 kg: 10 mg SC once daily • For at least 6 months **Prophylaxis of VTE** • 2.5 mg once daily
Patients with renal failure	no dose adjustment	Avoid in patients with CrCl < 20 mL/min	Avoid in patients with CrCl < 30 mL/min	Avoid in patients with CrCl < 30 mL/min	Avoid in patients with CrCl < 30 mL/min	Avoid in patients with CrCl < 30 mL/min

Abbreviations: CrCl, Cockroft Clairance; IU, international units ; IV, intravenous; SC, subcutaneously.

Table A.7.2. Pharmacokinetics and pharmacodynamics properties of oral anticoagulants used for the treatment and prophylaxis of cancer-associated venous thromboembolism.

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	FIIa, FVIIa, FIXa, FXa	FIIa (direct thrombin inhibitor)	FXa (direct factor Xa inhibitor)	FXa (direct factor Xa inhibitor)	FXa (direct factor Xa inhibitor)
Prodrug	NO	YES	NO	NO	Yes
Bioavailability	80–100%	3–7%	80%	50%	62%
Activity onset	4–5 days	1–2 h	0.5-4h	1-3 h	1-2 h
Half-life	20-60 h	12–17 h	5-13 h	12 h	10-14 h
Volume of distribution	10 L	50-70 L	50 L	23 L	>300 L
Protein binding	>99%	35%	92-95%	87%	55%
Elimination (% of administered dose)	80% excreted in the urine 20% feces	80% renal (unchanged) 20% feces	66 % renal 33% feces (inactive metabolites)	25% renal (unchanged) 75% feces (unchanged)	50%, renal (unchanged) 50% biliary /intestinal
Interaction	Many	P-gp inducers/inhibitors	P-gp inducers/inhibitors CYP3A4 inducers/inhibitors	P-gp inducers/inhibitors CYP3A4 inducers/inhibitors	P-gp inducers /inhibitors CYP3A4 inducers/inhibitors
Specific Antidote	Vitamin K	Idarucizumab Aripazine	Andexanet alfa Aripazine	Andexanet alfa Aripazine	Andexanet alfa Aripazine
Dosing	**Treatment of VTE** Initiate warfarin as soon as possible following diagnosis of VTE, preferably on the same day, in combination with UFH, LMWH or fondaparinux. The initial dose of warfarin should be 5 or 10 mg for most patients. Beginning on day 3 of therapy, INRs should be measured daily and warfarin doses adjusted to achieve an 2≤INR ≤ 3 as soon after day five of overlap therapy as possible For at least 6 months	**Treatment of VTE** 150 mg twice daily after at least 5 days 5-10 days of parenteral anticoagulant for at least 6 months	**Treatment of VTE** 15mg twice daily for 3 weeks followed by 20 mg once daily for at least 6 months **Prophylaxis of VTE** 10mg once daily for 6 months	**Treatment of VTE** 10 mg twice daily for 7 days, followed by 5 mg twice daily for at least 6 months **Prophylaxis of VTE** 2.5mg twice daily for 6 months	**Treatment of VTE** 60 mg once daily after at least 5 days of initial treatment with of parenteral anticoagulant (heparin, low-molecular-weight heparin or fondaparinux) for at least 6 months
Dose adjustment	Individualized	None	None	**Treatment of VTE** Reduce dose by 50% in patients coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors	**Treatment of VTE** 30 mg OD in patients who meet any of the following criteria: moderate renal impairment (CrCl 15-50 mL/min), body weight of 60 kg or less, or concomitant use of potent P-gp inhibitors (such as erythromycin, cyclosporine, dronedarone, quinidine, or ketoconazole)
Patients with renal failure	Vigilant monitoring including more frequent INR testing and bleeding risk assessment in patients with CrCl < 30 mL/min	Avoid in patients with CrCl < 30 mL/min	Limited clinical data in patients with CrCl < 30 mL/min Avoid in patients with CrCl < 15 mL/min	Avoid in patients with CrCl < 15 mL/min	Avoid in patients with CrCl < 15 mL/min

Abbreviations: CrCl, Cockroft Clairance; CYP3A4, Cytochrome P450 3A4; INR, International Normalized Ratio; P-gp, Glycoprotein.

Appendix 11: Prohibited Concomitant Medication in RCT Comparing DOACs to LMWH in Cancer Patients

Treatment of established cancer-associated thrombosis	
Edoxaban (Hokusai-VTE Cancer)	**P-glycoprotein inhibitors:** - ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study. - ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use was permitted (with appropriate dose reduction of edoxaban).
Rivaroxaban (SELECT-D)	**Strong cytochrome P-450 (CYP) 3A4 inhibitor**: human immunodeficiency virus protease inhibitors or systemic ketoconazole. **Strong CYP 3A4 inducers**: rifampicin, carbamazepine, or phenytoin. **P-glycoprotein inhibitors/ inducers**
Apixaban (ADAM VTE)	**CYP3A4 inducers**: rifampin, rifabutin, carbamazepine, efavirenz, phenobarbital, phenytoin, fosphenytoin, primidone, and St. John's Wort.
Apixaban (CARAVAGGIO)	**Strong inhibitors of both CYP3A4 and P-glycoprotein:** atazanavir, boceprevir, clarithromycin, conivaptan, darunavir, darunavir/ritonavir, erythromycin, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, nefazodone, posaconazole, ritonavir, saquinavir. **Strong inducers of both CYP3A4 and P-glycoprotein:** avasimibe, carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, rifampicin, St John's wort.
Primary prophylaxis of cancer-associated thrombosis	
Rivaroxaban (CASSINI)	**Combined P-glycoprotein and strong CYP3A4 inhibitors** such as but not limited to ketoconazole, telithromycin or protease inhibitors within 4 days before randomization, or planned use during the study. Use of itraconazole within 7 days before randomization or planned use during the study. **Combined P-glycoprotein and strong CYP3A4 inducers** such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort within 2 weeks before randomization, or planned use during the study.
Apixaban (AVERT)	**Strong inhibitors of both CYP 3A4 and P-glycoprotein**: ketoconazole, itraconazole, voriconazole, posaconazole, voriconazole and HIV protease inhibitors (*e.g.,* ritonavir) **Strong CYP3A4 and P-glycoprotein inducers:** rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort

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