CADTH Health Technology Review

Pharmacological Thromboprophylaxis in Patients With Cancer
# Table of Contents

Abbreviations .................................................................................................................. 6  
Key Messages .................................................................................................................. 7  
Context and Policy Issues ............................................................................................... 7  
Research Question .......................................................................................................... 8  
Methods .......................................................................................................................... 8  
  Literature Search Methods ............................................................................................. 8  
  Selection Criteria and Methods ...................................................................................... 8  
  Exclusion Criteria .......................................................................................................... 8  
Summary of Evidence ...................................................................................................... 9  
  Quantity of Research Available .................................................................................... 9  
  Summary of Study Characteristics ................................................................................ 9  
  Summary of Critical Appraisal ...................................................................................... 10  
  Summary of Findings .................................................................................................... 11  
Limitations ...................................................................................................................... 13  
Conclusions and Implications for Decision- or Policy-Making ........................................ 13  
References ....................................................................................................................... 15  
Appendix 1: Selection of Included Studies ..................................................................... 16  
Appendix 2: Characteristics of Included Publications .................................................... 17  
Appendix 3: Critical Appraisal of Included Publications .................................................. 21  
Appendix 4: Main Study Findings and Authors’ Conclusions .......................................... 23  
Appendix 5: References of Potential Interest .................................................................... 28
List of Tables

Table 1: Selection Criteria ......................................................................................................................... 8
Table 2: Characteristics of Included Guidelines ............................................................................................ 17
Table 3: Strengths and Limitations of Guidelines Using AGREE II 
........................................................................................................................................................................ 21
Table 4: Summary of Recommendations: Duration of Anticoagulation ............................................................ 23
Table 5: Summary of Recommendations: Choice of Anticoagulants for Long-Term Thromboprophylaxis .... 25
List of Figures

Figure 1: Selection of Included Studies ................................................................. 16
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
</tr>
<tr>
<td>CHEST</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>DIC</td>
<td>disseminated intravascular coagulation</td>
</tr>
<tr>
<td>DOAC</td>
<td>direct oral anticoagulant</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>ESVS</td>
<td>European Society for Vascular Surgery</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluations</td>
</tr>
<tr>
<td>ITAC</td>
<td>International Initiative on Thrombosis and Cancer</td>
</tr>
<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
</tbody>
</table>
Key Messages

• Six evidence-based guidelines were identified regarding the long-term (6 months or longer) use of pharmacological thromboprophylaxis for the management of cancer-associated thrombosis. The guidelines used rigorous methodology, systematically searched for evidence, and were clearly reported.

• Anticoagulation therapy for 6 months or longer is recommended by 5 guidelines for patients with active cancer and venous thromboembolism to prevent recurrences of venous thromboembolism. However, the recommendations are weak and made based on low-quality evidence or expert consensus.

• Two guidelines recommend a low-molecular-weight heparin or direct oral anticoagulant for long-term use (6 months or longer) in patients with cancer. This recommendation is based on low- to high-certainty evidence.

• Two guidelines strongly recommend direct oral anticoagulants in patients with cancers in locations other than gastrointestinal or genitourinary cancers. This recommendation is based on high-quality evidence.

• No guidelines were identified regarding arterial thrombosis or chronic disseminated intravascular coagulation associated with cancer.

Context and Policy Issues

Thrombosis or coagulation of blood within a blood vessel is a common complication of cancer and has been recognized since the 19th century. Cancer-associated thrombosis is the second leading cause of death in patients with cancer. Cancer causes a hypercoagulable or prothrombotic state that, when combined with a stasis of blood flow or endothelial injury, can result in thrombosis. The 3 types of cancer-associated thrombosis are venous thromboembolism (VTE), arterial thrombosis, and chronic disseminated intravascular coagulation (DIC). It has been estimated that approximately 20% to 30% of all first VTEs are associated with cancer. A 4- to 7-fold increased risk of VTE is observed in patients with cancer. There are 2 types of VTE: pulmonary embolism (PE) and deep vein thrombosis (DVT). The risk factors for cancer-associated VTE include patient factors (e.g., older age, medical comorbidities, previous history of VTE), cancer-associated risk factors (e.g., primary site of cancer, advanced stage), and treatment-associated risk factors (e.g., chemotherapy, hospitalization, and surgery).

Thromboprophylaxis or management strategies to prevent the occurrence of thrombotic events are warranted in patients with cancer due to the increased risk. Pharmacological thromboprophylaxis options include direct-acting oral anticoagulants (DOACs), such as apixaban, edoxaban, and rivaroxaban; low-molecular-weight heparins (LMWHs), such as dalteparin, enoxaparin, and tinzaparin; and vitamin K antagonists (VKAs), such as warfarin. The benefits and risks of extended or long-term anticoagulation (> 6 months) for the prevention of thrombotic events have been discussed in recent studies and reviews of trials. The purpose of this report is to summarize the evidence-based guidelines regarding the long-term use of pharmacological thromboprophylaxis for the management of cancer-associated thrombosis.
Research Question

What are the evidence-based guidelines regarding the long-term use of pharmacological thromboprophylaxis for the management of cancer-associated thrombosis?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were pharmacological thromboprophylaxis and cancer. Search filters were applied to limit retrieval to guidelines. Conference abstracts were excluded. When possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016, and September 27, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2016. When multiple versions of a guideline from the same group were identified, inclusion was limited to the latest version. Guidelines with unclear methodology were excluded.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with cancer</td>
</tr>
<tr>
<td>Intervention</td>
<td>Long-term (i.e., ≥ 6 months) pharmacological thromboprophylaxis (e.g., direct-acting oral anticoagulants [e.g., apixaban, edoxaban, rivaroxaban], low-molecular-weight heparins [e.g., dalteparin, enoxaparin, tinzaparin], unfractionated heparin, warfarin)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Recommendations regarding best practices (e.g., appropriate patient populations, recommended treatment protocols or strategies, contraindications)</td>
</tr>
<tr>
<td>Study designs</td>
<td>Evidence-based guidelines</td>
</tr>
</tbody>
</table>
Summary of Evidence

Quantity of Research Available
A total of 332 citations were identified in the literature search. Following screening of titles and abstracts, 293 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. Another 3 potentially relevant publications were retrieved from the grey literature search or handsearch for full-text review. Of these potentially relevant articles, 36 publications were excluded for various reasons, and 6 publications met the inclusion criteria and were included in this report. These comprised 6 evidence-based guidelines. Appendix 1 presents the PRISMA flow chart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics
Six evidence-based guidelines were included in the report. All included guidelines provided recommendations regarding several pharmacological and non-pharmacological interventions for the prevention and management of VTE. Three guidelines provided recommendations for all individuals with venous thromboses (with and without cancer). Only the recommendations relevant to the long-term (≥ 6 months) pharmacological thromboprophylaxis in patients with cancer will be described in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design
Six evidence-based guidelines were included in the report. They were the American Society of Hematology (ASH) guideline (2021), the American College of Chest Physicians (CHEST) guideline (2021), the European Society for Vascular Surgery (ESVS) guideline (2021), the American Society of Clinical Oncology (ASCO) guideline (2020), the National Institute for Health and Care Excellence (NICE) guideline (2020), and the International Initiative on Thrombosis and Cancer (ITAC) guideline (2019).

All included guidelines collected evidence using systematic literature review. Multiple electronic databases, as well as bibliographies and trial registries, were searched to identify evidence. Systematic reviews and randomized controlled trials (RCTs) were identified as evidence for developing recommendations. In the ESVS guideline, non-randomized studies were also included in the evidence base. In 3 guidelines, if limited or no evidence were identified for a particular question, expert judgment by the guideline panel was used to develop a recommendation.

The quality assessment of the evidence was conducted using several methods. In 5 guidelines, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used, and the certainty of evidence was graded from high quality to very low quality. In the ESVS guideline, certainty of evidence was graded from level A (evidence from multiple RCTs or meta-analyses) to level C (expert consensus or evidence from small retrospective studies).
In terms of the development and evaluation of recommendations, the ASH guideline\textsuperscript{12} and the CHEST guideline\textsuperscript{14} used Evidence-to-Decision framework to formulate the recommendations. The recommendations were finalized after panel discussions (ASH guideline\textsuperscript{12}) or panel consensus by modified Delphi technique (CHEST guideline\textsuperscript{14}). In the ESVS guideline,\textsuperscript{10} ITAC guideline,\textsuperscript{9} ASCO guideline,\textsuperscript{11} and the NICE guideline,\textsuperscript{13} the recommendations were formulated and finalized using panel discussions and consensus.

The strength of the recommendations was reported in the guidelines.\textsuperscript{9-14} The GRADE approach was employed in grading the recommendations in 4 guidelines.\textsuperscript{9,12-14} The recommendations were graded as \textit{strong} or \textit{weak} based on the degree of confidence in the benefit of the intervention over the risks.\textsuperscript{9,12-14} In the CHEST guideline\textsuperscript{14} and NICE guideline,\textsuperscript{13} the strength of the recommendation was noted in the wording of the recommendation. In the ITAC guideline,\textsuperscript{9} grades 1 and 2 were used to denote strong and weak recommendations, respectively. In the ASH guideline,\textsuperscript{12} recommendations were graded as \textit{strong} (worded as “panel recommends”) or \textit{conditional} (worded as “panel suggests”).

In the ESVS guideline,\textsuperscript{10} recommendations were graded from class I (intervention is beneficial and effective) to class III (intervention is not effective and may be harmful in some cases).\textsuperscript{10} In the ASCO guideline, recommendations were graded as \textit{strong}, \textit{moderate}, or \textit{weak} based on the extent of confidence in the risk-benefit profile of the intervention.\textsuperscript{11}

**Country of Origin**

The ASH guideline,\textsuperscript{12} CHEST guideline,\textsuperscript{14} and ASCO guideline\textsuperscript{11} were developed by North American groups. The ITAC guideline\textsuperscript{9} was developed by an international group. The ESVS\textsuperscript{10} guideline was developed by a European group, and the NICE guideline\textsuperscript{13} was developed in the UK.

**Patient Population**

The target population of the included guidelines, relevant to the current report, were patients with active cancer. The intended users of all guidelines included health care professionals such as clinicians (e.g., oncologists, internists, hematologists), nurses, and pharmacists. In 2 guidelines, patients, their families, and caregivers were also listed as intended users.\textsuperscript{11,13}

**Interventions and Comparators**

The relevant interventions considered in the guidelines were anticoagulants such as LMWHs, VKAs, and DOACs prescribed for long-term (i.e., ≥ 6 months) pharmacological thromboprophylaxis.

**Outcomes**

Recurrence of VTE and risk of major bleeding were considered as outcomes of interest in all included guidelines.\textsuperscript{9-14} Mortality was considered in 3 guidelines.\textsuperscript{9,12,14} In addition, risk of minor bleeding and thrombocytopenia were also considered as outcomes in the 2019 ITAC guideline.

**Summary of Critical Appraisal**

All 6 guidelines\textsuperscript{9-14} provided a clear description of the scope and purpose of the guideline. Overall objectives, health questions covered in the guideline, and the target population were described. The guideline development groups included individuals from all relevant professional groups.\textsuperscript{9-14} Patient preferences were sought during the development phase in
3 guidelines. Patient stakeholders were given an opportunity to review the summary of draft recommendations in 2 guidelines. In the CHEST guideline, it was unclear whether the views and preferences of the patient population were obtained. The target users were not clearly described in the CHEST guideline, although it was likely clinicians.

Among the included guidelines, 4 were updates to previously published versions and included an updated evidence base and recommendations. Two guidelines were newly developed. In all 6 guidelines, systematic methods were used to identify evidence, and selection criteria for the evidence were described. The strength and limitations of the evidence were reported in 4 guidelines but was unclear in the ESVS and ASCO guidelines. In all guidelines, methods for formulating and developing the guidelines were described. The ASH guideline and the CHEST guideline used Evidence-to-Decision framework, and the explicit link between evidence and recommendations were clearly described. Evidence contributing to each recommendation were also clear in 3 of the other guidelines. In the NICE guideline, the explicit link to evidence for each of the recommendations was unclear, although detailed discussions about the evidence base was included. The presentation was clear in all 6 guidelines. The recommendations were unambiguous and easy to identify. Different pharmacological and non-pharmacological treatment options for the condition of interest were considered. A procedure for updating the evidence base and recommendations was described in 3 guidelines. In the ESVS guideline, a plan for a future update was not included. In 2 other guidelines (by CHEST and by ITAC), which were updates from previous versions, the process for update was unclear. Lastly, all guidelines were externally reviewed by stakeholders and experts before publication.

In terms of the applicability of the recommendations, 5 guidelines described the facilitators and barriers to the implementation of the recommendations and addressed the potential resource implications. In the ESVS guideline, it was unclear whether these issues were considered. The ITAC guideline was accompanied by a web-based app for the implementations of the recommendations, which is likely beneficial to the users. In 3 guidelines, it was unclear whether any tools were provided to aid for that purpose. The NICE guideline included auditing criteria to monitor and evaluate whether the recommendations are being used and to obtain feedback from the users; similar monitoring or auditing criteria were not reported in 4 other guidelines and were unclear in the ASCO guideline.

There was editorial independence in all included guidelines. Competing interests of all members of the guideline development panel were recorded. It was available as supplemental information in 4 guidelines. It was also unlikely that the funding sources would have influenced the recommendations.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

**Summary of Findings**

Appendix 4 presents the detailed recommendations and supporting evidence that are relevant to the current report.
**Guidelines**

**Duration of Thromboprophylaxis**

The ASH guideline suggests long-term anticoagulation (> 6 months) versus short-term anticoagulation (3 to 6 months) for patients with active cancer and VTE. This is a conditional recommendation based on low-certainty evidence. For patients with active cancer and VTE who receive long-term anticoagulation, the guideline suggests that indefinite duration is preferred over discontinuation of treatment after a definite period. This is a conditional recommendation based on very low-quality evidence.

The CHEST guideline strongly recommends extended-phase anticoagulation (> 6 months) with a DOAC in patients with VTE and a persistent risk factor. This recommendation is based on moderate-quality evidence. Active cancer is considered a persistent risk factor.

The ASCO guideline recommends long-term anticoagulation with an LMWH, a DOAC, or a VKA for longer than 6 months for select patients with active cancer. Recommended patient groups include those with metastatic disease and those receiving chemotherapy. Additionally, intermittent reassessments are recommended beyond 6 months to evaluate the risk-benefit profile. This is a weak to moderate recommendation based on low-quality evidence as well as informal consensus.

The NICE guideline similarly recommends (weak recommendation) to consider continuing anticoagulation beyond 6 months for patients with active cancer. Individual risk of VTE recurrence and bleeding should also be considered. They suggest that patient preferences also be taken into consideration. The evidence base for this recommendation is unclear.

The ITAC guideline recommends that patients with active cancer and established VTE should be treated for at least 6 months with an LMWH or a DOAC to prevent recurrences. This is a strong recommendation based on high-quality evidence. After 6 months, a decision regarding termination or continuation of anticoagulation should be made by considering the individual’s risk-benefit profile, resources, patient preference, and cancer activity. However, this recommendation was based on expert opinion and consensus due to lack of evidence.

**Choice of Anticoagulants for Long-Term Thromboprophylaxis**

The ASH guideline suggests using DOACs or LMWHs for long-term anticoagulation for patients with active cancer and VTE. This is a conditional recommendation based on very low-certainty evidence.

The CHEST guideline suggests anticoagulation with VKA, for patients with VTE and a persistent risk factor (e.g., active cancer) who cannot receive DOAC. This is a weak recommendation based on moderate-quality evidence. It was unclear whether any or all of the evidence was formed by studies among patients with cancer.

The ESVS guideline strongly recommends switching from an LMWH to a DOAC after 3 to 6 months of treatment in patients with cancer-associated DVT. This is a grade I recommendation based on high-quality (grade A) evidence. The guideline also recommends DOACs for extended anticoagulation (as well as initial and principal phases of treatment) in select patients with cancer-associated DVT, whose cancer is not located in the gastrointestinal or genitourinary systems. This is a moderate-to-strong (grade IIa) recommendation based on high-quality (grade A) evidence.
The ASCO guideline\textsuperscript{11} recommends LMWHs, such as edoxaban or rivaroxaban, for a minimum duration of 6 months in patients with cancer-associated thrombosis. VKAs, although inferior, may be used if LMWHs or DOACs are not accessible. DOACs are associated with a higher risk of major bleeding in patients with gastrointestinal or genitourinary cancers. This is a strong recommendation based on high-quality evidence.

The NICE guideline\textsuperscript{13} suggests that current anticoagulation treatment be continued if well tolerated in patients with active cancer. However, this is a weak recommendation and was based on the opinion of the committee members due to the lack of evidence.

**Limitations**

The main limitation of this report is the lack of high-quality evidence regarding long-term pharmacological thromboprophylaxis in patients with cancer. Several of the recommendations were based on evidence of very low to low quality, and some were based on the expert opinion of the guideline panel. The authors of the included guidelines also noted the knowledge gap and the need for future research. The long-term studies were mostly 6 to 12 months in duration; therefore, clinical evidence regarding the benefits and risks of treatment longer than 12 months is limited. The authors of the guidelines also noted that studies specifically in patients with cancer were also limited. Because the strength of recommendations depends on the quality of the evidence identified, several recommendations were weak or conditional.

No guidelines were identified regarding long-term thromboprophylaxis for the other types of cancer-associated thrombosis such as arterial thrombosis or chronic DIC.

**Conclusions and Implications for Decision- or Policy-Making**

Six evidence-based guidelines were identified regarding long-term use of pharmacological thromboprophylaxis for the management of cancer-associated thrombosis.\textsuperscript{9-14} They were generally well developed, used rigorous methods, were clearly presented, and were reviewed by stakeholders. Three\textsuperscript{9,11,12} of the guidelines were specific to patients with cancer-associated thrombosis, and 3\textsuperscript{10,13,14} were more general and considered all patients with a VTE disease. Although the guidelines were developed by North American, European, and international groups, their use was not specifically restricted to those countries. No guidelines were identified regarding the long-term management of other types of cancer-associated thrombosis such as arterial thrombosis and chronic DIC.

In 5 guidelines,\textsuperscript{11-14} long-term (i.e., > 6 months) anticoagulation is recommended for patients with active cancer and VTE to prevent recurrence of VTE. These are conditional or weak recommendations based on low-quality evidence or by expert consensus. Three guidelines recommend regular reassessments of the risks and benefits of anticoagulation after 6 months of treatment.\textsuperscript{9,11,13} Patient preferences should also be taken into consideration.\textsuperscript{9,13} This recommendation is made based on expert consensus due to lack of evidence. One guideline
makes a conditional recommendation to continue anticoagulation for an indefinite period, rather than discontinue after a definite period, in patients with active cancer.\textsuperscript{12}

Regarding the type of anticoagulant to be used for long-term thromboprophylaxis, 2 guidelines\textsuperscript{11,12} recommend LMWHs or DOACs for patients with active cancer; 1 guideline\textsuperscript{12} based this recommendation on very low-certainty evidence and the other guideline\textsuperscript{11} based the recommendation on high-certainty evidence. The degree of certainty of evidence reflects the confidence of the guideline panel that the effect estimate is close to the true effect, ranging from high to very low. If the patients cannot receive DOACs or LMWHs, VKAs may be used, as recommended by 2 guidelines.\textsuperscript{11,14} The authors of 2 guidelines\textsuperscript{10,11} reported that in patients with gastrointestinal or genitourinary cancers there is high-quality evidence that DOACs are associated with a higher risk of major bleeding; therefore, DOACs are recommended for long-term treatment in patients with cancer not located in these sites (moderate-to-strong recommendation based on high-quality evidence).\textsuperscript{10} Lastly, 1 guideline\textsuperscript{13} suggests continuing current anticoagulation in patients with cancer, if it is well tolerated. However, the recommendation is weak and based on expert opinion.

Overall, the recommendations made by these different guidelines were consistent; however, several recommendations were weak or conditional due to a lack of high-quality evidence. The authors of the guidelines suggested that the weak evidence base was due to limited studies conducted specifically in patients with active cancer. As most of the long-term studies ranged from 6 months to 12 months in duration, the risks and benefits of anticoagulation beyond 12 months is less clear. Some recommendations about the duration of anticoagulation were therefore made based on expert judgment and consensus. Future research on the benefits and harms of pharmacological thromboprophylaxis beyond 12 months in patients with active cancer is warranted. Because some decisions were recommended to be made based on patient preferences and individual risk-benefit profiles, patient engagement may play an important role in clinical decision-making.
References


Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

- 332 citations identified from electronic literature search and screened
  - 293 citations excluded
  - 39 potentially relevant articles retrieved for scrutiny (full text, if available)
    - 3 potentially relevant reports retrieved from other sources (grey literature, handsearch)
    - 42 potentially relevant reports
      - 36 reports excluded:
        - irrelevant intervention (2)
        - published in language other than English (2)
        - previous versions, or summaries of included guidelines (5)
        - guidelines of unclear methodology (10)
        - other (review articles, consensus) (17)
      - 6 reports included in review
## Appendix 2: Characteristics of Included Publications

### Table 2: Characteristics of Included Guidelines

<table>
<thead>
<tr>
<th>Intended users, target population</th>
<th>Intervention and practice considered</th>
<th>Major outcomes considered</th>
<th>Evidence collection, selection, and synthesis</th>
<th>Evidence quality assessment</th>
<th>Recommendations development and evaluation</th>
<th>Guideline validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASH Guideline, 2021</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>All modalities for the prevention and treatment of VTE for patients with cancer. Relevant intervention: long-term (≥ 6 months) pharmacological thromboprophylaxis</td>
<td>Mortality, PE, DVT, major bleeding,</td>
<td>Evidence collected using a systematic literature review</td>
<td>Quality assessment of the studies done using Cochrane Risk of bias tool. Certainty of evidence was assessed using the GRADE approach. (ranging from very low to high certainty)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Recommendations were formulated using Evidence-to-Decision framework. Recommendations were developed by discussion and consensus by an expert interdisciplinary panel on balance of benefit and harms, assumptions and preferences related to the decision. Recommendations are labelled strong or conditional.</td>
<td>External review by stakeholders, reviews by Guideline Oversight Subcommittee and the ASH Committee on Quality, and peer review (before publication)</td>
</tr>
<tr>
<td><strong>CHEST Guideline, 2021</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>All modalities for the prevention and treatment of venous thromboses, Relevant intervention: Long-term (≥ 6 months) pharmacological thromboprophylaxis in patients with cancer</td>
<td>Recurrence of VTE, major bleeding, all-cause mortality</td>
<td>Evidence collected using a systematic literature review</td>
<td>Certainty of evidence was assessed using the GRADE approach. (ranging from very low to high certainty)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Recommendations were formulated using Evidence-to-Decision framework. Consensus by expert panel (modified Delphi technique) was used to finalize the recommendations. Strength of recommendations grouped as 2 categories: Strong and weak, based on the extend of confidence in the risk-benefit profile.</td>
<td>External review and peer review before publication</td>
</tr>
</tbody>
</table>

<sup>a</sup> GRADE: Grading of Recommendations Assessment, Development, and Evaluation.
<table>
<thead>
<tr>
<th>Intended users, target population</th>
<th>Intervention and practice considered</th>
<th>Major outcomes considered</th>
<th>Evidence collection, selection, and synthesis</th>
<th>Evidence quality assessment</th>
<th>Recommendations development and evaluation</th>
<th>Guideline validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESVS Guideline, 2021</strong></td>
<td>All modalities for the prevention and treatment of venous thromboses, Relevant intervention: Long-term (≥ 6 months) pharmacological thromboprophylaxis in patients with cancer</td>
<td>Recurrence of VTE, major bleeding</td>
<td>Evidence collected using a systematic literature review</td>
<td>Evidence levels A: evidence from multiple RCTs or meta-analyses B: evidence from single RCT or large non-randomized studies C: consensus of experts' opinion or evidence from small retrospective studies</td>
<td>Recommendations were formulated using consensus among the guideline development group. Class of Recommendations: Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective Class II: Conflicting evidence Class IIa: Weight of evidence/opinion is in favour usefulness/ efficacy Class IIb: Usefulness/ efficacy is less well established by evidence/opinion Class III: Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful</td>
<td>Lay summaries were evaluated by patients External review not reported</td>
</tr>
<tr>
<td><strong>ASCO Guideline, 2020</strong></td>
<td>All modalities for the prevention and treatment of VTE for patients with cancer Relevant intervention: Long-term (≥ 6 months) pharmacological thromboprophylaxis</td>
<td>Recurrence of VTE, major bleeding</td>
<td>Evidence collected using a systematic literature review</td>
<td>Assessed using GRADE approacha</td>
<td>Guideline developed using GRADE methodology. Consensus by expert panel (modified Delphi technique) was used in situations with limited or lack of evidence. Strength of recommendations grouped as 3 categories: strong, moderate, and weak, based on the extent of confidence in the risk-benefit profile.</td>
<td>By an expert panel; and peer review before publication</td>
</tr>
<tr>
<td>Intended users, target population</td>
<td>Intervention and practice considered</td>
<td>Major outcomes considered</td>
<td>Evidence collection, selection, and synthesis</td>
<td>Evidence quality assessment</td>
<td>Recommendations development and evaluation</td>
<td>Guideline validation</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>NICE Guideline, 2020</strong>¹³</td>
<td>All modalities for the diagnosis and management of VTE Relevant intervention: long-term (≥ 6 months) pharmacological thromboprophylaxis</td>
<td>Recurrence of VTE, major bleeding</td>
<td>Evidence collected using a systematic literature review</td>
<td>ROBIS tool for systematic reviews, PROBAST tool for individual studies Quality of evidence assessed using GRADE approachᵃ</td>
<td>Recommendations were formulated by discussion and consensus among the guideline development group. Strength of recommendations were graded as strong or weak based on the risk-benefit profile. Strength of recommendations were indicated in the wording.</td>
<td>Stakeholder review of the draft guideline.</td>
</tr>
<tr>
<td><strong>ITAC Guideline, 2019</strong>⁹</td>
<td>All modalities for the diagnosis and management of cancer-associated thrombosis Relevant intervention: long-term (≥ 6 months) pharmacological thromboprophylaxis</td>
<td>Recurrence of VTE, major and minor bleeding, mortality, thrombocytopenia</td>
<td>Evidence collected using a systematic literature review</td>
<td>Quality of evidence assessed using GRADE approachᵃ And graded from A (high) to D (very low)</td>
<td>Recommendations were formulated using consensus among the guideline development group. Expert judgment based on professional experience and consensus of experts were used in situations with limited or no evidence. Strength of recommendations grouped as 2 categories: Strong (Grade 1) and weak (grade 2), based on the extend of confidence in the risk-benefit profile.</td>
<td>Reviewed by an advisory panel, which included clinicians, nurses, and patient advocates. Additional peer review was conducted before publication in the journal.</td>
</tr>
</tbody>
</table>

ASC = American Society of Clinical Oncology; ASH = American Society of Hematology; CHEST = The American College of Chest Physicians; DVT = deep vein thrombosis; ESVS = European Society for Vascular Surgery; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITAC = International Initiative on Thrombosis and Cancer; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; PROBAST = Prediction model Risk Of Bias A3essment Tool; RCT = randomized controlled trial; ROBIS = A Risk of Bias Assessment Tool for Systematic Reviews; VTE = venous thromboembolism
Certainty of evidence was assessed using the GRADE approach, with the following ratings:

Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Note that this table has not been copy-edited.
Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines Using AGREE II\textsuperscript{15}

<table>
<thead>
<tr>
<th>Item</th>
<th>ASH Guideline, 2021\textsuperscript{12}</th>
<th>CHEST Guideline, 2021\textsuperscript{14}</th>
<th>ESVS Guideline, 2021\textsuperscript{10}</th>
<th>ASCO Guideline, 2020\textsuperscript{11}</th>
<th>NICE Guideline, 2020\textsuperscript{13}</th>
<th>ITAC Guideline, 2019\textsuperscript{9}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain 1: Scope and Purpose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The overall objective(s) of the guideline is (are) specifically described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. The health question(s) covered by the guideline is (are) specifically described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Domain 2: Stakeholder Involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The guideline development group includes individuals from all relevant professional groups.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. The views and preferences of the target population (patients, public, etc.) have been sought.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes- in the form of review of lay summary of guideline</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes- in the form of review of summary of guideline</td>
</tr>
<tr>
<td>6. The target users of the guideline are clearly defined.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Domain 3: Rigour of Development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Systematic methods were used to search for evidence.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8. The criteria for selecting the evidence are clearly described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9. The strengths and limitations of the body of evidence are clearly described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10. The methods for formulating the recommendations are clearly described.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11. The health benefits, side effects, and risks have been considered in formulating the recommendations.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Item</td>
<td>ASH Guideline, 2021&lt;sup&gt;12&lt;/sup&gt;</td>
<td>CHEST Guideline, 2021&lt;sup&gt;14&lt;/sup&gt;</td>
<td>ESVS Guideline, 2021&lt;sup&gt;15&lt;/sup&gt;</td>
<td>ASCO Guideline, 2020&lt;sup&gt;11&lt;/sup&gt;</td>
<td>NICE Guideline, 2020&lt;sup&gt;13&lt;/sup&gt;</td>
<td>ITAC Guideline, 2019&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>12. There is an explicit link between the recommendations and the supporting evidence.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear but likely</td>
<td>Yes</td>
</tr>
<tr>
<td>13. The guideline has been externally reviewed by experts before its publication.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>14. A procedure for updating the guideline is provided.</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Domain 4: Clarity of Presentation

<table>
<thead>
<tr>
<th>Item</th>
<th>ASH Guideline, 2021&lt;sup&gt;12&lt;/sup&gt;</th>
<th>CHEST Guideline, 2021&lt;sup&gt;14&lt;/sup&gt;</th>
<th>ESVS Guideline, 2021&lt;sup&gt;15&lt;/sup&gt;</th>
<th>ASCO Guideline, 2020&lt;sup&gt;11&lt;/sup&gt;</th>
<th>NICE Guideline, 2020&lt;sup&gt;13&lt;/sup&gt;</th>
<th>ITAC Guideline, 2019&lt;sup&gt;9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. The recommendations are specific and unambiguous.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>16. The different options for management of the condition or health issue are clearly presented.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>17. Key recommendations are easily identifiable.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Domain 5: Applicability

<table>
<thead>
<tr>
<th>Item</th>
<th>ASH Guideline, 2021&lt;sup&gt;12&lt;/sup&gt;</th>
<th>CHEST Guideline, 2021&lt;sup&gt;14&lt;/sup&gt;</th>
<th>ESVS Guideline, 2021&lt;sup&gt;15&lt;/sup&gt;</th>
<th>ASCO Guideline, 2020&lt;sup&gt;11&lt;/sup&gt;</th>
<th>NICE Guideline, 2020&lt;sup&gt;13&lt;/sup&gt;</th>
<th>ITAC Guideline, 2019&lt;sup&gt;9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. The guideline describes facilitators and barriers to its application.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>19. The guideline provides advice and/or tools on how the recommendations can be put into practice.</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes- using a web-based app</td>
</tr>
<tr>
<td>20. The potential resource implications of applying the recommendations have been considered.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>21. The guideline presents monitoring and/or auditing criteria.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Domain 6: Editorial Independence

<table>
<thead>
<tr>
<th>Item</th>
<th>ASH Guideline, 2021&lt;sup&gt;12&lt;/sup&gt;</th>
<th>CHEST Guideline, 2021&lt;sup&gt;14&lt;/sup&gt;</th>
<th>ESVS Guideline, 2021&lt;sup&gt;15&lt;/sup&gt;</th>
<th>ASCO Guideline, 2020&lt;sup&gt;11&lt;/sup&gt;</th>
<th>NICE Guideline, 2020&lt;sup&gt;13&lt;/sup&gt;</th>
<th>ITAC Guideline, 2019&lt;sup&gt;9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. The views of the funding body have not influenced the content of the guideline.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>23. Competing interests of guideline development group members have been recorded and addressed.</td>
<td>Yes</td>
<td>Yes-though not available with the publication</td>
<td>Yes-though not available with the publication</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Note that this table has not been copy-edited.
## Appendix 4: Main Study Findings and Authors’ Conclusions

### Table 4: Summary of Recommendations: Duration of Anticoagulation

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations and supporting evidence</th>
<th>Quality of evidence and strength of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASH Guideline, 2021</strong></td>
<td><strong>Recommendation:</strong> “For patients with active cancer and VTEs, the ASH guideline panel suggests long-term anticoagulation for secondary prophylaxis (&gt;6 months) rather than short-term treatment alone (3-6 months).” (p.957)(^{12})&lt;br&gt;<strong>Evidence:</strong> One study that directly compared short-term vs. long-term anticoagulation and 1 single-arm study provided evidence to inform this recommendation.&lt;br&gt;Long-term anticoagulation had no impact on mortality (1 study), may lower recurrent thrombotic events (i.e., VTE, PE, DVT) (2 studies) in patients with cancer.&lt;br&gt;Long-term anticoagulation may increase the risk of major bleeding (1 study) in patients with cancer.&lt;br&gt;10 RCTs conducted in patients without cancer provided additional indirect evidence to inform this recommendation.&lt;br&gt;The guideline authors pointed out the knowledge gap and the need for additional data on this topic.</td>
<td>Quality of evidence: Low certainty&lt;br&gt;Strength of recommendation: Conditional</td>
</tr>
<tr>
<td><strong>CHEST Guideline, 2021</strong></td>
<td><strong>Recommendation:</strong> &quot;In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), we recommend offering extended-phase anticoagulation with a DOAC.” (p.e4)(^{14})&lt;br&gt;Note: Active cancer was considered as a ‘persistent risk factor’ in the guideline&lt;br&gt;<strong>Evidence:</strong> A meta-analysis of 15 studies provided the evidence to form this recommendation. It was unclear whether any or all of these studies were among patients with active cancer.</td>
<td>Quality of evidence: Moderate&lt;br&gt;Strength of recommendation: Strong</td>
</tr>
<tr>
<td>Guideline</td>
<td>Recommendations and supporting evidence</td>
<td>Quality of evidence and strength of recommendations</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
</tbody>
</table>
| ASCO Guideline 2020¹¹             | **Recommendation:** “Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile.” (p.505)¹¹  
**Evidence:** Recommendation was formulated based on informal consensus.  
The authors noted the limited evidence about the risk-benefit profile of anticoagulation beyond 6 months. Expert panel suggested that, in selected patients, long-term anticoagulation (> 6 months) should be considered because of the risk of recurrence. | Quality of evidence: Low  
Strength of recommendation: Weak to moderate |
| NICE Guideline, 2020¹³            | **Recommendation:** “Consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) after an unprovoked DVT or PE. Base the decision on the balance between the person's risk of venous thromboembolism (VTE) recurrence and their risk of bleeding. Discuss the risks and benefits of long-term anticoagulation with the person, and take their preferences into account.” (p.19)¹³  
**Evidence:** Unclear.  
The committee members noted that the quality of the overall evidence base was very low.  
Strength of recommendation: Weak |Quality of evidence: Unclear.  
Strength of recommendation: Weak |
| ITAC Guideline, 2019⁹             | **Recommendation:** “LMWH or direct oral anticoagulants should be used for a minimum of 6 months to treat established VTE in patients with cancer.” (p.e569)⁹  
**Evidence:** 1 meta-analyses (of 16 studies) provided evidence to formulate this recommendation.  
Compared to VKA, LMWH was associated with a statistically significant (42%) reduction in the risk of recurrence of VTE, and no difference were found in the rates of major or minor bleeding, 12-month mortality or thrombocytopenia (8 studies). The meta-analysis did not find any significant differences between VKA and DOACs for these outcomes (5 studies).  
**Recommendation:** "After 6 months, termination or continuation of anticoagulation (LMWH, direct oral anticoagulants, or vitamin K antagonists) should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance in the absence of data).” (p.e569)⁹  
**Evidence:** Recommendation was formulated based on expert judgment and consensus due to limited/lack of evidence. | Quality of evidence: High (level A)  
Strength of recommendation: Strong (grade 1) |

AGREE II = Appraisal of Guidelines for Research and Evaluation II; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CHEST = The American College of Chest Physicians; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; ESVS = European Society for Vascular Surgery; ITAC = International Initiative on Thrombosis and Cancer; LMWH = low-molecular-weight heparin; NA = not applicable; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.  
Note that this table has not been copy-edited.
Table 5: Summary of Recommendations: Choice of Anticoagulants for Long-Term Thromboprophylaxis

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations and supporting evidence</th>
<th>Quality of evidence and strength of recommendations</th>
</tr>
</thead>
</table>
| ASH Guideline, 2021      | **Recommendation:** “For patients with active cancer and VTEs requiring long-term anticoagulation (>6 months), the ASH guideline panel suggests using DOACs or LMWH.” (p.957)<sup>12</sup>  
**Evidence:** One RCT provided evidence to inform this recommendation. Compared to LMWHs, DOACs may lower recurrent thrombotic events (i.e., VTE, PE, DVT) (1 study). DOACs may also increase the risk of mortality and major bleeding (1 study). | Quality of evidence: Very low certainty  
Strength of recommendation: Conditional |
| CHEST Guideline, 2021    | **Recommendation:** “In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, we suggest offering extended-phase anticoagulation with a VKA.” (p.e4)<sup>14</sup>  
**Note:** Active cancer was considered as a ‘persistent risk factor’ in the guideline.  
**Evidence:** A meta-analysis of 15 studies provided the evidence to form this recommendation. It was unclear whether any or all of these studies were among patients with active cancer.  
**Remarks:** “The recommendation to offer extended-phase anticoagulation would not automatically imply that all patients with unprovoked VTE receive extended therapy. Patient preference and predicted risk of recurrent VTE or bleeding should also influence the decision to proceed with, or continue, extended-phase anticoagulation therapy.” (p.e4)<sup>14</sup>  
“Patients who receive extended-phase anticoagulation should have this decision re-evaluated at least on an annual basis, and at times of significant change in health status.” (p.e4)<sup>14</sup>  
“Extended-phase anticoagulation does not have a predefined stop date. However, studies of extended-phase anticoagulation followed patients for durations of about 2 to 4 years. Although most patients in these studies did not stop anticoagulation therapy at the end of follow-up, the risk-to-benefit balance of continuing extended anticoagulation therapy beyond this time is uncertain.” (p.e4)<sup>13</sup> | Quality of evidence: Moderate  
Strength of recommendation: Weak |
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations and supporting evidence</th>
<th>Quality of evidence and strength of recommendations</th>
</tr>
</thead>
</table>
| **ESVS** Guideline, 2021<sup>10</sup> | **Recommendation:** “For patients with active cancer-associated deep vein thrombosis, switching from a low-molecular-weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment.” (p.62)<sup>10</sup>  
**Evidence:** From consensus. In a meta-analysis of 4 studies, it was found that DOACs are more effective than dalteparin in preventing recurrence of VTE. There were no significant differences in the rates of major bleeding between the 2 groups of drugs. | Quality of evidence: high (level A)  
Strength of recommendation: class I (given treatment or procedure is beneficial, useful, and effective) |
| **Recommendation:** “In selected patients with cancer-associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, an approved direct oral anticoagulant for initial, principal, and extended treatment should be considered.” (p.62)<sup>10</sup>  
**Evidence:** 5 studies provided evidence to form this recommendation. | Quality of evidence: High (level A)  
Strength of recommendation: Class IIa (There is some conflicting evidence but, weight of evidence is favours a benefit of treatment) |
| **ASCO** Guideline, 2020<sup>11</sup> | **Recommendation:** “For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or DOACs are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a DOAC.” (p.505)<sup>11</sup>  
**Evidence:**  
Evidence from 4 meta-analyses found that LMWH is more effective than VKAs in reducing risk of recurrence of VTE.  
Evidence from 3 MAs showed that risk of recurrent VTE was similar in DOACs and LMWHs; however, DOACs were associated with a higher risk of major bleeding.  
Evidence from 8 MAs that found that the risk of recurrent VTE and major bleeding were not different between DOACs and VKAs (1 MA found a significant benefit with rivaroxaban) However, these studies were not specific to patients with active cancer, so findings should be interpreted with caution. | Quality of evidence: High  
Strength of recommendation: Strong |
### NICE Guideline, 2020

**Recommendation:** For people with renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (less than 50 kg or more than 120 kg), consider carrying on with the current treatment if it is well tolerated.”(p.19)

**Evidence:** Unclear

Guideline authors noted the lack of evidence on long-term treatment for patients with active cancer and other conditions. Committee members suggested continuing the current treatment for this group if the current treatment is well tolerated, after considering patient preferences and clinical situation.

**Quality of evidence:** Unclear

**Strength of recommendation:** Weak

---

AGREE II = Appraisal of Guidelines for Research and Evaluation II; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CHEST = The American College of Chest Physicians; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; ESVS = European Society for Vascular Surgery; ITAC = International Initiative on Thrombosis and Cancer; LMWH = low-molecular-weight heparin; MA = meta-analysis; NA = not applicable; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Note that this table has not been copy-edited.
Appendix 5: References of Potential Interest

Review Articles

Consensus Statements

Guidance Documents, Methodology Not Reported

Additional References