CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

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Background: Venous thromboembolism (VTE) is a common complication among patients with cancer. Patients with cancer and VTE are at a markedly increased risk for morbidity and mortality.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the prevention and treatment of VTE in patients with cancer.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The guideline development process was supported by updated or new systematic evidence reviews. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess evidence and make recommendations.

Results: Recommendations address mechanical and pharmacological prophylaxis in hospitalized medical patients with cancer, those undergoing a surgical procedure, and ambulatory patients receiving cancer chemotherapy. The recommendations also address the use of anticoagulation for the initial, short-term, and long-term treatment of VTE in patients with cancer.

Conclusions: Strong recommendations include not using thromboprophylaxis in ambulatory patients receiving cancer chemotherapy at low risk of VTE and to use low-molecular-weight heparin (LMWH) for initial treatment of VTE in patients with cancer. Conditional recommendations include using thromboprophylaxis in hospitalized medical patients with cancer, LMWH or fondaparinux for surgical patients with cancer, LMWH or direct oral anticoagulants (DOAC) in ambulatory patients with cancer receiving systemic therapy at high risk of VTE and LMWH or DOAC for initial treatment of VTE, DOAC for the short-term treatment of VTE, and LMWH or DOAC for the long-term treatment of VTE in patients with cancer.

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Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Center with international collaborators. The panel followed best practice for guideline development recommended by the National Academy of Medicine (formerly Institute of Medicine) and the Guidelines International Network (GIN).[1-4] The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.[5-11] Patients with cancer are at greater risk for venous thromboembolism (VTE) compared with the general population, resulting in considerable morbidity, mortality, and costs. Although 5% to 20% of patients with cancer develop a VTE, ~20% of all VTE cases occur in patients with cancer. The risks of VTE, bleeding, and early mortality among patients receiving systemic cancer therapy vary by cancer type and treatment, as well as patient-specific factors. In addition to the overall increased risk for VTE among patients with cancer, VTE risk is especially high among certain cancer subgroups, hospitalized patients, those undergoing active antineoplastic therapy, and those receiving certain supportive care measures.[12,13] Cancer patients who develop VTE are at greater risk for recurrent VTE and early death. There are few data on the impact of thrombosis on quality of life for cancer patients. Nevertheless, the occurrence of VTE for patients with cancer may interfere with planned chemotherapy regimens, worsen patient quality of life, increase the risk of cancer recurrence and mortality, and result in increased costs compared with patients without cancer who experience VTE. Pharmacologic options for VTE treatment and prevention include unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux (an indirect synthetic inhibitor of activated factor Xa), vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs; previously known as novel oral anticoagulants), including direct thrombin inhibitors and direct factor Xa inhibitors. Treatment or prophylaxis of VTE for patients with cancer must always balance the risk of recurrent VTE events with the increased risk of anticoagulant-related bleeding and take into consideration the consequences of these outcomes (including mortality, financial cost, quality of life), as well as patient values and preferences.[14]

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Recommendations

Primary prophylaxis for hospitalized medical patients with cancer. RECOMMENDATION 1. For hospitalized medical patients with cancer without VTE, the American Society of Hematology (ASH) guideline panel *suggests* using thromboprophylaxis over no thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 2. For hospitalized medical patients with cancer without VTE, in which pharmacological thromboprophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 3. For hospitalized medical patients with cancer without VTE, the ASH guideline panel *suggests* using pharmacological thromboprophylaxis over mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 4. For hospitalized medical patients with cancer without VTE, the ASH guideline panel *suggests* using pharmacological thromboprophylaxis over a combination of

pharmacological and mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 5. For hospitalized medical patients with cancer, the ASH guideline panel *suggests* discontinuing thromboprophylaxis at the time of hospital discharge rather than continuing thromboprophylaxis beyond the discharge date (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Primary prophylaxis for patients with cancer undergoing surgery. RECOMMENDATION 6. For patients with cancer without VTE undergoing a surgical procedure at lower bleeding risk, the ASH guideline panel *suggests* using pharmacological rather than mechanical thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 7. For patients with cancer without VTE undergoing a surgical procedure at high bleeding risk, the ASH guideline panel *suggests* using mechanical rather than pharmacological thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 8. For patients with cancer without VTE undergoing a surgical procedure at high risk for thrombosis, except in those at high risk of bleeding, the ASH guideline panel *suggests* using a combination of mechanical and pharmacologic thromboprophylaxis rather than mechanical prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects) or pharmacologic thromboprophylaxis alone (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 9. For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using LMWH or fondaparinux for thromboprophylaxis rather than UFH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 10. For patients with cancer undergoing a surgical procedure, the ASH guideline panel makes no recommendation on the use of VKA or DOAC for thromboprophylaxis, because there were no studies available.

RECOMMENDATION 11. For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using postoperative thromboprophylaxis over preoperative thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 12. For patients with cancer who had undergone a major abdominal/pelvic surgical procedure, the ASH guideline panel *suggests* continuing pharmacological thromboprophylaxis postdischarge rather than discontinuing at the time of hospital discharge (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Primary prophylaxis in ambulatory patients with cancer receiving systemic therapy. RECOMMENDATION 13. For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, we *recommend* no thromboprophylaxis over parenteral thromboprophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no prophylaxis over parenteral prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* parenteral thromboprophylaxis (LMWH) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

RECOMMENDATION 14. For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel *recommends* no thromboprophylaxis over oral thromboprophylaxis with VKA (strong recommendation, very low certainty in the evidence of benefits ⊕◯◯◯, but high certainty about the harms ⊕⊕⊕⊕).

RECOMMENDATION 15. For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

RECOMMENDATIONS 16 AND 17. For multiple myeloma patients receiving lenalidomide, thalidomide, or pomalidomide-based regimens, the ASH guideline panel *suggests* using low-dose acetylsalicylic acid (ASA) or fixed low-dose VKA or LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Primary prophylaxis for patients with cancer with central venous catheter. RECOMMENDATION 18. For patients with cancer and a central venous catheter (CVC), the ASH guideline panel *suggests* not using parenteral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 19. For patients with cancer and a CVC, the ASH guideline panel *suggests* not using oral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Initial treatment (first week) for patients with active cancer and VTE. RECOMMENDATION 20. For patients with cancer and VTE, the ASH guideline panel *suggests* DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 21. For patients with cancer and VTE, we *recommend* LMWH over UFH for initial treatment of VTE for patients with cancer (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

RECOMMENDATION 22. For patients with cancer and VTE, the ASH guideline panel *suggests* LMWH over fondaparinux for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Short-term treatment for patients with active cancer (initial 3-6 months). RECOMMENDATION 23. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 24. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over VKA (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 25. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

RECOMMENDATION 26. For patients with cancer and incidental (unsuspected) pulmonary embolism (PE), the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 27. For patients with cancer and subsegmental PE (SSPE), the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 28. For patients with cancer and visceral/splanchnic vein thrombosis, the ASH guideline panel *suggests* treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 29. For patients with cancer with CVC-related VTE receiving anticoagulant treatment, the ASH guideline panel *suggests* keeping the CVC over removing the CVC (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 30. For patients with cancer and recurrent VTE despite receiving therapeutic LMWH, the ASH guideline panel *suggests* increasing the LMWH dose to a supratherapeutic level or continuing with a therapeutic dose (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 31. For patients with cancer and recurrent VTE despite anticoagulation treatment, the ASH guideline panel *suggests* not using an inferior vena cava (IVC) filter over using a filter (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Long-term treatment (>6 months) for patients with active cancer and VTE. RECOMMENDATION 32. For patients with active cancer and VTE, the ASH guideline panel *suggests* long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 33. For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel *suggests* continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 34. For patients with active cancer and VTE requiring long-term anticoagulation (>6 months), the ASH guideline panel *suggests* using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Values and preferences

The guideline panel rated mortality, PE, deep venous thrombosis (DVT), and major bleeding as critical for decision making and placed a high value on these outcomes and avoiding them with the interventions that were evaluated.

Explanations and other considerations

These recommendations take into consideration cost and cost-effectiveness, impact on health equity, acceptability, and feasibility.

Good practice statement 1. Patients with cancer are at increased risk for VTE, as well as major bleeding. Any consideration of thromboprophylaxis or treatment for patients with cancer should be based on an assessment of the patient's individual risk for thrombosis and major bleeding after full discussion of the potential benefits and harms.

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide graded evidence-based recommendations on the prevention and treatment of VTE for patients with cancer. Recommendations take into consideration the strength of the evidence, risks of mortality, VTE, and bleeding, as well as quality of life, acceptability, and cost considerations. Through improved provider and patient awareness of the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision making that will result in a reduction in the frequency of primary VTE or recurrent VTE, as well as the risk of bleeding complications, morbidity, and costs leading to improved quality of life and an enhanced patient experience.

The target audience for the guidelines includes patients, hematologists, oncologists, general practitioners, internists, and other clinicians involved in the care of patients with VTE and cancer. These guidelines will also be of interest to policy-developing local, national, or international efforts to reduce the incidence of VTE, morbidity, and mortality, as well as the cost of VTE to patients and society. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

Patients with cancer are at greater risk for VTE than is the general population, resulting in considerable morbidity, mortality, and costs.[13,15-23] Approximately 20% of all cases of VTE occur in

patients with cancer. In addition, VTE affects up to 20% of patients with cancer before death and has been reported in up to half of postmortem examinations of cancer patients. Cancer patients who develop VTE are at a greater risk for recurrent VTE and early death.[19,23] Although the average risk of VTE for patients with cancer who are eligible for clinical trials is low, the risk of VTE may be considerably greater for unselected patients with cancer.[13,24-26] The risks of VTE, bleeding, and early mortality among patients receiving systemic cancer therapy varies by cancer type, cancer treatment, and other patient-specific factors. Many cancer therapies, including surgery, chemotherapy, hormonal therapy, and some targeted cancer treatments, (eg, thalidomide and lenalidomide) appear to increase the risk of VTE.[16,27,28] Furthermore, VTE risk is especially high among certain subgroups, such as hospitalized patients, those undergoing systemic cancer therapy, and those with metastatic disease.[29-32] Other factors that have been associated with an increased risk for VTE include advanced age, male gender, and cancer-related factors, including cancer type and disease stage. Sites of cancer with the highest rates of VTE include the pancreas, kidney, ovary, lung, and stomach.[13,15] In addition to antineoplastic therapies, certain supportive care measures used in cancer treatment appear to increase the risk of VTE, including red blood cell transfusions, as well as erythropoietin-stimulating agents for managing anemia for patients undergoing cancer treatment.[33] The identification of multiple factors, including biomarkers, associated with the risk of cancer-associated VTE has prompted the development of risk scores for predicting VTE and its complications.[14]

The occurrence of VTE in patients with cancer may interfere with planned chemotherapy regimens, increase the risk of mortality, and result in increased costs compared with patients without cancer.[34,35] However, the impact of VTE extends beyond the physical and economic; it also has considerable effect on cancer patients' quality of life. Several qualitative studies have explored patients' experiences of cancer-associated thrombosis, with consistent reports of VTE causing considerable distress to patients with cancer and their families.[36-38] Some have even reported the experience of VTE to be more upsetting than that of the cancer. More than 50% of thrombotic events occur within 3 months of the cancer diagnosis, a time when most cancer treatments will be underway. Patients, who are still coming to terms with a recent cancer diagnosis, often view the occurrence of VTE as a further threat to life, confirmation of the severity of their condition, and a poor prognostic sign.

Pharmacologic prophylactic and treatment options for VTE consist of UFH, LMWHs, fondaparinux (an indirect synthetic inhibitor of activated factor Xa), VKAs, and DOACs, including direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban).[30,39] Consideration for the prophylaxis or treatment of VTE for patients with cancer must always balance the risk of VTE with the increased risk of bleeding with anticoagulation in patients with cancer. Treatment decisions should be individualized and take into consideration the potential consequences of VTE and/or bleeding events (including mortality, financial cost, quality of life), as well as patient values and preferences.[40] Clinicians should be aware that patients put particular trust in the opinions of their clinician when deciding on VTE treatment options.[41] As such, it is important to avoid assumptions regarding a patient's preferences. Intuitively, one might assume that patients would prefer an oral anticoagulant rather than a daily injection. However, data from discrete choice experiments and qualitative methodologies have shown that cancer patients most value an anticoagulant that does not interfere with their cancer treatment and has the best efficacy/safety profile over the convenience of oral administration.[36,41,42]

Likewise, patients will have differing views when balancing the risk of bleeding with a first or recurrent episode of VTE, depending on their experience and personal values. Sometimes, a high level of distress may seem to be incongruent with the severity of the bleeding event or VTE experienced, but it is more a reflection of what the event means to the patients. Longitudinal data have demonstrated that PE of minimal symptom burden may cause similar long-term psychological distress to those experiencing submassive PE and admission to intensive care.[43] This is a reflection of patients' understanding of PE, in that they are potentially life threatening and may occur again without warning.[37] Such patients may manifest symptoms similar to posttraumatic stress disorder.[44] Conversely, the distress and long-term psychological sequelae of experiencing a minor bleed (eg, self-limiting epistaxis or bruise) may be comparable to those experiencing major bleeding complications.[45] In summary, when engaging in shared decision-making, it is important to recognize that, for most patients, the diagnosis of cancer takes primacy over their VTE. It is also essential to understand that patients may have different values and priorities than those held by their clinician with respect to goals of anticoagulation and the risk/benefit ratio of bleeding vs recurrent VTE. These values and preferences may also change over time. Clinical decision-making tools may help to facilitate meeting patients' needs and avoid the risks associated with cognitive dissonance of the prescribing clinician.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[5-11] The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the National Academy of Medicine (formerly Institute of Medicine) and GIN.[1-4]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster GRADE Center (funded by ASH under a paid agreement).[46] Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (Adam Cuker) and vice chair (Holger J. Schünemann). ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Center vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process, including the use of the GRADE approach.[46] The membership of the panels and the GRADE center team is described in Supplement 1.

The panel included hematologists, internists, other physicians, and a pharmacist who all had clinical and research expertise on the guideline topic, methodologists with expertise in evidence appraisal and guideline development, and 1 patient representative. The panel cochairs were content experts. The vice chair was an internist and an expert in guideline-development methodology.

In addition to synthesizing evidence systematically, the McMaster GRADE Center supported the guideline-development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (http://www.surveymonkey.com and https://gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representative was offered, but declined, an honorarium of $200. The panelists received no other payments. Some researchers who contributed to the systematic evidence reviews received salary or grant support through the McMaster GRADE Center. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the National Academy of Medicine[47] and GIN.[4] At the time of appointment, a majority of the guideline panel, including 1 of the clinical cochairs and the vice chair, had no conflicts of interest as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process.

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms of all panel members. In Part A of the forms, individuals disclosed material interests for 2 years prior to appointment. In Part B, they disclosed interests that were not primarily financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was also used to manage conflicts of interest. During all deliberations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines were recused from making judgments about relevant recommendations.[4,48-50] The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2019, it was discovered that 1 panelist had direct financial conflicts with affected companies (travel reimbursement, spousal income for consulting) that had not been reported. In 2020, it was discovered that another panelist had a direct financial conflict with an affected company (stock ownership). Both disclosures were made after the recommendations were formed. Members of the Guideline Oversight Subcommittee reviewed the guidelines in relation to these late disclosures and agreed that these conflicts were unlikely to have influenced any of the recommendations.

None of the McMaster-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current material interest in a commercial entity with any product that could be affected by the guidelines. Supplement 3 provides the complete "Disclosure of Interest" forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (https://gradepro.org)[51] and SurveyMonkey (http://www.surveymonkey.com) to brainstorm and then prioritize the questions described in Table 1.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[52] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach. During this rating process, the panel used definitions of the outcomes ("marker states") that were developed for these guidelines. Rating outcomes by their relative importance can help to focus attention on those considered most important for clinicians and patients and help to resolve or clarify potential disagreements. The outcomes rated highly by the panel and those identified as important based on the literature reviews were further refined. While acknowledging considerable variation in the impact on patient outcomes, the panel considered the following outcomes as critical for clinical decision making across questions: mortality, PE, proximal DVT, distal DVT, major bleeding (including gastrointestinal [GI] bleeding), and heparin-induced thrombocytopenia (HIT). Reporting of thrombotic events across studies was inconsistent and variably reported as "any VTE," "any PE," "any DVT," "any proximal DVT," and "any distal DVT," sometimes preceded by "asymptomatic" or "symptomatic." Variation in event reporting resulted in considerable uncertainty for the panel in formulating recommendations.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Center prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (https://gradepro.org).[5,6,11] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before,

Table 1. Prioritized clinical questions

Primary prophylaxis for hospitalized medical patients with cancer
Thromboprophylaxis vs no thromboprophylaxis
LMWH vs UFH
Combination of methods vs pharmacological thromboprophylaxis
Mechanical vs pharmacological thromboprophylaxis
Continuation of thromboprophylaxis at home vs discontinuation at time of discharge
Primary prophylaxis for patients with cancer undergoing surgery
Pharmacological vs mechanical thromboprophylaxis
Combination of pharmacologic and mechanical prophylaxis vs mechanical thromboprophylaxis alone
Combination of pharmacologic and mechanical prophylaxis vs pharmacological thromboprophylaxis alone
LMWH vs UFH
Fondaparinux vs LMWH
Preoperative thromboprophylaxis vs immediate postoperative thromboprophylaxis
Extended (continue at home) vs limited (7-10 d; discontinue at the time of discharge)
Primary prophylaxis for ambulatory patients with cancer receiving systemic therapy
Parenteral thromboprophylaxis vs no thromboprophylaxis
VKA thromboprophylaxis vs no thromboprophylaxis
DOAC thromboprophylaxis vs no thromboprophylaxis
Low-dose ASA thromboprophylaxis vs fixed-dose VKA
Low-dose ASA vs LMWH
Primary prophylaxis for patients with cancer with CVC
Parenteral thromboprophylaxis vs no thromboprophylaxis
Oral thromboprophylaxis vs no thromboprophylaxis
Initial treatment (within first week) for patients with cancer
LMWH vs UFH
Fondaparinux vs LMWH
DOAC vs LMWH
Short-term treatment for patients with active cancer (initial 3-6 mo)
LMWH vs VKA
DOAC vs VKA
DOAC vs LMWH
Short-term treatment (3-6 mo) vs observation for patients with cancer and incidental PE
Short-term treatment (3-6 mo) vs observation for patients with cancer and SSPE
Short-term treatment (3-6 mo) vs observation for patients with cancer and visceral/splanchnic vein thrombosis
Keeping CVC vs removing CVC
Increasing dose to supratherapeutic levels vs continuing with standard therapeutic dose
Adding an IVC filter vs not for patients with cancer and recurrent VTEs, despite therapeutic anticoagulation treatment
Long-term treatment (>6 mo) for patients with active cancer and VTE
Long-term anticoagulation (>6 mo) vs short-term anticoagulation (3-6 mo)
Continuing indefinite anticoagulation vs stopping after completion of a definitive period of anticoagulation
DOAC vs LMWH for long-term anticoagulation

during, or after the guideline panel meeting, made suggestions for corrections, and identified missing evidence. To ensure that recent studies were not missed, searches (Supplement 4) originally conducted on 26 February 2016 have been continually updated for newly published studies. Panel members were also asked to identify any studies that may have been missed that fulfilled the inclusion criteria for the individual questions.

Under the direction of the McMaster GRADE Center, researchers followed the general methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (https://handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original investigators about risk of bias were randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or non-randomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.[5,6,11] Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of opposing plausible residual bias or confounding. The certainty was categorized into 4 levels ranging from very low to high and used a wording template to formulate statements that communicate findings combining size and certainty.[7-9] When conducting a GRADE assessment, investigators consider the width of the confidence intervals (CIs) and power of the analysis (ie, imprecision), as well as all of the other factors to determine the certainty in the evidence. Thus, the certainty around the point estimate varies depending on what domains demonstrate shortcomings; with the exception of imprecision, that certainty interval is not known. For this reason, when communicating an effect using statements, investigators should focus on the best estimate and on the certainty in that estimate, which considers multiple factors. The statements communicate the size of the effect based on the point estimate in a meta-analysis or on the summary estimate in a narrative synthesis instead of the CIs.

For each outcome, risk differences were calculated by applying baseline risk data to the relative effects. Representative cohort data were used as the source of baseline risk data, when available. When representative cohort data were not available, median or mean estimates of baseline risk of the control arms of the included studies were used. For cases in which more than a single baseline risk estimate was available, we used several baseline risks (eg, high risk and low risk). Baseline risk estimates are noted in the article along with the reference of the study data used. In cases in which the relative effects of PE or DVT were not available, the relative effects from VTE were used and applied to baseline risk data for PE or DVT.

In the evidence profiles, baseline risks (ie, control group event rate) from the trials were reported and included in the meta-analysis. Data from observational studies were reported in 2 separate rows in the Evidence Profiles. The risks selected from observational data were discussed and finalized with panel members prior to the panel voting on EtDs and formulating recommendations.

Following a 2-day in-person meeting along with subsequent online communication and conference calls, the panel developed clinical

Table 2. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. The approach is described in detail in the accompanying article describing the methods of development.[46]

Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The term "the guideline panel recommends" is used for strong recommendations, whereas the term "the guideline panel suggests" is used for conditional recommendations. Table 2 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and made available online on 17 October 2019 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Individuals or organizations submitted comments. The document was revised to include a newly published randomized controlled trial (RCT; Caravaggio trial) on 1 April 2020, which changed Recommendation 23.[53] On 8 September 2020, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline-development process was followed; on 11 September 2020, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared decision-making process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks, accompanying each recommendation are integral to the guideline and serve to facilitate more accurate interpretation. Qualifying remarks should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by forthcoming interactive decision aids and other implementation tools.[54] The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Recommendations

In the sections that follow, we summarize the evidence behind each recommendation, along with the following practice statement that should be considered across all recommendations. Given the complexity of anticoagulation management for cancer patients with VTE, the treatment course is divided as follows: initial treatment (within the first week), short-term anticoagulation (initial 3 to 6

months), and long-term anticoagulation (beyond 6 months). This is consistent with the terminology used in the "Treatment" section of the ASH VTE Guidelines.

We defined active cancer as (1) nonsquamous cell or basal cell invasive cancer diagnosed within 6 months before enrollment, (2) cancer treated within the previous 6 months, (3) recurrent or metastatic cancer, or (4) active cancer during the study. We included studies if the majority (>80%) of patients presented with active cancer, as defined above.

Primary prophylaxis for hospitalized medical patients with cancer

Should thromboprophylaxis vs no thromboprophylaxis be used for hospitalized medical patients with cancer without VTE?

Should LMWH vs UFH be used for hospitalized medical patients with cancer without VTE?

Recommendations 1 and 2

For hospitalized medical patients with cancer, the ASH guideline panel *suggests* using thromboprophylaxis over no thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). For patients in whom pharmacological thromboprophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: The panel acknowledges that some subgroups of patients may not benefit from VTE prophylaxis if their baseline risk of VTE is low or the associated risk of major bleeding is high. This may include patients admitted briefly for elective chemotherapy and those receiving palliative or end-of-life care. UFH is generally preferred over LMWH for patients with cancer and severe renal impairment defined as creatinine clearance <30 mL/min.

Thromboprophylaxis vs no thromboprophylaxis. SUMMARY OF THE EVIDENCE. We identified 1 systematic review[55] that analyzed subgroup data from patients with cancer from 3 RCTs (307 patients with cancer in 5134 study subjects).[56-58] Because of a lack of direct evidence, the guideline panel also included evidence from trials conducted on hospitalized medical patients from the 2018 ASH guidelines for management of VTE on prophylaxis for hospitalized and nonhospitalized medical patients.[59]

We found 17 systematic reviews that addressed VTE prophylaxis for medically ill patients,[60-76] with 24 studies in these reviews evaluating thromboprophylaxis vs no prophylaxis in acutely ill medical patients. All studies included hospitalized acutely ill medical inpatients but only a small proportion of patients had cancer.[57,77-97] The panel also considered the RCT by Cohen et al[57] (ARTEMIS) that compared fondaparinux against placebo and believed that the results were similar enough to include fondaparinux along with UFH and LMWH. The trials of hospitalized medical patients enrolled mixed populations of patients with acute medical conditions and/or reduced mobility, including patients with cancer or without cancer. No trials were identified that evaluated inpatient thromboprophylaxis in a cancer-specific population. Five included trials reported the proportion of patients with cancer, which ranged from 5% to 15% across trials. However, the definition of active cancer differed across studies, with some including a previous history of cancer in the definition. Primary thromboprophylaxis may not be appropriate for all cancer patients. An observational study of advanced cancer patients (Karnofsky score <50) admitted to specialist palliative care units identified that 28% (95% CI, 22-34) of scans were iliofemoral.[98] These patients had minimal attributable symptoms and no survival difference vs those with no DVT (mean survival, 44 days).[98] Coupled with a clinically relevant bleeding rate of 9.8% (95% CI, 8.3-11.6) associated with thromboprophylaxis use in specialist palliative care units, it could be argued that, in this particular cancer subgroup, the potential for harm outweighs any potential benefit that thromboprophylaxis may offer.[99] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/9pXn6iq6qng.

BENEFITS. Parenteral prophylactic anticoagulation (UFH, LMWH, or fondaparinux) compared with no thromboprophylaxis may reduce symptomatic proximal DVT, PE, and symptomatic distal DVT, as well as have little to no effect on mortality; however, the evidence is very uncertain. The panel judged these effects to be small (for symptomatic proximal DVT: relative risk [RR], 0.28; 95% CI, 0.06-1.37; absolute risk reduction [ARR], 22 fewer per 1000; 95% CI, 28 fewer to 11 more per 1000 based on a baseline risk of 3% for any DVT[100]; for PE: RR, 0.59; 95% CI, 0.45-0.78; ARR, 4 fewer per 1000; 95% CI, 2-6 fewer per 1000; for symptomatic distal DVT: RR, 0.75; 95% CI, 0.17-3.34; ARR, 8 fewer per 1000; 95% CI, 25 fewer to more per 1000 based on a baseline risk of 3% for any DVT[100]; for mortality: RR, 0.97; 95% CI, 0.91-1.04; ARR, 2 fewer per 1000; 95% CI, 6 fewer to 3 more per 1000) based on a baseline risk of 3% for any DVT.[100]

HARMS AND BURDEN. Parenteral prophylactic anticoagulation (UFH, LMWH, or fondaparinux) vs no thromboprophylaxis may result in little to no difference in major bleeding, but the evidence is very uncertain and likely results in little to no difference in thrombocytopenia. The panel judged these effects to be small (for major bleeding: RR, 1.48; 95% CI, 0.81-2.71; absolute risk increase [ARI], 3 more per 1000; 95% CI, 1 fewer to 12 more per 1000; for thrombocytopenia: RR, 0.95; 95% CI, 0.47-1.92; ARR, 0 per 1000; 95% CI, 1 fewer to 2 more per 1000), and 3 RCTs reported a potential small impact on thrombocytopenia (RR, 0.95; 95% CI, 0.47-1.92; ARR, 0 per 1000; 95% CI, 1 fewer to 2 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to the risk of bias, indirectness, and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. Three reports compared the cost-effectiveness of LMWH to no thromboprophylaxis for seriously ill medical patients and showed favorable cost-effectiveness for LMWH.[101-103] The panel concluded that there was no impact on health equity and that the use of any parenteral anticoagulant (UFH, LMWH, and fondaparinux) was considered acceptable and feasible.

LMWH vs UFH. SUMMARY OF THE EVIDENCE. We did not find any systematic reviews that addressed the question. Our systematic search for RCTs identified 2 analyses[104,105] that were conducted in hospitalized medical patients with cancer. One study is a post hoc analysis of the CERTIFY trial conducted in hospitalized

medical patients.[104] This post hoc analysis is a subgroup analysis of patients with cancer. The second study was not a trial of patients with cancer specifically; however, it was a large trial of hospitalized medical patients, some of whom had cancer.[105] For the evidence synthesis of this question, we pulled out data for the patients with cancer. The 2 studies reported on the effect of LMWH vs UFH on mortality:[104,105] 1 study on symptomatic DVT[104] and 1 study on major bleeding.[105] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/86dbRedTHj8.

BENEFITS. Compared with UFH, LMWH may reduce mortality slightly and may result in little or no difference in PE and symptomatic DVT, and the panel judged the effects to be small (for mortality: RR, 0.52; 95% CI, 0.18-1.53; ARR, 21 fewer per 1000; 95% CI, 36 fewer to 23 more per 1000; for PE: RR, 0.33; 95% CI, 0.01-8.04; ARR, 0 fewer per 1000; 95% CI, 0 fewer to 1 more per 1000 using a baseline risk of 0.01%[106]; for symptomatic DVT: RR, 0.98; 95% CI, 0.06-15.44; ARR, 1 fewer per 1000; 95% CI, 28 fewer to 433 more per 1000 using a baseline risk of 3%).[101]

HARMS AND BURDEN. Compared with UFH, LMWH may result in little to no difference in major bleeding, and the panel judged the impact to be trivial (RR, 1.06; 95% CI, 0.07-16.78; ARI, 2 more per 1000; 95% CI, 24 fewer to 410 more per 1000 using a baseline risk of 2.6%).[106]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low owing to serious imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel agreed that greater health care provider time is required with UFH, that multiple injections per days may also lead to dosing errors and disposal hazard, and that the drug acquisition cost of LMWH is higher than that of UFH. However, the overall resources required were judged negligible, and no direct data for cost-effectiveness were available. The panel concluded that there was no impact on health equity, and acceptability was judged to be variable. Utilization of LMWH was considered feasible because it is current practice.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel determined that there is low certainty in the evidence for a net health benefit from using anticoagulation prophylaxis for hospitalized medical patients with cancer. Nevertheless, an overall favorable benefit over harms seems to favor thromboprophylaxis in this setting. A conditional, rather than strong, recommendation was based on the low certainty in the evidence. As well, the panel acknowledges that some subgroups of patients may not benefit (eg, patients at the end of life) from VTE prophylaxis if their baseline risk of VTE is low or the associated risk of major bleeding is high.

The panel noted that hospitalized medical patients with cancer are considered at greater risk for VTE than are nonhospitalized patients with cancer.[107] By reducing the risk of VTE for hospitalized patients with cancer, thromboprophylaxis over no prophylaxis is probably cost-effective. Although many criteria did not favor either (eg, acquisition cost, health care provider time), of the 2 alternatives (ie, UFH and LMWH), the overall benefits vs harm ratio favored LMWH. However, UFH is generally preferred over LMWH for the patient with cancer with severe renal impairment (defined as creatinine clearance $<$30 mL/min).

The panel believed that implementation of the intervention might be facilitated by prompting the evaluation of eligibility for thromboprophylaxis for hospitalized medical patients with cancer. Hospitals caring for patients with cancer should potentially consider monitoring for compliance with recommendations of the use of appropriate thromboprophylaxis in this setting. Continuous medical education should be provided routinely related to this recommendation.

The panel agreed that further research is needed in hospitalized medical patients with cancer. More information is needed on the optimal choice, dosing, and duration of parenteral anticoagulation to prevent VTE for hospitalized patients with cancer. Further information is also needed on the dosing of anticoagulation for obese patients, underweight patients, patients with hematological malignancies or undergoing stem cell transplantation, and patients with renal disease.

Should mechanical thromboprophylaxis be used instead of or in addition to pharmacological prophylaxis for hospitalized medical patients with cancer without VTE?

Recommendations 3 and 4

For hospitalized medical patients with cancer without VTE, the ASH guideline panel *suggests* using pharmacological thromboprophylaxis over mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯) and over a combination of pharmacological and mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Hospitalized patients with cancer without VTE at high risk for major bleeding may be considered for mechanical thromboprophylaxis without pharmacologic thromboprophylaxis. A combination of pharmacological and mechanical prophylaxis may also be considered for selected hospitalized medical patients with cancer who are considered at very high risk for VTE (eg, patients with cancer with sustained and prolonged immobilization).

Combination of methods vs pharmacological thromboprophylaxis. SUMMARY OF THE EVIDENCE. No systematic review or clinical trial in hospitalized patients with cancer was identified that addressed these questions. The guideline panel considered evidence from trials conducted in hospitalized medical patients from the "ASH 2018 Guidelines for Management of VTE: Prophylaxis for Hospitalized and Nonhospitalized Medical Patients."[59] Trials were identified from 1 systematic review that included patients with trauma[108] and 1 systematic review that included patients with stroke.[109] We identified 1 additional clinical trial when updating these reviews.[110] The 4 trials reported the effect of the combination of mechanical prophylaxis (mechanical devices [Arthroflow device passively extends and plantarflexes],[111] pulsatile foot pumps,[112] and intermittent pneumatic compression devices [IPCs][113]) and pharmacological thromboprophylaxis (LMWH) compared with pharmacological thromboprophylaxis alone on mortality and PE,[111-113] 2 trials on proximal and distal DVT,[111] and 2 trials reported on major bleeding.[112] There are no data on graduated compression stockings (GCSs) in this setting. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/Ou7MNNaDgFM.

BENEFITS. The use of combined methods compared with pharmacological thromboprophylaxis may reduce mortality, PE, and proximal/distal DVT, but the evidence is very uncertain, and the panel judged the effects to be small (for mortality: RR, 0.99; 95% CI, 0.81-1.22; ARR, 1 fewer per 1000; 95% CI, 24 fewer to 27 more per 1000; for PE: RR, 0.69; 95% CI, 0.30-1.58; ARR, 3 fewer per 1000; 95% CI, 8 fewer to 6 more per 1000; for proximal DVT: RR, 0.37; 95% CI, 0.05-2.73; ARR, 38 fewer per 1000; 95% CI, 57 fewer to 104 more per 1000; for distal DVT: RR, 0.61; 95% CI; 0.18-2.11; ARR, 7 fewer per 1000; 95% CI, 14 fewer to 19 more per 1000).

HARMS AND BURDEN. Combination method vs pharmacological thromboprophylaxis may increase major bleeding, but the evidence is very uncertain, and the panel judged the effect to be trivial (for major bleeding: RR, 2.83; 95% CI, 0.30-26.70; ARI, 19 more per 1000; 95% CI, 7 fewer to 265 more per 1000). The panel concluded that the risk of major bleeding is unlikely to be increased by adding mechanical prophylaxis to anticoagulation.

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to serious indirectness and very serious imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel agreed that the cost, adherence, and proper application of the devices for different mechanical methods would vary. The costs are considered negligible for GCSs but moderate to high for IPCs. However, no direct data for cost-effectiveness were available. The panel concluded that there is a cost increase with adding mechanical prophylaxis that will vary across settings, along with the uncertainty in the net benefit vs harm.

The panel agreed that the impact on health equity is likely to vary, depending on the availability of mechanical prophylaxis methods. The panel concluded that, for all stakeholders, IPCs will likely be less acceptable to many patients and caregivers than GCSs, that GCSs are feasible to use, and that IPCs may not be feasible in some settings.

Mechanical vs pharmacological thromboprophylaxis.

SUMMARY OF THE EVIDENCE. We did not find any systematic reviews or trials addressing this question. Because of the lack of direct evidence, the guideline panel decided to include evidence from 8 trials conducted in the general population from the "ASH 2018 Guidelines for Management of VTE: Prophylaxis for Hospitalized and Nonhospitalized Medical Patients."[59] Our systematic search for trials identified 2 trials conducted on medical acutely or critically ill patients.[114,115] Because of the lack of direct evidence, the guideline panel decided to also include indirect evidence available from trials conducted on trauma patients. We found 1 systematic review that provided evidence on patients with trauma.[108] Seven trials reported the effect of mechanical thromboprophylaxis vs pharmacological thromboprophylaxis on mortality,[113,115-120] 7 trials reported on PE,[113-119] 3 trials reported on symptomatic DVT,[114,118,119] and 7 trials reported on major bleeding.[114,116-121] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/ne1WlYrq2RE.

BENEFITS. Mechanical vs pharmacological thromboprophylaxis may reduce mortality and major bleeding but the evidence is very uncertain, particularly with regard to its applicability to nonsurgical patients with cancer; the panel judged the effects to be trivial (for mortality: RR, 0.95; 95% CI, 0.42-2.16; ARR, 1 fewer per 1000; 95% CI, 11 fewer to 21 more per 1000; for major bleeding: RR, 0.87; 95% CI, 0.25-3.08; ARR, 1 fewer per 1000; 95% CI, 6 fewer to 16 more per 1000).

HARMS AND BURDEN. Mechanical vs pharmacological thromboprophylaxis may increase PE and symptomatic DVT but the evidence is uncertain, and the panel judged the effects to be small (for PE: RR, 1.54; 95% CI, 0.48-4.93; ARI, 5 more per 1000; 95% CI, 5 fewer to 39 more per 1000; for symptomatic DVT: RR, 2.20; 95% CI, 0.22-22.09; ARI, 36 more per 1000; 95% CI, 23 fewer to 633 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to serious risk of bias, very serious indirectness, and very serious imprecision of the estimates. The panel had very important concerns about indirectness, in particular because of the potential heightened risk of major bleeding in trauma patients receiving pharmacological thromboprophylaxis compared with medically ill hospitalized patients with cancer and the potential for mechanical devices to limit mobility of hospitalized patients, further increasing the risk of VTE.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel considered that the costs are likely to be negligible. However, cost, adherence, and proper application of the devices of mechanical prophylaxis will likely vary (eg, by device [IPC vs GCS] and setting). In-hospital LMWH costs are lower than mechanical prophylaxis but will also vary between settings (eg, country). Based on the available evidence, the panel concluded that the cost-effectiveness probably favors pharmacological thromboprophylaxis. The considerations for equity, acceptability, and feasibility are the same as for the comparison of combined prophylaxis vs mechanical or pharmacological prophylaxis alone.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. For the comparison of combination vs pharmacological thromboprophylaxis, the panel determined, based on very low certainty in the evidence, that the balance of effects probably does not favor the intervention or the comparison and that cost-effectiveness probably favors pharmacological prophylaxis alone. However, a combination of pharmacological and mechanical prophylaxis may be considered for selected hospitalized medical patients with cancer who are considered at very high risk for VTE (eg, patients with cancer with sustained and prolonged immobilization).

For the comparison of mechanical vs pharmacological thromboprophylaxis, the panel determined that there is very low certainty in the evidence for a net health harm from using mechanical prophylaxis for hospitalized medical patients with cancer and concluded that the balance probably favors pharmacological prophylaxis. However, patients at high risk for major bleeding may be considered for mechanical, rather than pharmacological, thromboprophylaxis.

The panel believed that additional research is needed to directly evaluate the potential benefits and harms of mechanical thromboprophylaxis, alone or in combination with pharmacological thromboprophylaxis, for hospitalized medical patients with cancer considered at high risk for VTE. The panel believed that implementation of the recommendation might potentially be facilitated by prompting the evaluation of eligibility for thromboprophylaxis for hospitalized medical patients with cancer. Prompting may be based on different technologies, but additional studies

assessing the optimal implementation strategy are warranted. Hospitals caring for patients with cancer should potentially consider monitoring for compliance with recommendations on the use of appropriate thromboprophylaxis in this setting.

Should thromboprophylaxis for hospitalized medical patients with cancer be continued after discharge or should thromboprophylaxis be discontinued at time of discharge?

Recommendation 5

For hospitalized medical patients with cancer, the ASH guideline panel *suggests* discontinuing thromboprophylaxis at the time of hospital discharge rather than continuing thromboprophylaxis beyond the discharge date (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Continuation of thromboprophylaxis following discharge may be considered for selected ambulatory patients with cancer receiving systemic treatment and whose risk of VTE is considered to outweigh the risk of bleeding.

Continuation of thromboprophylaxis at home vs discontinuation at time of discharge. SUMMARY OF THE EVIDENCE. No systematic review or individual clinical trial was found that addressed this question. Because of the lack of direct evidence, the guideline panel decided to include evidence from 4 trials conducted on hospitalized medical patients from the "ASH 2018 Guidelines for Management of VTE: Prophylaxis for Hospitalized and Nonhospitalized Medical Patients."[59] One systematic review[122] included 3 RCTs that provided evidence related to this question.[123-125] An update of the systematic review identified 2 additional studies that fulfilled the inclusion criteria.[126,127] All studies included acutely and critically ill medical patients. All trials used DOACs, with the exception of the EXCLAIM trial, which assessed LMWH. Three trials included data on the prevalence of patients with active cancer (range, 1.5-7.3%).[123-125] None of the trials included cancer subgroup analyses. Five studies reported the effect of extended pharmacological thromboprophylaxis vs cessation at discharge on mortality and major bleeding,[123-127] 4 studies reported on PE and symptomatic DVT,[123,124,126,127] and 1 study assessed the risk of developing HIT.[125] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/Wem_cUuhlog.

BENEFITS. Continuation of thromboprophylaxis at home vs discontinuation at time of hospital discharge may reduce symptomatic DVT, as well as mortality and PE, but the evidence is very uncertain, and the panel judged the effects to be trivial (for symptomatic DVT: RR, 0.54; 95% CI, 0.32-0.91; ARR, 3 fewer per 1000; 95% CI, 1-4 fewer per 1000 using a baseline risk of 0.74%[123]; for mortality: RR, 0.97; 95% CI, 0.87-1.08; ARR, 1 fewer per 1000; 95% CI, 4 fewer to 3 more per 1000; for PE: RR, 0.63; 95% CI, 0.39-1.03; ARR, 3 fewer per 1000; 95% CI, 0-5 fewer per 1000 using a baseline risk of 0.74%).[123]

HARMS AND BURDEN. Continuation of thromboprophylaxis at home vs discontinuation may increase the risk of major bleeding and may increase the risk of HIT, but the evidence is very uncertain, and the panel judged the effect to be trivial (for major bleeding: RR, 2.04; 95% CI, 1.42-2.91; ARI, 3 more per 1000; 95% CI, 1-6 more per 1000; for HIT: RR, 3.01; 95% CI, 0.12-73.93, with only 1 reported HIT event occurring in the extended prophylaxis group [n = 2975] and 0 events occurring in the group discontinuing prophylaxis at discharge [n = 2988]).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to indirectness and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is very low certainty in the evidence for a net health benefit from discontinuation at time of discharge (over continuation of thromboprophylaxis at home) in hospitalized medical patients with cancer and concluded that the balance probably favors discontinuation. The panel concluded that, based on the available evidence, the cost-effectiveness also probably favors discontinuation of thromboprophylaxis at time of discharge.

Continuation of thromboprophylaxis could cause inequity because of concerns about cost and/or the ability to self-inject. In addition, some patients might find having to continue anticoagulation (especially if given parenterally) at home unacceptable. Health care professionals would need to monitor and respond to complications (major bleeding) with continued anticoagulation. The trade-off between added cost of drug and possibly fewer rehospitalizations for VTE will probably not have an overall beneficial net effect; however, formal cost-effectiveness studies are not available.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for discontinuation of thromboprophylaxis at the time of hospital discharge over continuation at home for medical patients with cancer without VTE is due to a balance that probably favors discontinuation, in the context of very low certainty evidence, indirectness, moderate costs, and cost-effectiveness. Ambulatory patients with cancer receiving systemic therapy and at high risk for thrombosis are an exception. If thromboprophylaxis were continued beyond discharge, monitoring might be required (eg, platelet counts, bleeding, affordability).

The panel agreed that further research on risk stratification for selection of high-risk subgroups for continued thromboprophylaxis beyond hospitalization is needed.

Primary prophylaxis for patients with cancer undergoing surgery

Should pharmacological thromboprophylaxis vs mechanical thromboprophylaxis vs a combination of both be used for thromboprophylaxis for patients with cancer undergoing a surgical procedure?

Recommendations 6, 7, and 8

For patients with cancer undergoing a surgical procedure at low bleeding risk, the ASH guideline panel *suggests* using pharmacological rather than mechanical thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

For patients at high bleeding risk, the ASH guideline panel *suggests* using mechanical rather than pharmacological thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

For patients at high risk for thrombosis, with the exception of those also at high risk for bleeding, the ASH guideline panel

suggests using a combination of mechanical and pharmacologic thromboprophylaxis rather than mechanical prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects) or pharmacologic thromboprophylaxis alone (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Early ambulation should be favored over mechanical thromboprophylaxis when indicated. In situations in which there is a high risk for thrombosis and major bleeding, mechanical thromboprophylaxis alone is suggested until the patient is no longer at high risk for major bleeding, then adding pharmacological thromboprophylaxis is suggested.

Pharmacological vs mechanical thromboprophylaxis. SUMMARY OF THE EVIDENCE. We identified 4 systematic reviews addressing this question.[128-131] From these reviews, we identified 3 RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this question.[132-134] Our systematic search of RCTs identified 3 additional studies not included in the previous reviews that fulfilled the inclusion criteria.[135-137] Ten included trials reported that the proportion of patients with cancer ranged from 4% to 100% across trials. However, the site and stage of cancer included varied across trials. Types of surgery included in these studies were pelvic,[133,134,136] abdominal,[135,137] and neurosurgical.[132] Of the studies comparing pharmacological thromboprophylaxis with mechanical thromboprophylaxis, 2 studies reported the effect on mortality,[132,137] 3 studies reported the effect on any PE,[133,136,137] 5 studies reported the effect on symptomatic DVT,[133-137] 2 studies reported the effect on major bleeding,[132,137] and 1 study reported on reoperation for bleeding.[137] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/pfhapwl0BGM.

BENEFITS. For patients at low and at high risk for thrombosis, pharmacological prophylaxis compared with mechanical prophylaxis results in little to no difference in mortality and reoperation for bleeding, but the evidence is very uncertain (for mortality: RR, 1.05; 95% CI, 0.07-15.69; ARR, 0 fewer per 1000; 95% CI, 7 fewer to 103 more per 1000 using a baseline risk of 0.7%[138]; for reoperation for bleeding: RR, 0.12; 95% CI, 0.00-2.84 with only 1 reported event occurring in the mechanical thromboprophylaxis group (n = 38) and no events occurring in the pharmacological thromboprophylaxis group (n = 109).

For patients at low risk for thrombosis,[138] the panel determined the benefits of pharmacological prophylaxis over mechanical prophylaxis to be small with respect to thrombosis outcomes. Pharmacological prophylaxis may reduce any PE and any DVT, and it may increase symptomatic DVTs compared with mechanical prophylaxis, but the evidence is very uncertain (for any PE: RR, 0.13; 95% CI, 0.01-2.38; ARR, 2 fewer per 1000; 95% CI, 2 fewer to 3 more per 1000 using a baseline risk of 0.2%[138]; for any DVT: RR, 0.29; 95% CI, 0.03-2.80; ARR, 1 fewer per 1000; 95% CI, 2 fewer to 4 more per 1000 using a baseline risk of 0.2%[138]; for symptomatic DVT: RR, 1.65; 95% CI, 0.50-5.47; ARI, 1 more per 1000; 95% CI, 1 fewer to 9 more per 1000 using a baseline risk of 0.2%).[138]

For patients at high risk for thrombosis, the panel determined the benefits to be moderate. Pharmacological thromboprophylaxis may reduce any DVT and any PE, and it may increase symptomatic DVTs, but the evidence is very uncertain (for any DVT: RR, 0.29; 95% CI, 0.03-2.80; ARR, 44 fewer per 1000; 95% CI, 60 fewer to 110 more per 1000 using a baseline risk of 6.1%; for any PE: RR, 0.13; 95% CI, 0.01-2.38; ARR, 18 fewer per 1000; 95% CI, 20 fewer to 28 more per 1000 using a baseline risk of 2.1%; for symptomatic DVT: RR, 1.65; 95% CI, 0.50-5.47; ARI, 10 more per 1000; 95% CI, 8 fewer to 68 more per 1000 using a baseline risk of 1.5%).

HARMS AND BURDEN. Among patients at low risk for bleeding, pharmacological prophylaxis may increase major bleeding; the panel determined the harms to be moderate (RR, 2.52; 95% CI, 0.45-14.13; ARI, 12 more per 1000; 95% CI, 4 fewer to 105 more per 1000 using a baseline risk of 0.6%).[138] Among patients at high risk for bleeding, pharmacological prophylaxis may increase major bleeding, but the evidence is very uncertain (RR, 2.52; 95% CI, 0.45-14.13; ARI, 10 more per 1000, 95% CI, 3 fewer to 82 more per 1000 using a baseline risk of 0.8%.[138] Although the panel judged the harms to be small, the panel was concerned about potentially higher risks and higher morbidity of bleeding associated with some types of surgery (eg, neurosurgery with a nonsignificant trend toward an increased risk for bleeding with the addition of pharmacological thromboprophylaxis).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to serious risk of bias and very serious imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel considered that the costs of either strategy were negligible. However, the cost of mechanical thromboprophylaxis will vary depending on the device (eg, IPC vs GCS) and setting. The cost-effectiveness probably favors mechanical thromboprophylaxis given the results of the evaluations in the surgical setting.[139-144] Equity, acceptability, and feasibility are also likely to vary. Pharmacological thromboprophylaxis is likely to be acceptable; however, the acceptability of mechanical thromboprophylaxis is likely to vary depending on the type of device used (GCSs are feasible to use, but IPCs may be less feasible in some environments).

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel concluded that the primary factor to consider when choosing between mechanical and pharmacological thromboprophylaxis is the risk of major bleeding. The panel made a conditional recommendation for using pharmacological rather than mechanical thromboprophylaxis for patients with cancer without VTE at lower bleeding risk, as a result of a balance of effects that favors the intervention. The panel made a conditional recommendation for using mechanical rather than pharmacological thromboprophylaxis for patients with a higher risk for bleeding as a result of a balance of effects that favors mechanical thromboprophylaxis.

Combination of pharmacologic and mechanical prophylaxis vs mechanical thromboprophylaxis alone. SUMMARY OF THE EVIDENCE. We identified 1 systematic review addressing this question.[128] From this review, we identified 3 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this context.[132,145,146] Our systematic search of RCTs identified 4 additional trials not included in the previous review that fulfilled the inclusion criteria.[147-150] Ten included trials reported the proportion of patients with cancer (range, 4-100% across trials). However, the site and stage of cancer included varied across trials. The different types of surgeries included in these trials were neurosurgical,[132,145,146] abdominal,[147,150] thoracic,[149]

and pelvic.[148] Of these studies comparing a combination of mechanical and pharmacological thromboprophylaxis with mechanical thromboprophylaxis, 4 studies reported the effect on mortality,[132,145,146,148] 6 studies reported the effect on PE,[145-150] 5 studies reported the effect on symptomatic DVT,[145-148,150] and 5 studies reported the effect on major bleeding.[145-148,150] We identified an additional study through search alerts; however, it was not included because it was not believed that it would modify the findings substantially.[151] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/0v0MnziCyH0.

BENEFITS. The panel agreed that the effects vary according to the baseline risk of thrombosis. For patients at low risk for thrombosis, the panel determined the effects to be small. For patients at high risk for thrombosis, the panel determined the effects benefits to be moderate.

For patients at low risk for thrombosis, combination of mechanical and pharmacological prophylaxis compared with mechanical prophylaxis may result in little to no difference in any PE, symptomatic PE, symptomatic DVT, and any DVT (for any PE: RR, 0.68; 95% CI, 0.21-2.26; ARR, 1 fewer per 1000; 95% CI, 2 fewer to 3 more per 1000 using a baseline risk of 0.2%[138]; for symptomatic PE: RR, 0.24; 95% CI, 0.05-1.12; ARR, 2 fewer per 1000; 95% CI, 0-2 fewer per 1000 using a baseline risk of 0.2%[138]; for symptomatic DVT: RR, 0.22; 95% CI, 0.06-0.89; ARR, 2 fewer per 1000; 95% CI, 0-2 fewer per 1000 using a baseline risk of 0.2%[138]; for any DVT: RR, 0.54; 95% CI, 0.37-0.78; ARR, 1 fewer per 1000; 95% CI, 0-1 fewer per 1000 using a baseline risk of 0.2%).[138]

For patients at high risk for thrombosis, combination of mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone may reduce any PE and symptomatic PEs, and it reduces symptomatic DVTs and any DVT (for any PE: RR, 0.68; 95% CI, 0.21-2.26; ARR, 4 fewer per 1000; 95% CI, 10 fewer to 15 more per 1000 using a baseline risk of 1.2%; for symptomatic PE: RR, 0.24; 95% CI, 0.05-1.12; ARR, 13 fewer per 1000; 95% CI, 16 fewer to 2 more per 1000 using a baseline risk of 1.7%; for symptomatic DVT: RR, 0.22; 95% CI, 0.06-0.89; ARR, 10 fewer per 1000; 95% CI, 1-12 fewer per 1000 using a baseline risk of 1.3%; for any DVT: RR, 0.54; 95% CI, 0.37-0.78; ARR, 55 fewer per 1000; 95% CI, 26-75 fewer per 1000 using a baseline risk of 11.9%).

HARMS AND BURDEN. Combination of mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone likely increases mortality slightly and may increase major bleeding slightly (for mortality: RR, 1.36; 95% CI, 0.56-3.30; ARI, 3 more per 1000; 95% CI, 3 fewer to 16 more per 1000 using a baseline risk of 0.7%[138]; for major bleeding: RR, 1.88; 95% CI, 0.71-4.99; ARI, 7 more per 1000; 95% CI, 2 fewer to 32 more per 1000 using a baseline risk of 0.8%).[138] Although the panel judged the harms to be small, the panel was concerned about the higher risk for bleeding and mortality associated with some types of surgery (eg, neurosurgery with a nonsignificant trend toward an increased risk for bleeding with the addition of pharmacological thromboprophylaxis).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low owing to very serious imprecision.

OTHER ETD CRITERIA AND CONSIDERATIONS. The balance of benefits vs harms varies according to the baseline risk of thrombosis. For lower-risk patients, the balance does not favor combination thromboprophylaxis or mechanical thromboprophylaxis alone. For higher-risk patients, the balance probably favors the combination of mechanical and pharmacologic thromboprophylaxis.

Overall, the panel considered that the costs are likely to be negligible. However, the cost of mechanical thromboprophylaxis will vary depending on the device (eg, IPC vs GCS) and setting. The cost-effectiveness probably favors the combination, given the results of the evaluations in the surgical setting.[152] Equity, acceptability, and feasibility also are likely to vary. Health equity is likely to vary, depending on the availability of mechanical prophylaxis methods. Although pharmacological thromboprophylaxis is likely to be acceptable, the acceptability of mechanical thromboprophylaxis is likely to vary depending on the type of device used (GCSs are feasible to use, but IPCs may not be feasible in some settings).

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel concluded that the primary factor related to the choice between combined thromboprophylaxis methods and mechanical thromboprophylaxis alone is the risk of thrombosis. The panel made a conditional recommendation for using combination methods rather than mechanical thromboprophylaxis for patients with cancer without VTE at high risk for thrombosis, as a result of a balance of effect that probably favors the intervention. The panel made a conditional recommendation for mechanical thromboprophylaxis rather than combination thromboprophylaxis for patients with a lower risk for thrombosis or a high risk for bleeding. The panel did not identify high-priority future research questions.

Combination of pharmacologic and mechanical prophylaxis vs pharmacological thromboprophylaxis alone. SUMMARY OF THE EVIDENCE. We identified 7 systematic reviews addressing this question.[130,153-160] From these reviews, we identified 19 studies that fulfilled our inclusion criteria and measured outcomes relevant to this context.[112,132,135,161-176] Seven included trials reported the proportion of patients with cancer (range, 4-50% across trials). However, the site and stage of cancer included varied across trials. We identified 1 additional clinical trial when updating these reviews.[110] Although the trial compared the combination of pharmacological and mechanical prophylaxis with pharmacological thromboprophylaxis alone in patients admitted to the intensive care unit, the panel decided to include the trial given that it was a recent large RCT including high-risk patients and assessing IPCs as mechanical thromboprophylaxis. Eight studies reported the effect of the combination of pharmacological and mechanical thromboprophylaxis compared with pharmacological thromboprophylaxis alone on risk of mortality.[110,112,132,161-163,165,170] Eleven studies reported the effect on the development of symptomatic PEs,[110,112,132,135,163,165,167-170,176] and 6 studies reported the effect on the development of any PE.[161,162,166,171,175,176] Nine studies reported data on any proximal DVT.[110,112,135,162,166,171-173] Eight studies reported data on any distal DVT.[112,134,165,168,169,173-175] Seven studies reported the effect of combination pharmacological and mechanical thromboprophylaxis compared with pharmacological thromboprophylaxis alone on the risk of major bleeding,[110,112,132,162,167,170,171] and 2 studies reported the effect on the risk of reoperation.[165,176] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/czqor6q_zWY.

BENEFITS. Combination thromboprophylaxis compared with pharmacological thromboprophylaxis may reduce symptomatic

PEs, any PE, any proximal DVT, and any distal DVT, and it may increase symptomatic distal DVTs, but the evidence is very uncertain. Combination thromboprophylaxis compared with pharmacological thromboprophylaxis alone may have little to no effect on mortality, but the evidence is very uncertain. The panel judged these effects to be small (for symptomatic PE: RR, 0.47; 95% CI, 0.31-0.71; ARR, 12 fewer per 1000; 95% CI, 7-16 fewer per 1000; for any PE: RR, 0.67; 95% CI, 0.33-1.35; ARR, 4 fewer per 1000; 95% CI, 8 fewer to 4 more per 1000; for any proximal DVT: RR, 0.73; 95% CI, 0.45-1.17; ARR, 13 fewer per 1000; 95% CI, 27 fewer to 8 more per 1000; for any distal DVT: RR, 0.81; 95% CI, 0.52-1.26; ARR, 12 fewer per 1000; 95% CI, 31 fewer to 17 more per 1000; for symptomatic distal DVT: RR, 1.99; 95% CI, 0.35-11.33; ARI, 9 more per 1000; 95% CI, 6 fewer to 96 more per 1000; for mortality: RR, 0.98; 95% CI, 0.80-1.20; ARR, 1 fewer per 1000; 95% CI, 9 fewer to 9 more per 1000 using a baseline risk of 4.7%).

HARMS AND BURDEN. Combination thromboprophylaxis compared with pharmacological thromboprophylaxis alone may increase major bleeding, but the evidence is very uncertain. The panel judged these effects to be trivial (for major bleeding: RR, 1.05; 95% CI, 0.32-3.40; ARI, 0 more per 1000; 95% CI, 5 fewer to 17 more per 1000). We were unable to estimate the relative risk of major reoperation, with no events occurring in the 2 studies reporting this outcome.

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low owing to risk of bias, imprecision, and indirectness of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel further judged that the balance between benefits vs harms probably favors combination pharmacological and mechanical thromboprophylaxis over pharmacological thromboprophylaxis alone. The panel judged the costs associated with combined thromboprophylaxis to be negligible based on very low certainty in the evidence of resource requirements. Cost-effectiveness probably favors combined pharmacological with mechanical thromboprophylaxis. The panel agreed that the impact on health equity is likely to vary, depending on the availability of mechanical prophylaxis methods. Combined pharmacological and mechanical thromboprophylaxis would probably be acceptable to stakeholders and probably feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel made a conditional recommendation for using combination thromboprophylaxis rather than pharmacological thromboprophylaxis alone for patients with cancer without VTE, as a result of a balance of effects that probably favors the intervention. The moderate desirable effects of the combined prophylaxis method probably outweigh the trivial effect on harms. However, there is a very low certainty in the evidence. The panel agreed that, in the setting of patients with high VTE risk, they would particularly favor the combined approach.

The panel agreed that further high-quality comparative data would be of value to add more certainty to this recommendation. Studies enabling identification of baseline risk would be valuable to identify patients who are particularly likely to benefit from combined prophylaxis strategies. Finally, more information about the duration of compression (h/d) needed for VTE prevention with IPCs would be valuable, as would be data about device standardization.

Should LMWH, UFH, fondaparinux, VKAs, or DOACs be used for thromboprophylaxis for patients with cancer undergoing a surgical procedure?

Recommendations 9 and 10

For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using LMWH or fondaparinux for thromboprophylaxis rather than UFH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯). The panel did not make a recommendation on the use of VKAs or DOACs in this setting because there were no studies available.

Remarks: UFH is generally preferred over LMWH for patients with cancer and severe renal impairment (defined as creatinine clearance < 30 mL/min). If planning for extended thromboprophylaxis (continuing pharmacological thromboprophylaxis at home), the guideline panel *suggests* the use of LMWH (see Recommendation 12).

LMWH vs UFH. SUMMARY OF THE EVIDENCE We identified 3 systematic reviews that addressed this question.[51,129,131] From these reviews, we identified 13 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this context.[177-189] Our systematic search of RCTs identified 3 additional studies not included in the previous reviews that fulfilled the inclusion criteria.[190-192] All of these trials included only patients with active cancer. The different types of surgeries included in these studies were abdominal,[178,179,182,183,185-187,191,193] pelvic,[177,178,180,183,185,188,189,192] breast,[177,189,192] thoracic,[181,193] and neurosurgical.[190] One trial did not specify the type of surgery.[186] Of these studies comparing LMWH with UFH, 8 studies reported the effect on mortality,[178,179,186,187,189-191,193] 15 studies reported the effect on any PE,[177-183,185-188,190-193] 8 studies reported the effect on any symptomatic DVT,[177,178,180,183,187,190-192] 9 studies reported the effect on major bleeding,[177,178,180,181,183,186,187,190,193] and 4 studies reported on reoperation for bleeding.[178,180,188,193] We did not find any studies evaluating the role of VKAs or DOACs in this setting. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/bl0OZ3wdZCc.

BENEFITS. For patients with cancer undergoing a surgical procedure, LMWH compared with UFH probably results in little to no difference in mortality, any DVT, and reoperation for bleeding, and it results in little to no difference in any PE and any symptomatic DVT. The panel judged these effects to be small (for mortality: RR, 0.82; 95% CI, 0.63-1.07; ARR, 9 fewer per 1000; 95% CI, 19 fewer to 4 more per 1000; for any DVT: RR, 0.86; 95% CI, 0.69-1.06; ARR, 4 fewer per 1000; 95% CI, 8 fewer to 2 more per 1000; for reoperation for bleeding: RR, 0.93; 95% CI, 0.57-1.50; ARR, 4 fewer per 1000; 95% CI, 22 fewer to 26 more per 1000; for any PE: RR, 0.52; 95% CI, 0.20-1.34; ARR, 6 fewer per 1000; 95% CI, 10 fewer to 4 more per 1000 using a baseline risk of 1.3%[194]; for any symptomatic DVT: RR, 0.67; 95% CI, 0.27-1.69; ARR, 3 fewer per 1000; 95% CI, 7 fewer to 7 more per 1000).

HARMS AND BURDEN. For patients with cancer undergoing a surgical procedure, LMWH compared with UFH results in little to no difference in major bleeding, and the panel judged this effect to be

trivial (for major bleeding: RR, 1.01; 95% CI, 0.69-1.48; ARI, 1 more per 1000; 95% CI, 17 fewer to 27 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as moderate owing to imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is moderate certainty for a net health benefit from LMWH (over UFH) for patients with cancer undergoing surgery. This was supported by the fact that, given the relationship between desirable and undesirable effects, there is probably no important uncertainty or variability in how much patients value the outcomes. The panel concluded that costs and savings are likely to be negligible and that, based on the available evidence, the cost-effectiveness probably favors LMWH.

The panel agreed that there is probably minimal impact on health equity because, despite the variability in impact on health equity, for short-term scenarios like hospitalized patients, the impact is less likely (eg, in the United States, in-hospital drugs would typically be covered by insurance plans or Medicare/Medicaid). The intervention (LMWH) is probably acceptable for most patients and is feasible given current practice.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for LMWH rather than UFH for patients with cancer undergoing a surgical procedure is due to moderate certainty in evidence, negligible costs and savings, and cost-effectiveness that probably favors LMWH. The evidence was graded as moderate certainty as a result of some imprecision in the risk estimates for benefits and harms. The panel notes that UFH is generally preferred over LMWH for patients with cancer with severe renal impairment (creatinine clearance $<$30 mL/min). The panel noted that resource and economic parameters are likely to vary between institutions and regions.

The panel agreed that, given the imprecision of the observed effects, additional studies could increase the certainty in evidence.

Fondaparinux vs LMWH. SUMMARY OF THE EVIDENCE. We did not identify any systematic review addressing this question. Our systematic search of RCTs identified 3 that compared fondaparinux with LMWH and fulfilled the inclusion criteria.[195-197] These RCTs included patients with cancer undergoing abdominal surgery,[195] pelvic surgery,[196] or surgery for esophageal cancer.[197] None of the identified studies reported on mortality, but all reported on VTE (symptomatic and asymptomatic) and major bleeding. It was not possible to abstract data on PE and symptomatic DVT; instead, aggregate data on VTE rates were reviewed, and baseline risks for any PE and symptomatic DVT were applied to calculate absolute effects. The EtD framework is available at https://guidelines.ash.-gradepro.org/profile/kC-K0WVaiPY.

BENEFITS. Compared with LMWH, fondaparinux may reduce PEs and symptomatic DVTs slightly; the panel judged the effect to be small (for PE: RR, 0.40; 95% CI, 0.14-1.12; ARR, 6 fewer per 1000; 95% CI, 9 fewer to 9 more per 1000 using a baseline risk of 1%[194]; for symptomatic DVT: RR, 0.40; 95% CI, 0.14-1.12; ARR, 11 fewer per 1000; 95% CI, 16 fewer to 2 more per 1000 using a baseline risk of 1.9%).[194]

HARMS AND BURDEN. Compared with LMWH, fondaparinux may increase major bleeding slightly; the panel judged the effect to be small (for major bleeding: RR, 1.34; 95% CI, 0.81-2.22; ARI, 7 more per 1000; 95% CI, 4 fewer to 27 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low owing to the risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is low certainty in the evidence for a net health benefit from using fondaparinux (over LMWH) for patients with cancer undergoing surgery and concluded that neither strategy is favored over the other. The panel believed that the resource impact (costs and savings) is likely to be negligible and that there is probably no impact on health equity. No cost-effectiveness evidence was identified.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation (rather than strong) for using fondaparinux or LMWH is due to a balance that may favor fondaparinux; however, the certainty in the evidence is low, and costs and/or savings are likely negligible. If planning for extended thromboprophylaxis (continuing pharmacological thromboprophylaxis at home), the guideline recommends considering using LMWH to facilitate logistics and transition of thromboprophylaxis to the outpatient setting (see Recommendation 27). The guideline panel considered further information on the comparative effectiveness and safety of fondaparinux vs LMWH a research priority. The panel agreed that further research on efficacy and cost-effectiveness is needed.

Should preoperative thromboprophylaxis vs postoperative thromboprophylaxis be used for patients with cancer undergoing a surgical procedure?

Recommendation 11

For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using postoperative thromboprophylaxis over preoperative thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: The panel defined preoperative thromboprophylaxis as a dose of LMWH or UFH given 12 hours (or the evening before) prior to the procedure and not the dose given at the time of the surgery (or on the operating table). The panel did not recognize a large advantage to preoperative prophylaxis and took a precautionary approach because of the bleeding and logistical considerations with neuraxial anesthesia. Patients with cancer already hospitalized prior to the surgery are suggested to receive thromboprophylaxis as per Recommendations 1 and 2.

Preoperative thromboprophylaxis vs postoperative thromboprophylaxis. SUMMARY OF THE EVIDENCE. The panel defined preoperative thromboprophylaxis as a dose of LMWH or UFH received 12 hours prior to the procedure (or the evening before) and not a dose (eg, UFH, 5000 IU) that can be given at the time of the surgery (or on the operating table). We did not identify any systematic review addressing this question. Our systematic search

of RCTs identified 1 that fulfilled the inclusion criteria.[198] This RCT included patients undergoing major laparotomy in the peritoneal and/or retroperitoneal space and/or pelvis. It compared the effect of an ultra-LMWH starting 8 ± 1 hour postoperation with prophylactic LMWH starting before surgery, with the first postoperative injection starting 12 ± 1 hour postoperation. Outcomes included mortality, PE, symptomatic DVT, and major bleeding. It was noted that many studies assessing thromboprophylaxis in this patient population initiated thromboprophylaxis preoperatively,[201-203] whereas others started it during the postoperative period.[202,203] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/boP4bq0N0s8.

BENEFITS. Preoperative thromboprophylaxis compared with postoperative thromboprophylaxis may reduce mortality, any PE, and any symptomatic DVT but the evidence is very uncertain. The panel judged these effects to be small (for mortality the RR was 0.74, 95% CI 0.50 to 1.09; ARR 7 fewer per 1000, 95% CI from 13 more to 2 more per 1000; for any PE, the RR was 0.20, 95% CI 0.01 to 4.16; ARR, 10 fewer per 1000, 95% CI from 13 fewer to 41 more per 1000 using a baseline risk of 1.3%[204]; for any symptomatic DVT the RR was 0.86, 95% CI 0.62 to 1.19; ARR 1 fewer per 1000, 95% CI from 2 fewer to 1 more per 1000 using a baseline risk of 0.4%).[204]

HARMS AND BURDEN. Preoperative thromboprophylaxis compared with postoperative thromboprophylaxis increases major bleeding, but the evidence is very uncertain. The panel judged these effects to be small (for major bleeding: RR, 1.55; 95% CI, 1.14-2.12; ARI, 16 more per 1000: 95% CI, 4-32 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low because of indirectness and imprecision of the estimates. With regard to indirectness, in the single identified RCT, the drug used for postoperative administration was ultra-LMWH, which does not reflect the current practice. Also, both arms of the trial had the anticoagulant administered for 7 to 10 days, including the group that started enoxaparin preoperatively. Additionally, because the experimental arm involved a different drug and a different timing compared with the control arm, it is challenging to interpret the results.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is very low certainty in the evidence for a net health benefit of preoperative thromboprophylaxis vs postoperative thromboprophylaxis and concluded that the balance probably favors immediate postoperative thromboprophylaxis. The panel further discussed that preoperative prophylaxis seemed to only modestly decrease the risk of VTE, but it also seemed to increase the risk of bleeding. The recommendation is conditional because of low-quality evidence. The panel believed that the resource use (cost and savings) may be negligible but noted that preoperative administration might require preoperative admission in certain settings, resulting in a cost increase.

The panel agreed that there is probably no impact on health equity because, despite the variability in impact on health equity, for short-term scenarios like hospitalized patients, the impact is less likely. No cost-effectiveness evidence was identified. The panel noted that acceptability and feasibility may vary between settings, particularly given that, in some settings, preoperative administration of prophylaxis may require preoperative admission that may be difficult to organize and that issues concerning neuraxial anesthesia must also be considered.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for using postoperative, rather than preoperative, thromboprophylaxis is due to a balance of effects that probably favors postoperative thromboprophylaxis, because of the small potential reduction in VTE and mortality but, more likely, an increase in the risk of bleeding. The panel did not recognize a large advantage to preoperative prophylaxis and took a precautionary approach because of bleeding and logistical considerations with neuraxial anesthesia, which were based on very low certainty in the evidence. The panel strongly recommends future research into the optimal timing of perioperative anticoagulation.

Should extended thromboprophylaxis (continuing pharmacological thromboprophylaxis at home) vs limited thromboprophylaxis (7-10 days; discontinuing thromboprophylaxis at the time of discharge) be used for patients with cancer who have undergone a surgical procedure?

Recommendation 12

For patients with cancer who had undergone a major abdominal/pelvic surgical procedure, the ASH guideline panel *suggests* continuing pharmacological thromboprophylaxis postdischarge rather than discontinuing at the time of hospital discharge (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Although we searched for evidence for all surgical procedures, we only identified evidence to assess the benefits and harms of extended thromboprophylaxis for patients undergoing major abdominal/pelvic surgery; this recommendation should not be extended to other surgical procedures (see Recommendations 9 and 10). Patients should be provided comprehensive anticoagulation education, including self-injection technique, during hospitalization to facilitate continuation of thromboprophylaxis after discharge.

Extended (continue at home) vs limited (7-10 days; discontinue at the time of discharge). SUMMARY OF THE EVIDENCE. We identified 4 systematic reviews addressing this question.[205-208] We identified 5 studies that fulfilled our inclusion criteria and measured outcomes relevant to this context.[199-201,203,209] Our systematic search for RCTs identified 1 additional study that fulfilled the inclusion criteria.[202] Four studies included only patients with cancer,[199,201-203] whereas in the remaining 2 studies, the majority of the patients had cancer.[200,209] All trials reported on abdominal cancer, and 2 also included pelvic cancer.[199,203] All studies included patients undergoing abdominal/pelvic surgery. Five studies compared LMWH administered for 4 weeks postoperatively with LMWH administered for 1 week postoperatively.[199-201,203,209] One study compared the use of extended thromboprophylaxis with LMWH vs discontinuation of LMWH upon hospital discharge.[202] Two studies reported the use of compression stockings in both study arms for 1 week.[200,209] All 6 studies reported on mortality.[199-203,209] Five studies reported on PEs and symptomatic DVTs.[199-201,203,209] Four studies reported data on asymptomatic DVTs.[199-201,203] Five studies reported data on major bleeding,[199-203] 1 study reported on HIT,[200] and 1 study reported on rates of reoperation for bleeding.[201]

The EtD framework is available at https://guidelines.ash.gradepro.org/profile/2GovinJ5W_0.

BENEFITS. Extended thromboprophylaxis (up to 4 weeks) compared with limited thromboprophylaxis (7-10 days; discontinuing at the time of hospital discharge) may reduce PEs and symptomatic DVTs, but the evidence is very uncertain. Extended thromboprophylaxis reduces asymptomatic DVTs slightly. The panel judged these benefits to be small (for PE: RR, 0.18; 95% CI, 0.02-1.46; ARR, 14 fewer per 1000; 95% CI, 17 fewer to 8 more per 1000 using a baseline risk of 1.7%[210]; for symptomatic DVT: RR, 0.67; 95% CI, 0.11-4.06; ARR, 10 fewer per 1000; 95% CI, 26 fewer to 89 more per 1000 using a baseline risk of 2.9%[210]; for asymptomatic DVT: RR, 0.50; 95% CI, 0.33-0.74; ARR, 14 fewer per 1000; 95% CI, 8-19 fewer per 1000 using a baseline risk of 2.9%).[210]

HARMS AND BURDEN. Extended thromboprophylaxis (up to 4 weeks) compared with limited thromboprophylaxis (7-10 days; discontinuing at the time of hospital discharge) may result in little to no effect on major bleeding and reoperation for bleeding, but the evidence is very uncertain. It may increase mortality slightly, and the panel judged these effects to be small (for major bleeding: RR, 0.83; 95% CI, 0.29-2.35; ARR, 2 fewer per 1000; 95% CI, 7 fewer to 14 more per 1000; for reoperation for bleeding: RR, 0.50; 95% CI, 0.05-5.48; ARR, 9 fewer per 1000; 95% CI, 17 fewer to 79 more per 1000; for mortality: RR, 1.14; 95% CI, 0.73-1.78; ARI, 6 more per 1000; 95% CI, 12 fewer to 35 more per 1000). We were unable to estimate the relative risk of HIT, because no events occurred in the study reporting this outcome.[200]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low because of the risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that, although there is very-low-certainty evidence of a net health benefit from extending thromboprophylaxis rather than discontinuing at the time of hospital discharge, the balance probably favors extended thromboprophylaxis. The panel believed that the resources (cost and savings) were moderate and that cost-effectiveness probably favors the intervention.

The panel noted that extended prophylaxis could cause inequity because of concerns about cost and the ability to self-inject. Some patients might find the intervention unacceptable with respect to having to continue with injections at home. For some patients, the intervention might not be feasible (eg, if they are transferred to home or long-term care without support for injections).

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for extending thromboprophylaxis, rather than discontinuing at the time of hospital discharge, is due to a balance between desirable and undesirable effects that probably favor continuing pharmacological thromboprophylaxis after discharge based on very-low-quality evidence and possible favorable cost-effectiveness.

The panel noted that, in case of a shorter hospital stay, the current recommendation would likely not differ, because the risk of VTE persists for a long period after surgery. The panel agreed that more data are required because most of the evidence comes from abdominal or pelvic surgery.

Primary prophylaxis for ambulatory patients with cancer receiving systemic therapy

Should parenteral thromboprophylaxis vs no thromboprophylaxis be used for ambulatory patients with cancer receiving systemic therapy?

Recommendation 13

For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel *recommends* no thromboprophylaxis over parenteral thromboprophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no prophylaxis over parenteral prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* parenteral thromboprophylaxis (LMWH) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Remarks: Classification of patients as being low-, intermediate-, or high-risk for VTE should be based on a validated risk-assessment tool (ie, Khorana score) complemented by clinical judgment and experience. The panel noted that, even for patients at high risk for thrombosis, thromboprophylaxis should be used with caution in those with a high risk for bleeding.

Parenteral thromboprophylaxis vs no thromboprophylaxis.

SUMMARY OF THE EVIDENCE. We identified 13 systematic reviews addressing this question.[211-222] From these reviews, we identified 17 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this clinical setting.[223-238] One systematic review evaluated the efficacy and safety of LMWH prophylaxis for patients receiving chemotherapy for lung cancer.[222] This systematic review included 5 Chinese studies that we could not retrieve as full texts.[239-243] The panel decided to base the meta-analysis on individual participant data. Of the 17 eligible RCTs, we included 12 RCTs for which we had access to their individual participant data in the meta-analysis.[223-225,228-234,237,238] One study used UFH as the intervention,[229] and another used ultra-LMWH[223]; the rest used LMWH.[224,225,228,230-234,237,238] We did not identify any study using fondaparinux as the intervention. Cancers included in these studies were abdominal,[223,228,233,234,237,238] thoracic,[223-225,228-231,233,234] breast,[225,228,233] pelvic,[223,228,233,234] skin,[228] and neurological.[232] The result of the individual participant data meta-analysis was not significantly different from the results from the group-level data systematic review.[211] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/5Fxh8ECm1hk.

BENEFITS. Parenteral thromboprophylaxis compared with no thromboprophylaxis probably reduces mortality slightly, reduces any VTE and symptomatic VTEs, results in little to no difference in asymptomatic VTEs, and reduces PEs slightly. Parenteral thromboprophylaxis results in a large reduction in any symptomatic DVT for patients at high risk for thrombosis, reduces any symptomatic DVT for patients at intermediate risk for thrombosis, and reduces any symptomatic DVT slightly for patients at low risk for thrombosis. The panel judged the benefits to be small for patients at low risk for

thrombosis, moderate for patients at intermediate risk for thrombosis, and large for patients at high risk for thrombosis. For mortality: RR, 0.97; 95% CI, 0.90-1.03; ARR, 15 fewer per 1000; 95% CI, 50 fewer to 15 more per 1000. For any VTE: RR, 0.57, 95% CI, 0.46-0.71; ARR, 30 fewer per 1000; 95% CI, 20-38 fewer per 1000. For symptomatic VTE: RR, 0.53; 95% CI, 0.40-0.70; ARR, 27 fewer per 1000; 95% CI, 18-35 fewer per 1000. For asymptomatic VTE: RR, 0.63; 95% CI, 0.39-1.02; ARR 5 fewer per 1000; 95% CI, 0-8 fewer per 1000. For PE: RR, 0.53; 95% CI, 0.39-0.73; ARR, 13 fewer per 1000; 95% CI, 8-18 fewer per 1000. For any symptomatic DVT: RR, 0.55; 95% CI, 0.38-0.80; ARR, 16 fewer per 1000; 95% CI, 7-21 fewer per 1000 using a baseline risk of 3.5%; ARR, 45 fewer per 1000; 95% CI, 20-62 fewer per 1000 using a baseline risk of 10%[244]; ARR, 86 fewer per 1000; 95% CI, 38-119 fewer per 1000 using a baseline risk of 19.2%.[244] Parenteral thromboprophylaxis probably results in little to no difference in quality-of-life impairment.[231,233]

HARMS AND BURDEN. Parenteral thromboprophylaxis compared with no thromboprophylaxis likely results in little to no difference in major bleeding, and the panel judged the effect to be trivial (RR, 1.16; 95% CI, 0.85-1.59; ARI, 3 more per 1000; 95% CI, 3 fewer to 11 more per 1000). With input from the patient representative, the panel agreed that the burden of treatment and additional side effects, such as local hematomas in the context of cancer treatment, may represent a small or unimportant burden. However, qualitative research demonstrates that the burden may vary and is likely to be higher between patients who are receiving anticoagulation for treatment and those who are receiving anticoagulation for prophylaxis.[41]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as moderate for patients at immediate risk for thrombosis and high for patients at high risk for thrombosis because of risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that for patients with cancer receiving systemic cancer therapy at low risk for thrombosis, there is moderate certainty in the evidence that neither parenteral thromboprophylaxis nor thromboprophylaxis is favored; thus, they recommended against thromboprophylaxis. For patients at intermediate risk for thrombosis, there is moderate certainty in the evidence for a net health benefit from parenteral thromboprophylaxis, and the panel agreed that the balance probably favors parenteral thromboprophylaxis. For patients at high risk for thrombosis, there is high-certainty evidence favoring parenteral thromboprophylaxis.

The panel thought that the resources (cost and savings) were moderate and that cost-effectiveness probably favors the intervention for patients at high risk for thrombosis. The cost of managing VTE and anticoagulation will vary by health system, region, and payer setting. Costs in the United States are greater than in many other developed countries, and out-of-pocket expenses continue to increase.

The panel agreed that equity would probably be reduced with the use of parenteral thromboprophylaxis because there are groups of patients who would not have access to expensive outpatient medications, and drug approval for this indication will differ. The panel also agreed that acceptability will vary. From the patients' perspective, it may depend on baseline risk for patients, being more acceptable for patients with a higher risk for thrombosis. From the health care professionals' perspective, it may also depend on baseline risk of thrombosis. Some clinicians and patients may be concerned about cost-effectiveness and the burden of prescribing when LMWH is not routinely covered by insurance plans.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. Overall, the panel concluded that primary prophylaxis with LMWH for ambulatory patients receiving cancer chemotherapy reduces the risk of VTE with a minor increase in the risk of bleeding and with no impact on overall survival. The panel made 3 different recommendations, depending on the baseline risk of thrombosis (eg, Khorana score).[245] For patients at low risk for thrombosis, the panel made a strong recommendation against the use of routine parenteral thromboprophylaxis. For patients at intermediate risk for thrombosis, the panel made a conditional recommendation against the use of routine parenteral thromboprophylaxis. For patients at high risk for thrombosis, the panel made a conditional recommendation for the use of parenteral thromboprophylaxis.

Research priorities highlighted by the panel include determining the benefits and harms of VTE prophylaxis for patients at intermediate risk for thrombosis and determining the benefits and harms by tumor type. The panel believed that development of additional validated decision aids and educational material (awareness of thrombosis risk and symptoms) could be helpful. The panel agreed that additional cost-effectiveness data may be required in different health care settings and for different risk groups, particularly high-risk patients, to address the cost-effectiveness of this intervention.

Should oral thromboprophylaxis vs no thromboprophylaxis be used for ambulatory patients with cancer receiving systemic therapy?

Recommendations 14 and 15

For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel *recommends* no thromboprophylaxis over oral thromboprophylaxis with VKAs (strong recommendation, very low certainty in the evidence of benefits ⊕◯◯◯ but high certainty about the harms ⊕⊕⊕⊕). For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Remarks: Classification of patients as being at low, intermediate, or high risk for VTE should be based on a validated risk assessment tool (ie, Khorana score) complemented by clinical judgment and experience. The panel noted that, even for patients at high risk for thrombosis, thromboprophylaxis should be used with caution for those at high risk for bleeding. The direct factor Xa inhibitors apixaban and rivaroxaban are the only DOACs that were evaluated for the primary prophylaxis for ambulatory patients with cancer receiving chemotherapy.

VKA thromboprophylaxis vs no thromboprophylaxis.

SUMMARY OF THE EVIDENCE. We identified 4 systematic reviews that addressed, in part, this question.[214,217,246,247] From these reviews, we identified 6 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this context among ambulatory patients with cancer receiving systemic therapy.[248-253] Five trials reported on the effect of VKA vs no prophylaxis on mortality,[248-253] 1 trial report on PEs and symptomatic DVTs,[249] and 5 studies reported on major bleeding.[248-250,252,253] The different types of cancers included in these studies were thoracic,[248,250-253] abdominal,[252] breast,[249] urological,[254] and head and neck.[252] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/rvJlcDQvhhU.

BENEFITS. For ambulatory patients with cancer receiving systemic therapy, VKA thromboprophylaxis compared with no thromboprophylaxis probably reduces mortality, may have little to no effect on PEs, and may reduce symptomatic DVTs; however, the evidence is very uncertain. The panel judged these desirable effects as moderate across groups with a low or intermediate risk for DVT and as large for the high-risk group (for mortality: RR, 0.95; 95% CI, 0.87-1.03; ARR, 29 fewer per 1000; 95% CI, 17 more to 75 fewer per 1000; for PE: RR, 1.05; 95% CI, 0.07-16.58; ARR, 0 fewer per 1000, 95% CI, 6 fewer to 98 more per 1000; for symptomatic DVT: RR, 0.08; 95% CI, 0.0046-1.42; ARR, 35 fewer per 1000 using a baseline risk of 3.8%; ARR, 92 fewer per 1000 using a baseline risk of 10%[244]; ARR, 177 fewer per 1000 using a baseline risk of 19.2%).[244]

HARMS AND BURDEN. VKA thromboprophylaxis compared with no thromboprophylaxis increases major bleeding, and the panel judged the harms and burden to be large (RR, 2.89; 95% CI, 2.07-4.04; ARI, 106 more per 1000; 95% CI, 60-170 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in the evidence for the benefits was judged as very low because of indirectness and imprecision of the estimates. However, the certainty in the evidence for the harm from bleeding was judged as high.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel concluded that there is very-low-certainty evidence of a net health benefit from VKA thromboprophylaxis and high certainty about the harms (with the risk of major bleeding outweighing the benefits of DVT reduction across risk groups) and concluded that the balance of effects probably favors no thromboprophylaxis.

Although the panel agreed that the costs of VKAs are very low, VKA monitoring and major bleeding are costly. Given the lack of cost-effectiveness data, the panel concluded that the cost-effectiveness favors no thromboprophylaxis over thromboprophylaxis with VKA. The panel agreed that equity would probably be reduced with the use of VKA thromboprophylaxis, because there are groups of patients who would face difficulty with ensuring adequate access to VKA monitoring. Nevertheless, the panel also agreed that, although some patients and caregivers might find the logistics of VKA monitoring unacceptable, the intervention would probably be acceptable to key stakeholders.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The strong recommendation for no thromboprophylaxis over thromboprophylaxis with a VKA for ambulatory patients with cancer without VTE and receiving systemic therapy is due to the low certainty in the evidence of the benefits and the high certainty about the harms, moderate costs, and cost-effectiveness, such that the balance of effects probably favors no thromboprophylaxis. The GRADE approach includes situations in which strong recommendations are warranted, despite very low certainty in the evidence of the effects, including situations in which high certainty about the harms of the intervention outweighs the potential benefit.[255] The panel agreed that this question is not a research priority, given the potential alternative interventions.

DOAC thromboprophylaxis vs no thromboprophylaxis.

SUMMARY OF THE EVIDENCE. We identified 5 systematic reviews that addressed, in part, this question.[214,217,246,247,256] From these reviews, we identified 3 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this context.[257-259] The most common types of cancer included gynecologic, lymphoma, lung, and pancreatic. Patients in the AVERT and CASSINI trials had a moderate to high risk for VTE (Khorana score $\geq$ 2).[257,258] Apixaban was the intervention in 2 of the studies,[257,259] whereas rivaroxaban was used in the third study.[258] All 3 studies assessed the efficacy of DOACs compared with no prophylaxis or placebo on mortality, PEs, symptomatic DVTs, and major bleeding. The EtD framework for populations with low risk for thrombosis is available at https://guidelines.ash.gradepro.org/profile/rPFlhvr3GUE. The EtD framework for populations with intermediate risk for thrombosis is available at https://guidelines.ash.gradepro.org/profile/7D9gHSZbMnE. The EtD framework for populations with high risk for thrombosis is available https://guidelines.ash.gradepro.org/profile/qmBqSB7Txqg.

BENEFITS. For ambulatory patients with cancer receiving systemic therapy, thromboprophylaxis with a DOAC (apixaban or rivaroxaban) compared with no thromboprophylaxis probably reduces mortality, PEs, and symptomatic DVTs. The panel judged desirable effects as small for patients with a low risk for DVT and as moderate for patients with a moderate or high risk for DVT (for mortality: RR, 0.94; 95% CI, 0.64-1.38; ARR, 11 fewer per 1000; 95% CI, 67 fewer to 70 more per 1000; for PE: RR, 048; 95% CI, 0.24-0.98; ARR, 24 fewer per 1000; 95% CI, 1-34 fewer per 1000; for symptomatic DVT: RR, 0.61; 95% CI, 0.31-1.21; ARR, 7 fewer per 1000; 95% CI, 12 fewer to 4 more per 1000 using a baseline risk of 1.7%[260]; ARR, 20 fewer per 1000; 95% CI, 34 fewer to 10 more per 1000 using a baseline risk of 5%[244]; ARR, 37 fewer per 1000; 95% CI, 66 fewer to 20 more per 1000 using a baseline risk of 9.5%).[244]

HARMS AND BURDEN. Thromboprophylaxis with a DOAC compared with no thromboprophylaxis probably increases major bleeding slightly, and the panel judged this effect as small (RR, 1.65; 95% CI, 0.72-3.80; ARI, 12 more per 1000; 95% CI, 50 more to 5 fewer per 1000 using a baseline risk of 1.8%).[244]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as moderate because of imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is moderate certainty in the evidence that, in the low-risk group, there is not a net health benefit from DOAC thromboprophylaxis and concluded that the balance of effects does not favor thromboprophylaxis with a DOAC or no thromboprophylaxis. In the case of the intermediate-risk group, the panel concluded that the balance probably favors the use of DOACs, and it favors the use of DOACs in the high-risk group.

The panel agreed that costs will vary depending on the risk of thrombosis and that the intervention is likely to be more cost-effective if applied in the high-risk group. The panel agreed that

equity would probably be reduced with the use of DOAC thromboprophylaxis, because there are groups of patients who would not have the financial resources to cover the medications. Furthermore, drug availability and approval for this indication will likely differ across settings. The panel also agreed that acceptability will vary. In the case of patients, it may depend on the baseline risk for VTE, being more acceptable for patients with a higher risk for thrombosis. Some patients might also be concerned about not receiving any intervention. In the case of health care professionals, it may also depend on the baseline risk of VTE.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. Overall, the panel concluded that primary prophylaxis with a DOAC for ambulatory patients receiving systemic therapy reduces the risk of VTE with a minor increase in the risk of bleeding. The panel made 3 recommendations, depending on the baseline risk of thrombosis (ie, Khorana score).[245] For patients at low risk for thrombosis, the panel made a conditional recommendation (rather than strong) against the use of DOACs for ambulatory patients with cancer and without VTEs who are receiving systemic therapy. For patients at intermediate risk for thrombosis, the panel made a conditional recommendation (rather than strong) for either DOAC or nonprophylaxis. For patients at high risk for thrombosis, the panel made a conditional recommendation (rather than strong) for the use of DOACs.

Classification of patients as having a low, moderate, or high risk for VTE should be based on a validated score (ie, Khorana score)[245] complemented by clinical judgment and experience. For patients at high risk for thrombosis, thromboprophylaxis should be used with caution for those with a high risk for bleeding. The panel believed that additional trials comparing thromboprophylaxis with LMWH vs DOACs are required to help inform decisions for this patient population.

Should low-dose ASA thromboprophylaxis vs LMWH vs fixed-dose VKA thromboprophylaxis be used for ambulatory patients with multiple myeloma receiving lenalidomide-, thalidomide-, or pomalidomide-based regimens?

Recommendations 16 and 17

For multiple myeloma patients receiving lenalidomide-, thalidomide-, or pomalidomide-based regimens, the ASH guideline panel *suggests* using low-dose ASA, fixed low-dose VKA, or LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: Treatment with ASA, low-dose VKA, or LMWH depends on patient preferences and the cost-effectiveness, which may vary across settings. When cost and feasibility are less of a concern, LMWH may be the better choice. Because of greater efficacy, LMWH should be considered for patients at higher risk for VTE; however, the panel notes that subcutaneous administration of LMWH over a long period of time may not be acceptable to some patients. An increased risk for bleeding is likely in patients on ASA who are also receiving steroids. Data on thromboprophylaxis for patients receiving pomalidomide-based regimen are lacking, but the panel believed that the benefits and harms of thromboprophylaxis were likely similar to those in patients receiving thalidomide- or lenalidomide-based regimens.

Low-dose ASA thromboprophylaxis vs fixed-dose VKA. SUMMARY OF THE EVIDENCE. We identified 1 systematic review that addressed this question.[261] From this review, we identified 1 eligible RCT that fulfilled our inclusion criteria and measured outcomes relevant to this context.[262] The trial assessed the effect of low-dose ASA vs fixed-dose VKA (1.25 mg daily) on mortality, PEs, symptomatic DVTs, and major bleeding at 6 months for ambulatory patients with multiple myeloma receiving lenalidomide- or thalidomide-based regimens. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/Ir8bZ95T8vw.

BENEFITS. Low-dose ASA thromboprophylaxis compared with fixed-dose VKA thromboprophylaxis probably results in little to no difference in mortality and any PEs and may reduce any symptomatic DVTs slightly. The panel judged the desirable effects as small (for mortality: RR, 3.00; 95% CI, 0.12-73.24, with only 1 reported event occurring in the low-dose ASA thromboprophylaxis group [n = 220] and no events occurring in the fixed-dose VKA thromboprophylaxis group [n = 220]; for PE: RR, 1.00; 95% CI, 0.25-3.95; ARR, 0 fewer per 1000; 95% CI, 14 fewer to 54 more per 1000; for any symptomatic DVT: RR, 0.57; 95% CI, 0.24-1.33; ARR, 27 fewer per 1000; 95% CI, 48 fewer to 21 more per 1000).

HARMS AND BURDEN. Low-dose ASA thromboprophylaxis compared with fixed-dose VKA thromboprophylaxis may slightly increase the risk of major bleeding. The panel judged the undesirable effects as small (for major bleeding: RR, 7.00; 95% CI, 0.36-134.72; ARI, 14 more per 1000; 95% CI, 1 fewer to 308 more per 1000 using a baseline risk of 0.2%).[262]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in the evidence for the benefits was judged as low because of imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is low-certainty evidence of a net health benefit from low-dose ASA over fixed-dose VKA thromboprophylaxis and concluded that the balance of effects does not favor either. The panel agreed that the anticipated benefits are similar to the harms, because the bleeding was considered to be of greater importance and possibly more frequent than the prevented DVTs; overall, this led to a balanced assessment of the health benefits and harms.

The panel was uncertain about the magnitude of resource requirements (and associated costs), and no study about cost-effectiveness was available. There is probably no impact on equity with either intervention, with monitoring probably already taking place through health care visits because of myeloma treatment. VKA is less acceptable to patients and clinicians because of the associated burden, including monitoring.

Low-dose ASA vs LMWH. SUMMARY OF THE EVIDENCE. We identified a systematic review that addressed this question.[261] From this review, we identified 2 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this context.[262,263] The trials assessed the effect of low-dose ASA vs LMWH on mortality, PEs, symptomatic DVTs, and major bleeding at 6 months for ambulatory patients with multiple myeloma and without VTE receiving lenalidomide- or thalidomide-based regimens. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/IPXqGJq4cY8.

BENEFITS. Low-dose ASA vs LMWH thromboprophylaxis may result in little to no difference in mortality, PEs, and any symptomatic DVTs. The panel judged the desirable effects as trivial (for mortality: RR, 1.00; 95% CI, 0.06-15.81; ARR, 0 fewer per 1000; 95% CI, 2 fewer to 38 more per 1000; for PE: RR, 7.71; 95% CI, 0.97-61.44; with only 7 reported events occurring in the low-dose ASA thromboprophylaxis group [n = 396] and 0 events occurring in the LMWH thromboprophylaxis group [n = 385]; for any symptomatic DVT: RR, 1.23; 95% CI, 0.49-3.08; ARI, 5 more per 1000; 95% CI, 11 fewer to 43 more).

HARMS AND BURDEN. Low-dose ASA thromboprophylaxis compared with LMWH thromboprophylaxis may increase major bleeding slightly. The panel judged the undesirable effects as trivial (major bleeding: RR, 6.97; 95% CI, 0.36-134.11; ARI, 8 more per 1000; 95% CI, 1 fewer to 173 more using a baseline risk of 0.1%).[262,263]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in the evidence for the benefits was judged as low because of imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is low-certainty evidence of a net health harm from low-dose ASA over LMWH thromboprophylaxis and concluded that the balance of effects probably favors LMWH.

The panel judged as moderate the magnitude of resource requirements (and associated costs) and that the cost-effectiveness probably favors low-dose ASA thromboprophylaxis. Given the burden of LMWH administered over a long period of time, low-dose ASA is likely more acceptable for patients and is probably more acceptable for payers. Feasibility is likely to be reduced with LMWH, but low-dose ASA is feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for low-dose ASA thromboprophylaxis or fixed-dose VKA thromboprophylaxis for ambulatory patients with multiple myeloma receiving lenalidomide-, thalidomide-, or pomalidomide-based regimens is due to a balance of effects that does not favor either in the context of low-certainty evidence of the effects, uncertain costs, and no information about cost-effectiveness. Increased bleeding risk is likely for patients on ASA who are also receiving steroids.

The conditional recommendation for low-dose ASA thromboprophylaxis or LMWH thromboprophylaxis for ambulatory patients with multiple myeloma receiving lenalidomide-, thalidomide-, or pomalidomide-based regimens is due to a balance of effects that probably favors LMWH, in the context of low-certainty evidence of the effects, and cost-effectiveness that probably favors low-dose ASA.

The panel agreed that RCTs that evaluate the effect of DOACs, as well as decision aids, are needed to answer this question. Further evaluation of risk factors for VTE in this population is needed, with prospective trials assessing thromboprophylaxis based on validated risk models for VTE.

Primary prophylaxis for patients with cancer with a CVC

Should parenteral thromboprophylaxis vs oral thromboprophylaxis vs no thromboprophylaxis be used for patients with cancer with a CVC?

Recommendations 18 and 19

For patients with cancer and a CVC, the ASH guideline panel *suggests not* using parenteral or oral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: The recommendation applies to fixed- and adjusted-dose VKA. Thromboprophylaxis may be considered for selected patients with cancer who are considered at high risk for VTE or for patients receiving thalidomide-, lenalidomide-, or pomalidomide-based regimens for myeloma.

Parenteral thromboprophylaxis vs no thromboprophylaxis.

SUMMARY OF THE EVIDENCE. We identified 6 systematic reviews addressing this question.[264-269] From these reviews, we identified 6 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this question.[270-275] Our systematic search of RCTs did not identify any additional studies. Five trials reported on the effect of LMWH compared with no prophylaxis on mortality,[270-273,275] 6 trials reported on symptomatic catheter-related thrombosis,[270-275] and 4 trials reported on major bleeding.[270,271,274,275] All studies reported primarily on solid tumors, with the exception of the study by Niers et al, which focused on hematological tumors.[274] The timing of LMWH administration ranged from 2 hours prior to CVC insertion to 90 days after, CVC removal, or thrombosis diagnosis, whichever occurred first. In most studies, the CVC was inserted in the subclavian vein. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/XuHZ1KtjScI.

BENEFITS. LMWH thromboprophylaxis compared with no thromboprophylaxis may reduce mortality and symptomatic catheter-related thrombosis, but the evidence is very uncertain. The panel judged desirable effects as moderate (for mortality: RR, 0.82; 95% CI, 0.53-1.26; ARR, 14 fewer per 1000; 95% CI, 36 fewer to 20 more per 1000; for symptomatic catheter-related thrombosis: RR, 0.48; 95% CI, 0.27-0.86; ARR, 14 fewer per 1000; 95% CI, 4-20 fewer using a baseline risk of 2.7%).[276]

HARMS AND BURDEN. LMWH compared with no thromboprophylaxis may have little to no effect on major bleeding, but the evidence is very uncertain. The panel judged undesirable effects as trivial (for major bleeding: RR, 0.49; 95% CI, 0.03-7.84; ARR, 1 fewer per 1000; 95% CI, 2 fewer to 16 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in the evidence for the benefits was judged as very low because of indirectness and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is low-certainty evidence of a net health benefit from LMWH over no thromboprophylaxis and concluded that the balance of effects probably favors LMWH. The panel judged that resource requirements (and associated costs) varies and that the cost-effectiveness is uncertain. The panel also agreed that acceptability varies; it may depend on baseline risk for patients, being more acceptable for patients with a higher risk for thrombosis. In the case of health care professionals, it may also depend on the baseline risk of thrombosis. Some clinicians may be concerned about cost-effectiveness and the burden of prescribing when LMWH is not routinely covered by insurance plans. Feasibility is likely to be reduced with LMWH.

Oral thromboprophylaxis vs no thromboprophylaxis. SUMMARY OF THE EVIDENCE. We identified 6 systematic reviews addressing this question.[264-269] The panel was not interested in fixed-dose VKA because it does not reflect current practice. Thus, from the identified systematic reviews, there was only 1 eligible RCT that reported on adjusted-dose VKA and fulfilled our inclusion criteria.[277] Our systematic search of RCTs did not identify any additional studies. This included trial reported the effect of adjusted-dose VKA compared with no prophylaxis on mortality, symptomatic catheter-related thrombosis, and major bleeding. VKA was adjusted to maintain the international normalized ratio (INR) between 1.5 and 2.0. It was administered 3 days prior to CVC insertion and continued until thrombosis occurred or the catheter had to be removed for any reason. The most common site of cancer was colorectal. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/th_JPGUVWCE.

BENEFITS. Compared with no thromboprophylaxis, dose-adjusted VKA may reduce mortality and symptomatic catheter-related thrombosis, but the evidence is very uncertain. The panel judged desirable effects as moderate (for mortality: RR, 0.91; 95% CI, 0.76-1.08; ARR, 35 fewer per 1000; 95% CI, 94 fewer to 31 more per 1000; for symptomatic catheter-related thrombosis: RR, 0.46; 95% CI, 0.24-0.90; ARR, 15 fewer per 1000; 95% CI, 3-21 fewer).

HARMS AND BURDEN. Dose-adjusted VKA may increase major bleeding, but the evidence is very uncertain. The panel judged undesirable effects as moderate (for major bleeding: RR, 13.67; 95% CI, 1.82-102.60; ARI, 31 more per 1000; 95% CI, 2-251 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in the evidence for the benefits was judged as very low because of imprecision and indirectness.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel determined that there is very-low-certainty evidence of a net health harm from dose-adjusted VKA over no thromboprophylaxis and concluded that the balance of effects probably favors no thromboprophylaxis. The panel perceived that the lower baseline risk of catheter-related thrombosis with new catheters (<2.7%) will reduce the absolute effects of VKA. The risk of bleeding was considered important and outweighing the reduction in catheter-related thrombosis.

The panel judged that resource requirements and associated costs are moderate and that the cost-effectiveness is uncertain. The panel also agreed that equity will probably be reduced because there are subgroups who would have difficulty getting adequate VKA monitoring. Although dose-adjusted VKA is probably acceptable to stakeholders, some patients and/or caregivers might find the logistics for VKA monitoring unacceptable.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. For patients with cancer with a CVC, the ASH guideline panel suggests not using LMWH or VKA as thromboprophylaxis. This recommendation does not apply to patients who have a CVC, have a high or intermediate risk for thrombosis, and are also receiving systemic therapy (see Recommendations 13 and 15).

The conditional recommendation against the use of LMWH over no thromboprophylaxis for patients with cancer with a CVC takes into account that, although the benefit may favor LMWH, it is in the context of low-certainty evidence, variable costs, no data available on cost-effectiveness, and a probable reduction in equity.

The conditional recommendation against using adjusted-dose VKA over no thromboprophylaxis for patients with cancer with a CVC is due to a balance of effects that probably favors no thromboprophylaxis in the context of low-certainty evidence, moderate costs, and reduction in equity. Data on cost-effectiveness are not available. The risk of bleeding was considered important and outweighing the reduction in catheter-related thrombosis. The recommendation applies to fixed-dose and adjusted-dose VKA. The panel agreed that more research is needed, primarily about the use for high-risk patients, treatment duration, and best agent (eg, DOACs).

Initial treatment (within first week) for patients with cancer

Should LMWH vs UFH vs fondaparinux vs DOAC be used for patients with cancer with VTE for initial treatment in the first week?

Recommendations 20, 21, and 22

For patients with cancer and VTE, the ASH guideline panel *suggests* that DOACs (apixaban or rivaroxaban) or LMWH be used for initial treatment (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). If a DOAC is not used, the ASH guideline panel *recommends* LMWH over UFH (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯) and LMWH over fondaparinux (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯) for initial treatment of VTE for patients with cancer.

Remarks: The period of initial treatment is 5 to 10 days, covering the early period of care starting from the time of diagnosis of VTE. Only 2 DOACs (apixaban and rivaroxaban) have been approved for the initial treatment period. DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding. UFH might be preferred over LMWH for the patient with cancer with severe renal impairment (defined as creatinine clearance <30 mL/min). The use of fondaparinux might be considered for patients with cancer and VTE and a history of HIT (see "American Society of Hematology 2018 guidelines for the management of venous thromboembolism: heparin-induced thrombocytopenia").[402]

LMWH vs UFH. SUMMARY OF THE EVIDENCE. We identified 2 systematic reviews that partially addressed this question, including 1 review reporting outcomes for cancer patients.[278,279] These reviews included 14 trials.[254,280-292] Our update of the systematic review identified 1 additional trial that fulfilled the inclusion criteria.[293] All RCTs included hemodynamically stable patients who did not require thrombolysis and compared initial treatment with LMWH vs UFH administered during the first 10 days, followed by VKA (target INR between 2 and 3), for the management of acute DVT or PE. Given that all RCTs used VKA during the follow-up period, the event rates for the total duration of follow-up were used to assess the efficacy and safety of LMWH or UFH for the initial treatment of VTE for this patient population. Eleven trials reported on the effect of LMWH compared with UFH

on mortality,[254,281-286,288-291] 3 trials reported on recurrent VTE,[280,287,288] and none reported on major bleeding, quality-of-life impairment, HIT, or chronic thrombotic pulmonary hypertension. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/F2xpTxLx5I8.

BENEFITS. LMWH probably results in a large reduction in mortality and recurrent VTE, and the panel judged the effects to be large (for mortality: RR, 0.75; 95% CI, 0.56-1.02; ARR, 46 fewer per 1000; 95% CI, 82 fewer to 4 more per 1000; for recurrent VTE: RR, 0.69; 95% CI, 0.27-1.76; ARR, 30 fewer per 1000; 95% CI, 70 fewer to 73 more per 1000).

HARMS AND BURDEN. Indirect data from surgical patients with cancer suggest that there is no important difference in bleeding between LMWH and UFH for thromboprophylaxis.[294] Indirect data from noncancer patients suggest that there is no important difference between LMWH and UFH with respect to bleeding for initial treatment, and a higher risk for HIT is associated with UFH.[295]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as moderate because of imprecision of the estimates. The panel decided not to rate down further for indirectness, because there were enough data from thromboprophylaxis for surgical patients with cancer.

OTHER ETD CRITERIA AND CONSIDERATIONS. The major driver of cost will be the decision to provide initial treatment in the hospital or ambulatory setting. Hospitalization for administration of UFH is costly, and a reduction in cost with LMWH in the ambulatory setting justifies a judgment of large cost savings, with cost-effectiveness data favoring LMWH over UFH. Similarly, a lower risk for suspected and confirmed HIT associated with LMWH use will also result in cost savings. The panel noted that, in some settings (eg, United States, as well as some patients in Canada), patients may bear the cost of outpatient LMWH, whereas in other countries (eg, the United Kingdom, Austria, and Spain) they will not. LMWH was judged to be probably acceptable and feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The strong recommendation (rather than conditional) for initial treatment with LMWH over UFH for patients with cancer with VTE in the first week was due to a balance of effects that favors LMWH in the context of moderate-certainty evidence, large savings, and cost-effectiveness that favors an intervention that is acceptable and feasible.

UFH might be preferred over LMWH for the patient with cancer with severe renal impairment (defined as creatinine clearance $<$30 mL/min). LMWH is often preferred based on the ease and frequency of administration; therefore, it might be easier to implement in practice. With UFH there is a need for hospitalization, continuous IV infusion, and repeat venipunctures to monitor (anti–factor Xa or activated partial thromboplastin time) and adjust the dose. Both require monitoring for the occurrence of active bleeding. The panel does not consider this question comparing 2 parenteral agents a research priority at this time.

Fondaparinux vs LMWH. SUMMARY OF THE EVIDENCE. No systematic review addressing this question was identified. Our systematic search of RCTs identified 1 study that fulfilled the inclusion criteria.[296] This study is a post hoc (retrospective) subgroup analysis of 2 previous RCTs with subsequent treatment with VKAs.[297,298] The investigators compared initial treatment with fondaparinux vs LMWH administered for 5 to 10 days for the acute treatment of DVT or PE. All participants received VKA therapy within 72 hours after commencing initial therapy, which continued for $\geq$3 months. Given that both RCTs used VKA for 3 months, the event rates for the total duration of follow-up were used to assess the efficacy and safety of LMWH and fondaparinux in this patient population. The included study reported on the effect on mortality, recurrent VTE, and major bleeding. All outcomes occurred after treatment with LMWH or fondaparinux had been stopped. Even the investigators recognize the severe limitations and that the results should merely be considered hypothesis generating. Consequently, our very low certainty in this evidence is reflected below. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/JnUTLNyxQbY.

BENEFITS. The panel noted the lack of benefit and trivial desirable effects of fondaparinux (compared with LMWH).

HARMS AND BURDEN. Fondaparinux may increase mortality and probably increases recurrent VTE, and the panel judged the effects to be large (for mortality: RR, 1.19; 95% CI, 0.67-2.11; ARI, 29 more per 1000; 95% CI, 51 fewer to 170 more per 1000; for recurrent VTE: RR, 2.35; 95% CI, 0.95-5.79; ARI, 117 more per 1000; 95% CI, 34 fewer to 417 more per 1000 using a baseline risk of 8.7%).[299] No apparent differences were observed for the outcome major bleeding (RR, 0.99; 95% CI, 0.40-2.48; ARR, 0 fewer per 1000; 95% CI, 22 fewer to 53 more per 1000 using baseline risk of 3.6%).[299]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low because of imprecision and indirectness of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel noted that costs may be moderate because of the higher cost associated with the use of fondaparinux over LMWH. Despite important uncertainty and limited direct data, the panel judged that the cost-effectiveness probably favors LMWH. The impact of health equity is likely to vary, because some patients might not be able to afford the interventions if they have to pay for them (eg, in the United States). Both interventions were judged to be probably acceptable and feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for LMWH over fondaparinux for patients with cancer and VTE for initial treatment of VTE in the first week was due to a balance of effects that probably favors LMWH in the context of very-low-certainty evidence, moderate costs, and cost-effectiveness. The use of fondaparinux might be considered for patients with cancer and VTE and a prior history of HIT (see "American Society of Hematology 2018 guidelines for the management of venous thromboembolism: heparin-induced thrombocytopenia").[402]

The panel does not consider this question comparing 2 parenteral agents a research priority at this time, despite the very low certainty in the existing evidence. Current research priorities are the comparative safety and efficacy of oral agents vs conventional parenteral therapy.

DOAC vs LMWH. SUMMARY OF THE EVIDENCE. No systematic review addressing this question was identified. Our systematic search of RCTs identified 3 studies that fulfilled the inclusion criteria.[300-302] Data from 2 studies could be included in the analyses.[300,301] Both studies

included patients with active cancer who had VTE. One study also included upper extremity DVT and splanchnic vein thrombosis. Both studies reported on the effect of dalteparin on mortality, recurrent VTE, and major bleeding during the first week compared with rivaroxaban[300] or apixaban.[301] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/A4TBFFTabtU.

BENEFITS. Compared with LMWH, DOACs may reduce the risk of recurrent VTE and major bleeding, but the evidence is very uncertain, and the panel judged this effect to be small (for recurrent VTE: RR, 0.20; 95% CI, 0.01-4.04; ARR, 11 fewer per 1000; 95% CI, 14 fewer to 43 more per 1000; for major bleeding: RR, 0.33; 95% CI, 0.01-8.13; ARR, 2 fewer per 1000; 95% CI, 3 fewer to 21 more per 1000).

HARMS AND BURDEN. Compared with LMWH, DOACs may increase mortality, but the evidence is very uncertain, and the panel judged this effect to be small (for mortality: RR, 3.00; 95% CI, 0.12-73.21; with only 1 death reported in the DOAC group [n = 348] and 0 events occurring in the LMWH group [n = 345]).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low because of the risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. Based on the available evidence, the balance of effects favors initial treatment with a DOAC or LMWH. The panel considered that cost would vary (LMWH at therapeutic doses is generally more expensive than DOACs but it might depend on the country and setting) and that there are no data on cost-effectiveness. Both options were considered feasible and probably acceptable for most individuals

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. With no net benefit for 1 treatment option over the other, as well as the variable cost and no data on cost-effectiveness, the panel suggests using a DOAC (apixaban or rivaroxaban) or LMWH for initial treatment for patients with cancer and VTE. The period of initial treatment may range from 5 to 10 days, covering the early period of care starting from the time of diagnosis of VTE. The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of bleeding risk, drug-drug interactions, patient preference, and the availability of treatment options, including cost considerations. DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding and for patients with prior upper GI resections.[303]

Short-term treatment for patients with active cancer (initial 3-6 months)

Should LMWH, VKA, or DOAC be used for the short-term treatment of VTE (first 3-6 months) for patients with active cancer?

Recommendations 23, 24, and 25

For the short-term treatment of VTE (first 3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯). DOAC is also *suggested* over VKA (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). If a DOAC is not used, the ASH guideline panel *suggests* LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Remarks: DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding. The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of potential drug-drug interactions, bleeding risk, patient preference, and the availability of treatment options, including cost considerations. VKA is generally preferred over LMWH and DOAC for patients with cancer and severe renal impairment defined as creatinine clearance <30 mL/min. The direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are the only DOACs that were evaluated for the short-term treatment of VTE for patients with cancer. Different DOACs have different drug-drug interactions.

LMWH vs VKA. SUMMARY OF THE EVIDENCE. We identified 11 systematic reviews addressing this question.[304-313] From these reviews, we identified 8 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this question.[314-319] In all studies, LMWH was administered over 3 to 6 months, and the outcomes were assessed during that time frame. For patients initiating VKA, bridging with a minimum of 5 days of LMWH or UFH was required in 5 studies[314,316-319] or 1 study,[315] respectively. Four studies reported on mortality,[314,316-318] 6 studies reported on recurrent VTE,[314-319] 5 studies reported on major bleeding,[314-318] and 1 study reported on HIT.[314] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/O7wwrVBUfVU.

BENEFITS. Compared with VKA, LMWH probably results in little to no difference in mortality and probably reduces recurrent VTE. The panel judged the effects to be moderate (for mortality: RR, 1.00; 95% CI, 0.88-1.13; ARR, 0 fewer per 1000; 95% CI, 45 fewer to 48 more per 1000; for recurrent VTE: RR, 0.56; 95% CI, 0.42-0.74; ARR, 57 fewer per 1000; 95% CI, 34-76 fewer per 1000).

HARMS AND BURDEN. Compared with VKA, LMWH probably results in little to no difference in major bleeding, and the panel judged the effects to be trivial (for major bleeding: RR, 1.06; 95% CI, 0.64-1.77; ARI, 3 more per 1000; 95% CI, 17 fewer to 35 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as moderate because of the risk of bias and imprecision of the estimates. The panel had a discussion about the importance of HIT as an outcome for this particular clinical question. The panel lowered the importance of HIT from "critical" to "important" because it was believed that this outcome did not influence the direction or the strength of the recommendation.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel considered that resource requirements were moderate but noted a high level of uncertainty, with lack of direct evidence for the comparisons of resource utilization during this treatment period. The results of the available cost-effectiveness analyses vary based on baseline assumptions and input. Based on a NICE evaluation focusing on the Aujesky et al 2005 study,[320] the cost for 3 months of LMWH will alter cost-effectiveness results and may reduce cost considerably. Thus, treatment with LMWH may reduce inequity. LMWH was also believed to be an intervention that is probably acceptable and feasible.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for LMWH over VKA for short-term treatment (3-6 months) for patients with active cancer and VTE was due to a balance of effects that probably favors LMWH in the context of moderate-certainty evidence, uncertain and variable resource use and cost-effectiveness, a probable reduction in inequity, and an intervention that is probably acceptable and feasible.

VKA is generally preferred over LMWH for most patients with cancer and severe renal impairment defined as creatinine clearance <30 mL/min. Adherence may be a challenge when continuing daily injections vs switching to an oral agent, even with routine monitoring. Drug-drug interactions are common with VKA and often unpredictable for patients on multiagent chemotherapeutic regimens. VKA should be accompanied by increased INR monitoring, especially for patients on drugs that may alter pharmacokinetics and for patients with significant GI toxicity (eg, nausea, vomiting, diarrhea, colitis) and inconsistent dietary and alcohol habits.

As research priorities, the panel suggested identifying the agent of choice to use for treatment and conducting cost-effectiveness analyses exploring different combinations of treatment.

DOAC vs VKA. SUMMARY OF THE EVIDENCE. We identified 12 systematic reviews addressing this question.[305,307,310,312,313,321-327] We considered only studies that provided results for patients with active cancer at enrollment. From these reviews, we identified 3 post hoc analyses of 3 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this question.[328-330] The 3 trials compared different DOACs (rivaroxaban, edoxaban, and apixaban) with LMWH followed by VKA. All 3 RCTs reported on mortality, recurrent VTE, and major bleeding. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/mNr37__9Hdl.

BENEFITS. Compared with VKAs, DOACs may reduce mortality, recurrent VTE, major bleeding, and quality-of-life impairment, and the panel judged the effects to be moderate (for mortality: RR, 0.92; 95% CI, 0.68-1.69; ARR, 24 fewer per 1000; 95% CI, 98 fewer to 211 more per 1000 using a baseline risk of 30.6%[316]; for recurrent VTE: RR, 0.56; 95% CI, 0.28-1.12; ARR, 44 fewer per 1000; 95% CI, 72 fewer to 12 more per 1000 using a baseline risk of 10.4%[316]; for major bleeding: RR, 0.68; 95% CI, 0.31-1.47; ARR, 8 fewer per 1000; 95% CI, 17 fewer to 11 more per 1000 using a baseline risk of 2.4%[316]; for quality-of-life impairment, patients showed better scores).[329]

HARMS AND BURDEN. Compared with VKA, DOACs had trivial undesirable effects other than in rare circumstances when plasma concentration of DOACs might be helpful but not readily available.

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low because of indirectness and imprecision of the estimates. We rated down for indirectness because higher-risk cancer patients were not included in the trials evaluating DOAC vs VKA. Therefore, we used the best baseline risk from previously reported studies. The time in the therapeutic range of VKAs in the control arms of these studies varied, providing additional uncertainty about the magnitude of the observed effects. We did not rate down for risk of bias because the results were consistent across individual trials with open-label and double-blinded design. We included subgroups of patients with cancer from the different studies. We did not consider this a potential risk for bias because these post hoc analyses included large samples of patients with cancer, and other patient characteristics were similar between the intervention and control arms.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel noted that the cost of DOACs varies between settings. VKA cost is similar across settings and is universally inexpensive, but resources for monitoring (laboratory costs or time to review results) will be different. The panel noted that these studies did not focus on patients with cancer and that costs will likely vary across different health care settings. The impact on equity will vary depending on access to DOACs and differences in out-of-pocket costs across settings.

Although DOACs are orally administered without routine monitoring and, therefore, are generally feasible, they are not appropriate for some clinical settings (severe renal dysfunction defined as creatinine clearance <30 mL/min, pregnancy, drug-drug interactions, upper GI resection) and may not be available in all clinical practice settings. Although DOACs and VKAs are reasonably easy to implement, DOACs are often preferred based on the ease of administration (no need for laboratory monitoring); therefore, they may be easier to implement in practice but probably are associated with higher costs.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for short-term treatment with DOAC over VKA for patients with active cancer and VTE to prevent VTE recurrence is due to a probably favorable balance between desirable and undesirable effects, in the context of low certainty in the evidence (serious imprecision and serious indirectness), variable resource use and cost-effectiveness, variable impact on equity, and an intervention that is probably acceptable and feasible.

The panel noted that, in this group of cancer patients, the overall mortality is very different from the LMWH data[305] and the Hokusai VTE cancer data.[330] These patients have about half of the mortality risk compared with those populations. These studies included earlier-stage cancer patients and a much healthier population with a lower risk of recurrent VTE or bleeding complication than the average cancer patient accounted in clinical practice.

Different DOACs have different drug-drug interactions.[331] Furthermore, the availability and costs of rapid-reversal agents differ for VKAs and DOACs. This might be an important consideration for patients with a high risk for bleeding.

The panel does not consider this question a research priority at this time.

DOAC vs LMWH. SUMMARY OF THE EVIDENCE. We identified 8 systematic reviews addressing this question.[305,307,310,312,313,321,326,334] We considered only studies that provided results for patients with active cancer at enrollment. From these reviews, we identified 4 eligible RCTs that fulfilled our inclusion criteria and measured outcomes relevant to this question.[300-302,333] All 4 RCTs reported on recurrent VTE and major bleeding.[300-302,333] The EtD framework is available at https://guidelines.ash.gradepro.org/profile/CNXrHZBGxHs.

BENEFITS. Compared with LMWH, DOACs (apixaban, edoxaban and rivaroxaban) may reduce recurrent VTE, recurrent DVT, and recurrent PE, and the panel judged the effects to be moderate (for recurrent VTE: RR, 0.62; 95% CI, 0.43-0.90; ARR, 32 fewer per 1000; 95% CI, 8-47 fewer per 1000; for recurrent DVT: RR, 0.62; 95% CI, 0.38-0.99; ARR, 15 fewer per 1000; 95% CI, 0-24 fewer

per 1000; for recurrent PE: RR, 0.71; 95% CI, 0.49-1.02; ARR, 13 fewer per 1000; 95% CI, 1-24 fewer per 1000).

HARMS AND BURDEN. Compared with LMWH, DOACs (apixaban, edoxaban, and rivaroxaban) may increase major bleeding, and the panel judged the effects to be small (for major bleeding: RR, 1.31; 95% CI, 0.83-2.02; ARI, 10 more per 1000; 95% CI, 6 fewer to 36 more per 1000). The risk of bleeding associated with DOACs appears to vary with cancer type and the type of DOAC; a threefold to fourfold higher risk is reported for patients with GI cancers.[336]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low because of risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. No study of resource utilization was available, and the panel noted that resource use varies, depending on the risk of major bleeding, settings, and populations. Only cost-effectiveness data from the general population were available. Equity might vary depending on access to the drug because DOACs might not be widely available. The interventions are probably acceptable and feasible to implement. Although DOACs are orally administered without routine monitoring and, therefore, are generally feasible, they are not appropriate for some clinical settings (severe renal dysfunction defined as creatinine clearance <30 mL/min, pregnancy and lactation, drug-drug interactions), and they may not be available in all clinical practice settings.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. For patients with active cancer and VTE, the ASH guideline panel suggests using DOACs (apixaban, edoxaban, and rivaroxaban) over LMWH for short-term treatment to prevent recurrent VTE. The conditional recommendation was a result of a probably favorable balance between desirable and undesirable effects, in the context of low certainty in the evidence and uncertainty in the relative cost-effectiveness.

Decisions about the type of anticoagulant should take into consideration drug-drug interactions because different DOACs have different drug-drug interactions. The choice of treatment must also be based on the specific clinical setting to minimize risks, patient preference to ensure adherence with recommended treatment, and the availability of treatment options, including cost considerations. The direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are the only DOACs that were evaluated for the short-term treatment of VTE in patients with cancer. There are no data for the direct thrombin inhibitor dabigatran for this indication. There are also potential concerns for higher bleeding rates in patients with GI cancers using a DOAC.[336] Therefore, DOACs should be used very carefully in this patient population.

Additional studies comparing different DOACs (specifically the direct thrombin inhibitor) with LMWH are warranted. Similarly, more studies with patients with severe thrombocytopenia, hematological malignancies, or unusual site thrombosis are needed.

Should short-term (first 3-6 months) treatment vs observation be used for patients with incidental (unsuspected) PE?

Should short-term (first 3-6 months) treatment vs observation be used for patients with SSPE?

Should short-term (first 3-6 months) treatment vs observation be used for patients with visceral/splanchnic vein thrombosis?

Recommendations 26, 27, and 28

For patients with cancer and incidental (unsuspected) PE or SSPE, the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

For patients with cancer and visceral/splanchnic vein thrombosis, the ASH guideline panel *suggests* treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Clinicians should use clinical judgment when considering anticoagulation for incidental PEs, SSPEs, or splanchnic vein thrombosis. Factors that should be considered include diagnostic certainty, chronicity (age of thrombus), extent of thrombosis, associated symptoms, and bleeding risks. Caution should be observed to ensure a favorable balance of benefits vs harms when anticoagulating patients with a higher bleeding risk. The choice of anticoagulant (eg, LMWH, VKA, or DOACs) should also depend on a patient's underlying risk for bleeding. If therapeutic anticoagulation is warranted, the ASH guideline panel recommends the use of the same anticoagulants recommended for cancer-associated thrombosis (see the questions associated with Recommendations 23, 24, and 25 [DOACs vs LMWH vs VKAs for short-term treatment]). If long-term anticoagulation is considered, please see long-term treatment recommendations.

Short-term (first 3-6 months) treatment vs observation for patients with cancer and incidental (unsuspected) PE. SUMMARY OF THE EVIDENCE. We did not identify any systematic review or RCT that addressed this question. A pooled analysis of individual patient data, including a total of 926 patients with cancer and incidental PE from 11 cohorts, was identified.[335] This study presented the effect of LMWH compared with observation on the weighted 6-month risks of mortality, recurrent VTE, and major bleeding. Our search also identified 2 additional cohorts that fulfilled the inclusion criteria.[303,336] One cohort study included 715 patients with active cancer diagnosed with incidental PE from the RIETE (Registro Informatizado de Enfermedad Trombo Embólica) registry, of which 98% were initially started on LMWH and 86% remained on LMWH for short-term treatment.[336] The other cohort study is an international prospective cohort of 695 patients with active cancer and a recent diagnosis of incidental PE, of which 97% received anticoagulant therapy.[303] Both cohort studies compared the effect of continuing anticoagulation (mean follow-up of 235 days[336] and median follow-up of 216 days[303]) vs discontinuing anticoagulation (mean follow-up of 117 days) on mortality, recurrent VTE, and major bleeding. These 2 cohorts provided the main source of data for this analysis. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/HK7prWM9WvI.

BENEFITS. Short-term treatment with anticoagulation compared with observation may reduce mortality, symptomatic PE, and symptomatic recurrent DVT, but the evidence is very uncertain, and the panel

judged these benefits to be large (for mortality: RR, 0.81; 95% CI, 0.67-0.98; ARR, 89 fewer per 1000; 95% CI, 9-155 fewer per 1000 using a baseline risk of 47%[335]; for symptomatic PE: RR, 0.36; 95% CI, 0.18-0.72; ARR, 77 fewer per 1000; 95% CI, 34-98 fewer per 1000 using a baseline risk of 12%[335]; for symptomatic recurrent DVT: RR, 0.19; 95% CI, 0.08-0.48; ARR, 97 fewer per 1000; 95% CI, 62-110 fewer per 1000 using a baseline risk of 12%).[335]

HARMS AND BURDEN. Compared with observation, short-term treatment may increase major bleeding, but the evidence is very uncertain, and the panel judged it to be large (for major bleeding: RR, 3.00; 95% CI, 1.21-7.47; ARI, 128 more per 1000; 95% CI, 13-414 more per 1000 using a baseline risk of 6.4%[335]).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low because of a risk of bias, inconsistency, and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel noted that costs may be moderate as a result of the cost associated with short-term treatment of all incidental PEs and the increase in major bleeding (despite the savings in events prevented). No cost-effectiveness information is available. The impact of health equity is likely to vary because some patients might not be able to afford the interventions if they have to pay for them (eg, in the United States). Short-term treatment was judged to be probably acceptable and feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for short-term treatment over observation for patients with cancer and incidental PE was due to a balance of effects that probably favors treatment in the context of very-low-certainty evidence and moderate costs. The panel noted that caution should also be observed to ensure a favorable balance of benefits vs harms when anticoagulating patients with a higher bleeding risk. The choice of anticoagulant (eg, LMWH, VKA, or DOACs) should also consider a patient's underlying risk for bleeding. Patient preference will be an important factor given the need for daily treatment and any potential need for interruption of cancer treatment.

The panel noted that because of the very low certainty about the evidence of effects, this question in the cancer patient population with incidental PEs should be a research priority.

Short-term (first 3-6 months) treatment vs observation for patients with cancer and SSPE. SUMMARY OF THE EVIDENCE. We did not identify any systematic reviews or RCTs that addressed this question. Our systematic search identified 9 observational studies that fulfilled, in part, the inclusion criteria.[303,337-344] The certainty in the evidence from these observational studies of patients with single or multiple SSPEs was judged to be very low and was considered unreliable. Thus, the panel relied on indirect evidence from other populations. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/uQTREWSCBho.

BENEFITS. The panel relied on indirect evidence from other populations because the quality of observational studies for patients with cancer with single or multiple SSPEs was judged to be very low and was considered unreliable. Overall, the results showed a reduction in risk of recurrent VTE. This indirect evidence suggests that patients with single or multiple SSPEs may benefit from anticoagulation therapy (rather than observation), especially if they are at moderate/high risk for recurrent VTE and have a lower risk for major bleeding.

HARMS AND BURDEN. The guideline panel considered that the risk of major bleeding was probably moderate considering that cancer patients with VTE treated with LMWH for up to 6 months showed a risk of 7.7%,[299] whereas a systematic review of cohort and RCTs in noncancer patients with PEs treated with anticoagulation therapy showed a risk for major bleeding of 1.8% (1.1-2.6%).[345]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low because of risk of bias, inconsistency, indirectness, and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. Despite the high uncertainty, the panel agreed that the desirable effects are likely to be larger than the undesirable; hence, the balance of effects probably favors short-term treatment vs observation. The panel was unable to judge the resources required because of the high uncertainty about the evidence of effects. No cost-effectiveness information was available. The impact of health equity is likely to vary, because some patients might not be able to afford the interventions if they have to pay for them (eg, in the United States). Treatment was judged to be probably acceptable and feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for short-term treatment over observation for patients with single or multiple SSPEs was due to a balance of effects that probably favors treatment in the context of very-low-certainty evidence and moderate costs. For patients with a single SSPE and no concomitant DVT, the possibility of a false-positive computed tomography scan should be considered along with the uncertain benefits of treatment and the increased risk of major bleeding.

Patient preferences will be an important factor, given the need for daily treatment and any potential need for interruption of cancer treatment. The panel noted that because of the very low certainty about the evidence of effects, this question should be a research priority in cancer patients with SSPEs.[346]

Short-term (first 3-6 months) treatment vs observation for patients with cancer and visceral/splanchnic vein thrombosis. SUMMARY OF THE EVIDENCE. We did not identify any systematic review or RCT that addressed this question. Our systematic search identified 5 observational studies that reported, in part, on anticoagulation in cancer patients with incidental and symptomatic visceral/splanchnic vein thrombosis.[347-351] Three of these studies did not provide sufficient data.[348,349,351] The other 2 articles are reports of the same study from the Registry on Splanchnic Vein Thrombosis.[347,350] The certainty in the evidence from this observational study of patients with visceral/splanchnic vein thrombosis was judged to be very low and was considered inadequate to determine the optimum approach to the management of these patients, particularly with regard to the need for therapeutic anticoagulation. Thus, to determine the potential benefits and harms of anticoagulation therapy in this patient population, the panel took into consideration 1 study that evaluated the safety of LMWH in cancer patients with VTEs[298] and a systematic review of patients with symptomatic VTEs who received anticoagulation therapy for ≥3 months.[345] It should be noted that neither of these studies examined patients with splanchnic vein thrombosis. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/OYY_yPXFMHE.

BENEFITS. The panel noted the high uncertainty in the available data about the magnitude of the benefits (refer to the above summary for more details).

HARMS AND BURDEN. The panel noted the high uncertainty in the available data about the magnitude of the harms. The guideline panel considered that the risk of major bleeding was 7.7% in cancer patients with acute VTEs treated with LMWH for 6 months.[298]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low because of indirectness and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. With the high uncertainty in the evidence, the panel agreed that the balance of desirable and undesirable effects is not known. The panel was unable to judge the resources required because of the high uncertainty about the evidence of effects. No cost-effectiveness information was available. The impact of health equity is likely to vary, because some patients might not be able to afford the interventions if they have to pay for them (eg, in the United States). Treatment in these patients was judged to be probably acceptable and feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. There is inadequate evidence available to determine the optimum management of visceral/splanchnic vein thrombosis in patients with cancer, particularly with regard to the need for therapeutic anticoagulation. The conditional recommendation for short-term treatment with anticoagulants or observation for patients with visceral/splanchnic vein thrombosis is due to the unknown balance of effects between treatment and observation in the context of very-low-certainty evidence of effects and about costs. However, clinicians should consider a number of factors in their treatment decision, including diagnostic certainty, chronicity, extent of thrombosis, associated symptoms, and bleeding risks. Patient preferences will be an important factor given the need for daily treatment and potential need for interruption of cancer treatment. More research is needed because no RCT and few cohort studies focus on anticoagulation in the setting of visceral/splanchnic vein thrombosis diagnosed incidentally in cancer patients.

Should keeping a CVC in place vs removing a CVC be used for patients with cancer and CVC-related VTEs on anticoagulant treatment?

Recommendation 29

For patients with cancer with CVC-related VTE receiving anticoagulant treatment, the ASH guideline panel *suggests* keeping the CVC over removing the CVC (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: If a VTE develops and the CVC is left in place, anticoagulation is required. The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of bleeding risk, drug-drug interactions, patient preference, and the availability of treatment options, including cost considerations. Patients with infected, mispositioned, or malfunctioning CVCs or those no longer requiring their CVC should have it removed. Similarly, patients who cannot receive anticoagulant treatment (eg, severe refractive thrombocytopenia, bleeding) may need CVC removal if not required for optimal care.

Keeping CVC vs removing CVC. SUMMARY OF THE EVIDENCE. No systematic review or RCT addressing this question was found. Our systematic search identified 2 case series that reported on removing the CVC as the outcome and not the intervention of interest to the guideline question.[352,353] One study followed 70 cancer patients with CVC-related symptomatic DVTs receiving DOACs for 12 weeks.[352] The second study followed 74 adults cancer patients with CVC-related symptomatic DVTs receiving LMWH or VKA for 12 weeks.[353] Both studies were considered case series (no direct control). The studies found that none of the patients had the CVC removed because of thrombosis. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/523QHQAYXeQ.

BENEFITS. The panel considered keeping the CVC to have a large benefit compared with removing it in patients who are receiving anticoagulation.

HARMS AND BURDEN. The panel considered the harms and burden to be small.

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low because of the risk of bias, indirectness, and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. Despite the high uncertainty in the evidence, the panel agreed that the desirable effects are likely to be larger than the undesirable effects; hence, the balance probably favors keeping the CVC. The panel believed that the intervention (keeping the catheter) will be associated with less resources than the comparator, because insertion of another CVC will likely be required in the setting of ongoing anticancer treatment (eg, chemotherapy or transfusion). The intervention probably has no impact on equity, is probably acceptable, and is feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. Despite the very low certainty in the evidence, the panel was reassured that there were low rates of recurrent VTEs that did not appear to be different from the baseline rates. The conditional recommendation for keeping a CVC over removing a CVC in patients with cancer and CVC-related VTEs receiving anticoagulation is due to a balance of effects that probably favors keeping it in the context of moderate cost savings and probably no impact on equity. Monitoring for resolution of symptoms and concomitant signs of infection is warranted.

Comparative observational or interventional studies are needed because of the very low certainty about the evidence of effects.

Should increasing the dose of LMWH to supratherapeutic levels vs continuing a standard therapeutic dose be used for patients with active cancer and recurrent VTEs, despite therapeutic anticoagulation treatment?

Recommendation 30

For patients with cancer and recurrent VTEs, despite receiving therapeutic LMWH, the ASH guideline panel *suggests* increasing the LMWH dose to supratherapeutic levels or continuing with a therapeutic dose (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Supratherapeutic dosing of LMWH should be considered carefully for patients with a high risk for bleeding.

Increasing dose to supratherapeutic levels vs continuing with standard therapeutic dose. SUMMARY OF THE EVIDENCE. We did not identify any systematic review or RCT that addressed this question. Our systematic search identified 3 observational studies that partially fulfilled the inclusion criteria.[354-356] The certainty in the evidence from these observational studies was judged to be very low and was considered unreliable. Thus, the panel relied on indirect evidence from studies of VKAs in other high-risk patient populations (antiphospholipid antibody syndrome[357] and mechanical valve disease).[358,359] The EtD framework is available online at https://guidelines.ash.gradepro.org/profile/qG3RaTEAXEQ.

BENEFITS. The panel considered that, from a biochemical perspective, it makes sense to provide a higher concentration of an anticoagulant for patients generating greater levels of thrombin or patients with heightened nonspecific binding of LMWH. However, the panel considered that the efficacy and safety of increasing the LMWH dose to supratherapeutic levels in cancer patients with recurrent VTEs, despite therapeutic LMWH, are unknown and that the evidence of the effect is very uncertain.

HARMS AND BURDEN. The panel considered that, given the lack of evidence, any effect is very uncertain.

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low owing to the risk of bias, indirectness, and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel was unable to judge the resources required because of the high uncertainty about the evidence of effects. No cost-effectiveness information was available. The intervention probably would have no impact on health equity. Treatment in these patients was judged to be probably acceptable and probably feasible to implement.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for optimizing the LMWH dose to supratherapeutic levels or continuing on a therapeutic dose for patients with cancer and recurrent VTEs receiving therapeutic LMWH is due to an unclear balance between desirable and undesirable effects. Supratherapeutic dosing of LMWH may pose an unacceptable risk for patients with a high risk for bleeding. Comparative observational or interventional studies are needed because of the very low certainty about the evidence of effects. Only a few cohort studies focusing on recurrent VTEs during LMWH are available, whereas no study has assessed the management of recurrent VTEs despite DOACs.

Should an IVC filter be used or not in patients with cancer with recurrent VTEs, despite anticoagulation treatment?

Recommendation 31

For patients with cancer and recurrent VTEs, despite anticoagulation treatment, the ASH guideline panel *suggests* not using an IVC filter over using a filter (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: An IVC filter may be required if there is a contraindication to anticoagulation therapy (active bleeding or urgent surgery required). If an IVC filter is required, a retrievable filter is preferred, and it should be removed once anticoagulation can be safely resumed.

Adding an IVC filter vs not in patients with cancer and recurrent VTEs, despite anticoagulation treatment. SUMMARY OF THE EVIDENCE. We did not identify any systematic review or RCT that addressed this question. Our systematic search identified 1 observational study that fulfilled, in part, the inclusion criteria.[364] This international registry within the International Society on Thrombosis and Haemostasis explored how the different antithrombotic regimens were used to manage patients with cancer and recurrent VTEs, despite anticoagulation treatment. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/JCgX8Z1ru8g.

BENEFITS. Adding an IVC filter vs not in patients with cancer and recurrent VTEs, despite anticoagulation, did not show any apparent benefits (recurrent PE), but the evidence is very uncertain. The panel judged this potential desirable effect to be trivial.

HARMS AND BURDEN. Adding an IVC filter vs not in patients with cancer and recurrent VTEs, despite anticoagulation, may increase the risk of mortality, second recurrent VTE, and major bleeding; the panel judged these effects to be large. However, the evidence is very uncertain (for mortality: RR, 1.36, 95% CI, 0.69-2.68; ARI, 132 more per 1000; 95% CI, 114 fewer to 618 more per 1000; for second recurrent VTE: RR, 5.80, 95% CI, 1.96-17.13; ARI, 331 more per 1000; 95% CI, 66-1000 more per 1000; for major bleeding: RR, 2.90; 95% CI, 0.94-8.99; ARI, 197 more per 1000; 95% CI, 6 fewer to 827 more per 1000).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects based on observational studies was judged as very low because of the risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. The panel judged the resources required as moderate, despite the lack of studies, and judged that the cost-effectiveness probably favors not inserting an IVC filter in this population. The intervention probably would have no impact on health equity. Treatment in these patients was judged to be probably acceptable, although the feasibility may vary because IVC filters may not be accessible or possible in all centers.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation against adding an IVC filter in patients with cancer and recurrent VTEs, despite anticoagulant treatment, is due to a balance of effects that probably favors not adding an IVC filter in the context of very low certainty about the effects, as well as the fact that cost-effectiveness probably favors not adding an IVC filter. Comparative observational or interventional studies are needed because of the very low certainty about the evidence of effects.

Long-term treatment (>6 months) for patients with active cancer and VTE

Should long-term (>6 months) anticoagulation vs short-term (3-6 months) anticoagulation be used for secondary prophylaxis for patients with active cancer and VTEs?

Should indefinite anticoagulation be continued vs stopped after completion of a definitive period of anticoagulation?

Should DOACs vs LMWH be used for long-term (>6 months) anticoagulation for patients with active cancer and VTEs?

Recommendations 32, 33, and 34

For patients with active cancer and VTEs, the ASH guideline panel *suggests* long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

For patients with active cancer and VTEs receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel *suggests* continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

For patients with active cancer and VTEs requiring long-term anticoagulation (>6 months), the ASH guideline panel *suggests* using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Remarks: Long-term anticoagulation for secondary VTE prophylaxis should be considered for patients with active cancer. In the absence of contraindications to anticoagulation, such as major bleeding, the panel concluded that the benefits of long-term anticoagulation outweigh the harms.

Long-term anticoagulation can be discontinued when patients are no longer at high risk for recurrent VTEs or if patients are entering the last weeks of life. The decision to use long-term anticoagulation will depend on the type and stage of cancer (eg, metastatic or not), overall prognosis, periodic reevaluations of the risk of recurrent VTE and bleeding, comorbidities, costs and patients' preferences. The choice of anticoagulant must also be based on the specific clinical setting to minimize risk, after careful consideration of bleeding risk, drug-drug interactions, patient preference, and the availability of treatment options, including cost considerations.

Long-term anticoagulation (>6 months) vs short-term anticoagulation (3-6 months). SUMMARY OF THE EVIDENCE. We did not find any systematic review addressing this question. Two single-arm cohort studies assessing the safety and efficacy of LMWH for long-term use (up to 12 months) were identified.[299,360] One trial included a second randomization, after the initial 6 months of anticoagulation treatment, of patients with cancer with PEs or residual venous obstruction to receive long-term DOACs or observation (≤12 months).[361] However, because of the lack of direct evidence for comparisons for the cohort studies and the very small sample size (N = 92) and number of events in this trial, the guideline panel decided to include evidence from 10 trials conducted in the general population from the "American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism."[403] Nineteen systematic reviews[362-380] and 13 RCTs[381-393] (N = 8593) were identified to inform this recommendation. Trials included adults with objectively confirmed DVTs or PEs who had been treated with DOACs, LMWH, VKAs, or ASA for ≥3 months without subsequent recurrence. The panel decided not to include ASA as an intervention of interest, and 1 RCT was excluded.[393] Patients who received short-term anticoagulation were randomized to receive placebo or continue long-term treatment for ≥6 months. The mean follow-up time ranged from 24 to 28 months for different outcomes. The outcomes were measured in both groups until the end of the extended-duration treatment. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/mtyOjXF7LTk.

BENEFITS. Long-term anticoagulation (>6 months) had no impact on mortality and may decrease recurrent VTEs, PEs, and all DVTs. The panel judged the effect to be moderate (for mortality: RR, 1.38; 95% CI, 0.85-2.23; ARI, 9 more per 1000; 95% CI, 4 fewer to 30 more per 1000; for recurrent VTE: RR, 0.54; 95% CI, 0.23-1.27; ARR, 51 fewer per 1000; 95% CI, 85 fewer to 30 more per 1000 using a baseline risk of 11.1%[299]; for PE: RR, 0.66; 95% CI, 0.29-1.51; ARR, 38 fewer per 1000; 95% CI, 79 fewer to 57 more per 1000 using a baseline risk of 11.1%[299]; for all DVTs: RR, 0.50; 95% CI, 0.27-0.95; ARR, 56 fewer per 1000; 95% CI, 6-81 fewer per 1000 using a baseline risk of 11.1%).[299] In 1 trial that directly compared long-term vs short-term anticoagulation for secondary prophylaxis specifically for patients with cancer and PEs or residual vein obstruction (up to 12 months), long-term anticoagulation for secondary prophylaxis was associated with a lower rate of recurrent VTEs (hazard ratio [HR]: 0.32; 95% CI, 0.06-1.58), without an increased rate of major bleeding complications (no event occurring in either group: DOACs, n = 46 and no treatment n = 46).[361]

HARMS AND BURDEN. Long-term anticoagulation may increase major bleeding (for major bleeding: RR, 1.25; 95% CI, 0.68-2.30; ARI, 26 more per 1000; 95% CI, 33 fewer to 133 more per 1000 using a baseline risk of 10.2%).[299]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low because of indirectness and imprecision of the estimates. The certainty in the evidence for the only available trial was judged as low because of serious imprecision and indirectness.

OTHER ETD CRITERIA AND CONSIDERATIONS. There was only 1 trial directly comparing long-term vs short-term anticoagulation for secondary prophylaxis specifically for patients with cancer and PEs or residual vein obstruction.[361] Because of its very low certainty, the panel relied on additional indirect evidence from trials conducted with patients without cancer. Therefore, there is uncertainty related to the balance of benefits and harms in continuing anticoagulation beyond 6 months in this setting.

The panel assumed that the costs were moderate and that the cost-effectiveness would vary. Although the panel assumed that the impact on health equity would vary, the use of long-term anticoagulation was considered acceptable and feasible.

It is important that clinicians use their best judgment based on experience and their knowledge of the patient's specific clinical situation (eg, cancer, treatment, comorbidities) and consider the patient's values and preferences. Routine and regular assessment of the likely benefits and harms of continued anticoagulation are essential because the disease status and patient preferences may change over time. At all times, the added risk for recurrent VTE, as

well as bleeding associated with active cancer and cancer therapies, should be considered when evaluating the balance of benefits and harms associated with continued anticoagulation. This is particularly pertinent to patients in the last weeks of life. One observational study followed 214 cancer patients receiving treatment for VTEs.[394] The majority remained anticoagulated up to the point of death, and this was associated with a clinically relevant bleeding rate of 7% in the last week of life.[394] A larger observational study of 1079 cancer patients, 95% with a Karnofsky score <50, admitted to specialist palliative care units reported a clinically relevant bleeding rate of 9.8% (95% CI, 8.3-11.6).[99] Bleeding was strongly associated with anticoagulant and platelet transfusion (HR, 1.48; 95% CI, 1.02-2.15 and HR, 1.67; 95% CI, 1.15-2.44), respectively. These data would support stopping anticoagulants and antithrombotics as death approaches.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel determined that there is low certainty in the evidence for a net health benefit from using long-term anticoagulation for secondary prophylaxis over short-term anticoagulation for patients with active cancer at high risk for recurrent VTEs. Despite the moderate costs, the panel made a conditional recommendation in favor of long-term anticoagulation over short-term anticoagulation in this patient population.

The panel believed that secondary prophylaxis should be considered in cancer patients at high risk for recurrent VTEs, including those receiving palliative-intent anticancer treatment, those in whom treatment has not been curative (eg, recurrent or progressive disease), and those in whom anticancer treatment is ongoing.[395] In the absence of a contraindication to anticoagulation because of major bleeding, the panel has concluded that the benefits of continued anticoagulation outweigh the harms. Decisions for patients with cancer to continue long-term anticoagulation should weigh the benefits and harms and integrate the person's values and preferences for the important outcomes and alternative management strategies.

The panel identified this as an important knowledge gap for which additional data are needed.

Continuing indefinite anticoagulation vs stopping after completion of a definitive period of anticoagulation. SUMMARY OF THE EVIDENCE. We did not find any systematic review or trial addressing this question. Two prospective single-arm cohort studies assessing the safety and efficacy of LMWH for long-term use (≤12 months) were identified.[299,360] However, because of the lack of direct evidence for comparisons, the guideline panel decided to include evidence from 8 trials conducted in the general population from the "American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism."[403] Nineteen systematic reviews[362-380] and 13 RCTs[381-393] (N = 8593) were identified to inform this recommendation. Trials included adults with objectively confirmed DVTs or PEs who had been treated with DOACs, LMWH, VKAs or ASA for ≥3 months without subsequent recurrence. The panel decided not to include ASA as an intervention of interest, and 1 RCT was excluded.[393] Patients who received short-term anticoagulation were randomized to receive placebo or to continue long-term treatment of ≥6 months. The mean follow-up time ranged from 24 to 28 months for different outcomes. The outcomes were measured in both groups until the end of the extended-duration treatment. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/Av-arKu5_7w.

BENEFITS. An indefinite duration of anticoagulation for secondary prophylaxis compared with stopping after a definitive period of anticoagulation had no impact on mortality and may reduce recurrent VTEs, PEs, and all DVTs. The panel judged the effect to be moderate (for mortality: RR, 0.70; 95% CI, 0.45-1.09; ARR, 5 fewer per 1000; 95% CI, 8 fewer to 1 more per 1000; for recurrent VTE: RR, 0.20; 95% CI, 0.11-0.38; ARR, 89 fewer per 1000; 95% CI, 69-99 fewer per 1000 using a baseline risk of 11.1%[299]; for PE: RR, 0.23; 95% CI, 0.12-0.44; ARR, 85 fewer per 1000; 95% CI, 62-98 fewer per 1000 using a baseline risk of 11.1%[299]; for all DVTs: RR, 0.16; 95% CI, 0.11-0.22; ARR, 93 fewer per 1000; 95% CI, 87-99 fewer per 1000 using a baseline risk of 11.1%).[299]

HARMS AND BURDEN. An indefinite duration of anticoagulation for secondary prophylaxis compared with stopping after a definitive period of anticoagulation increased the risk of major bleeding. The panel judged the effect to be small (for major bleeding: RR, 2.21; 95% CI, 1.42-3.44; ARI, 123 more per 1000; 95% CI, 43-249 more per 1000 with a baseline risk of 10.2%).[299]

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as low owing to very serious indirectness of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. No direct data for cost-effectiveness of indefinite duration over limited duration of anticoagulation were available. Three reports from the general population concluded that long-term anticoagulation strategies are likely to be cost-effective. However, the panel judged cost-effectiveness to be variable. Equity and acceptability were also judged to be variable. An indefinite strategy was judged to be probably feasible.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The panel determined that there is low certainty in the evidence for a net health benefit from using an indefinite duration of anticoagulation for secondary prophylaxis over a defined duration for patients with active cancer and VTEs. Instead of a defined treatment duration, the panel believed that long-term anticoagulation for secondary prophylaxis can be discontinued when patients are no longer at high risk for recurrent VTEs. The decision on indefinite anticoagulation will be dependent on the type of cancer, prognosis, and periodic reevaluation of the risk of thrombosis and bleeding, comorbidities, cancer status, costs, and patient preferences and values.

The panel identified this as an important knowledge gap, and additional studies are needed.

DOACs vs LMWH for long-term anticoagulation. SUMMARY OF THE EVIDENCE. We identified 4 systematic reviews addressing, in part, this question.[307,312,313,332] We considered only studies that provided results for patients with active cancer at enrollment. From these reviews, we identified 1 eligible RCT that fulfilled our inclusion criteria and measured outcomes relevant to this question.[396] Assessed outcomes were recurrent VTEs, major bleeding, and mortality. The EtD framework is available at https://guidelines.ash.gradepro.org/profile/kP1qhVfvjlw.

BENEFITS. In the setting of long-term anticoagulation for secondary prophylaxis, compared with LMWHs, DOACs may reduce recurrent VTEs, recurrent PEs, and recurrent DVTs, but the evidence is very uncertain. The panel judged the effect to be moderate (for recurrent VTEs beyond 6 months: RR, 0.69; 95% CI, 0.47-1.01; ARR, 34 fewer per 1000; 95% CI, 59 fewer to 1 more per 1000 using a baseline risk of 11.1%[299]; for recurrent DVTs beyond 6 months: RR, 0.54; 95% CI, 0.31-0.93; ARR, 51 fewer per 1000; 95% CI, 8-77 fewer per 1000 using a baseline risk of 11.1%[299]; for recurrent PEs beyond 6 months: RR, 0.96; 95% CI, 0.57-1.61; ARR, 4 fewer per 1000; 95% CI, 48 fewer to 68 more per 1000 using a baseline risk of 11.1%).[299]

HARMS AND BURDEN. In the setting of long-term anticoagulation for secondary prophylaxis, compared with LMWHs, DOACs may increase the risk of mortality and major bleeding, but the evidence is very uncertain. The panel judged this effect to be small (for mortality beyond 6 months: RR, 1.07; 95% CI, 0.92-1.25; ARI, 24 more per 1000; 95% CI, 28 fewer to 87 more per 1000 using a baseline risk of 34.7%[299]; for major bleeding beyond 6 months: RR, 1.71; 95% CI, 1.01 to 2.88; ARI, 72 more per 1000; 95% CI, 1-192 more per 1000 using a baseline risk of 10.2%).

CERTAINTY IN THE EVIDENCE OF EFFECTS. The certainty in these estimated effects was judged as very low because of the risk of bias and imprecision of the estimates.

OTHER ETD CRITERIA AND CONSIDERATIONS. No study about resource utilization was identified, and the panel noted that resource use varies, depending on the risk of recurrent VTEs and other complications, such as major bleeding, settings, and populations, which will also vary over time. Only cost-effectiveness data from the general population were available. Equity might vary depending on the access to drugs, such as DOACs or LMWHs, which might not be widely available. The interventions are probably acceptable and feasible to implement. Although DOACs are administered orally without routine monitoring and, therefore, are generally feasible, they are not appropriate for some clinical settings (severe renal dysfunction defined as creatinine clearance $<$30 mL/min, pregnancy, drug-drug interactions), and they may not be available in all clinical practice settings. For some patients, drug interactions could also be a concern.

CONCLUSIONS AND RESEARCH NEEDS FOR THESE RECOMMENDATIONS. The conditional recommendation for continuing indefinite anticoagulation using DOACs or LMWH was a result of the overall balance of efficacy and safety that does not favor the intervention or the comparison, in the context of low certainty in the evidence and uncertainty in the relative cost-effectiveness. The choice of treatment must be based on the specific clinical setting (to minimize risk), patient preference, and the availability of treatment options, including cost considerations.

Although there is a critical need for further studies to confirm the benefits of long-term anticoagulation for secondary prevention for patients with active cancer, the panel recognizes the challenges in conducting such studies because of limitations of enrollment.

What others are saying and what is new in these ASH guidelines?

There are 3 other recent guidelines available on the prevention and treatment of VTEs in patients with cancer: the 2019 American Society of Clinical Oncology (ASCO) guidelines,[397] the 2019 International Initiation on Thrombosis and Cancer (ITAC) guidelines,[398] and the 2020 National Comprehensive Cancer Network guidelines.[399] Two major differences between the ASH guidelines and the others is the consistent use of systematic reviews and EtDs, which increases transparency and trustworthiness, as well as the use of marker states to estimate the relative importance of key outcomes of treatment to patients.

All guidelines recommend assessing the risk of VTE and bleeding in hospitalized medical and surgical patients with cancer. For patients with a high risk for thrombosis and a low risk for bleeding, routine pharmacological thromboprophylaxis is recommended. However, recommendations around the timing of initiation of pharmacological thromboprophylaxis among patients undergoing cancer-related major abdominal surgery differ, which highlights the lack of data in that setting and the requirements for additional studies. For patients undergoing major cancer surgery, the ASCO guidelines advise starting thromboprophylaxis preoperatively. ITAC also suggests initiation 2 to 12 hours preoperatively, whereas the ASH guidelines recommend initiating thromboprophylaxis postoperatively, given the limited advantages to initiating thromboprophylaxis preoperatively, in addition to the potential bleeding and logistical considerations associated with neuraxial anesthesia. Similarly, the 3 other clinical practice guidelines acknowledge the importance of stratifying ambulatory cancer patients beginning chemotherapy according to their underlying risk of VTE. The ASH guideline suggests stratifying patients into groups who are at low, intermediate, or high risk for VTEs, and it provides recommendations on the use of pharmacological thromboprophylaxis in these different subgroups. The DOACs are also now considered pharmacological options for ambulatory cancer patients at intermediate to high risk for VTEs. DOACs (apixaban and rivaroxaban) are considered safe and effective options for the treatment of cancer-associated thrombosis. All clinical practice guidelines have assessed and incorporated new data comparing LMWH with DOACs for this indication.

The ASCO guidelines divide the treatment course into initial anticoagulation and long-term ($\geq$6 months) anticoagulation. LMWH, UFH, fondaparinux, or rivaroxaban is suggested for the initial treatment of VTEs in patients with cancer. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for $\geq$6 months is preferred because of improved efficacy over VKAs. The ITAC guideline also suggests using LMWH, UFH, DOACs, or fondaparinux during the treatment initiation and LMWH or DOACs during early maintenance treatment (initial 6 months). Given the complexity of anticoagulation management in cancer patients with VTEs, the ASH guidelines divided the treatment course into initial treatment (within the first week), short-term anticoagulation (initial 3-6 months), and long-term anticoagulation ($>$6 months). The ASH guidelines suggest LMWH or DOACs (rivaroxaban or apixaban) for initial treatment; if a DOAC is not chosen, the ASH guidelines recommend LMWH over UFH or fondaparinux. For the short-term treatment of VTEs (3-6 months), DOACs (apixaban, edoxaban, and rivaroxaban) are suggested over LMWH. VKAs are not recommended; the same regimen is recommended for long-term anticoagulation ($>$6 months). All guidelines recommend caution in using DOACs in patients with GI cancers because of the higher reported risk of bleeding complications. Finally, the ASH guidelines consider other important issues related to the management of cancer-associated

thrombosis, including splanchnic vein thrombosis, incidental PEs, and SSPEs.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence that we identified for many of the questions.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[400] The Agency for Healthcare Research and Quality in the United States provides a guide for implementing effective quality improvement in this patient population.[401]

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Authorship

Contribution: P.A.-C. and L.A.K. wrote the first draft of this manuscript and EtD frameworks based on input from all panel members; P.A-C., L.A.K., M.C., and G.H.L. revised the manuscript following additional comments from panel members; all guideline panel members contributed to the manuscript writing, critically reviewed the manuscript, and provided suggestions for improvement; P.A.-C. and L.A.K. addressed the comments of the panel members and public comments; and all authors approved the content. Members of the knowledge synthesis team (Elie Akl, Victor Yosuico, Charbel Matar, Francesca Sperati, Irene Terrenato, Maddalena Barba, Ibrahim Tsolakian, Maram Hakoum, and Holger Schünemann) contributed evidence summaries to the guidelines. G.H.L. and P.A.-C. were the chair and vice chair of the panel. M.C. was appointed as clinical co-chair in October of 2018.

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