CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

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Background: Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries. Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians and others in decisions about the prevention and management of pregnancy-associated VTE.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations.

Results: The panel agreed on 31 recommendations related to the treatment of VTE and superficial vein thrombosis, diagnosis of VTE, and thrombosis prophylaxis.

Conclusions: There was a strong recommendation for low-molecular-weight heparin (LWMH) over unfractionated heparin for acute VTE. Most recommendations were conditional, including those for either twice-per-day or once-per-day LMWH dosing for the treatment of acute VTE and initial outpatient therapy over hospital admission with low-risk acute VTE, as well as against routine anti-factor Xa (FXa) monitoring to guide dosing with LMWH for VTE treatment. There was a strong recommendation (low certainty in evidence) for antepartum anticoagulant prophylaxis with a history of unprovoked or hormonally associated VTE and a conditional recommendation against antepartum anticoagulant prophylaxis with prior VTE associated with a resolved nonhormonal provoking risk factor.

Summary of recommendations

Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries.[1,2] Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.[3-6] The diagnosis, prevention, and treatment of pregnancy-associated VTE are particularly difficult because of the need to consider fetal as well as maternal well-being. These guidelines address these challenging issues.

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Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page hematology.org/vte.

The full-text version of this article contains a data supplement.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[7-10] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.[11,12]

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either 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 recommendation.

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 individuals risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with his or her 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: policy making 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 identify possible research gaps.

Recommendations

Treatment of acute VTE and superficial vein thrombosis

Recommendations 1 and 2. For pregnant women with acute VTE, the American Society of Hematology (ASH) guideline panel *recommends* antithrombotic therapy compared with no antithrombotic therapy (strong recommendation, high certainty in evidence about effects ⊕⊕⊕⊕). For pregnant women with acute VTE, the ASH guideline panel *recommends* low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) (strong recommendation, moderate certainty in evidence about effects ⊕⊕⊕◯).

Recommendation 3. For pregnant women with proven acute superficial vein thrombosis, the ASH guideline panel *suggests* using LMWH over not using any anticoagulant (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 4. For pregnant women with acute VTE treated with LMWH, the ASH guideline panel *suggests* either once-per-day or twice-per-day dosing regimens (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 5. For pregnant women receiving therapeutic-dose LMWH for the treatment of VTE, the ASH guideline panel *suggests against* routine monitoring of anti-FXa levels to guide dosing (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 6. For pregnant women with acute lower-extremity deep vein thrombosis (DVT), the ASH guideline panel *suggests against* the addition of catheter-directed thrombolysis therapy to anticoagulation (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendations 7 and 8. For pregnant women with acute pulmonary embolism and right ventricular dysfunction in the absence of hemodynamic instability, the ASH guideline panel *suggests against* the addition of systemic thrombolytic therapy to anticoagulation compared with anticoagulation alone (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯). For pregnant women with acute pulmonary embolism and life-threatening hemodynamic instability, the ASH guideline panel *suggests* administering systemic thrombolytic therapy in addition to anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 9. For pregnant women with low-risk acute VTE, the ASH guideline panel *suggests* initial outpatient therapy over hospital admission (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Management of anticoagulants around the time of delivery

Recommendation 10. For pregnant women receiving therapeutic-dose LMWH for the management of VTE, the ASH guideline panel *suggests* scheduled delivery with prior discontinuation of anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 11. For pregnant women receiving prophylactic-dose LMWH, the ASH guideline panel *suggests against* scheduled delivery with discontinuation of prophylactic anticoagulation compared

with allowing spontaneous labor (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Anticoagulant use in breastfeeding women

Recommendations 12 and 13. For breastfeeding women who have an indication for anticoagulation, the ASH guideline panel *recommends* using UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯). For breastfeeding women who have an indication for anticoagulation, the ASH guideline panel *recommends against* using direct-acting oral anticoagulants (strong recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Prevention of VTE

Recommendations 14 and 15. For unselected women undergoing assisted reproductive therapy, the ASH guideline panel *suggests against* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯). For women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome, the ASH guideline panel *suggests* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendations 16 and 17. For women not already receiving long-term anticoagulant therapy who have a history of VTE that was unprovoked or associated with a hormonal risk factor, the ASH guideline panel *recommends* antepartum anticoagulant prophylaxis over no anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯). For women not already receiving long-term anticoagulant therapy who have a history of prior VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors, the ASH guideline panel *suggests against* antepartum anticoagulant prophylaxis (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 18. For women not already receiving long-term anticoagulant therapy who have a history of VTE, the ASH guideline panel *recommends* postpartum anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendations 19, 20, and 21. For women who are heterozygous for the factor V Leiden or prothrombin mutation and in those who have protein C or S deficiency, regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women who have no family history of VTE but have antithrombin deficiency or are homozygous for the prothrombin gene mutation, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women with antithrombin deficiency who have a family history of VTE and for those who are homozygous for the factor V Leiden mutation or who have combined thrombophilias, regardless of family history of VTE, the ASH guideline panel *suggests* antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 22, 23, 24, 25, and 26. For women without a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women with a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation, the ASH guideline panel *suggests against* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women with a family history of VTE who have antithrombin deficiency, the ASH guideline panel *recommends* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (strong recommendation, moderate certainty in evidence about effects ⊕⊕⊕◯). For women with a family history of VTE who have protein C or protein S deficiency, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women with combined thrombophilias or who are homozygous for the factor V Leiden mutation or prothrombin gene mutation, regardless of family history, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 27. For women with no or 1 clinical risk factor (excluding a known thrombophilia or history of VTE), the ASH guideline panel *suggests against* antepartum or postpartum prophylaxis (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 28 and 29. For pregnant women who require prophylaxis, the ASH guideline panel *suggests against* intermediate-dose LMWH prophylaxis compared with standard-dose LMWH prophylaxis during the antepartum period (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯). For women who require prophylaxis, the ASH guideline panel *suggests* either standard- or intermediate-dose LMWH prophylaxis during the postpartum period (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Diagnosis of VTE

Recommendation 30. For pregnant women with suspected pulmonary embolism, the ASH guideline panel *suggests* ventilation-perfusion (V/Q) lung scanning over computed tomography (CT) pulmonary angiography (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 31. For pregnant women with suspected DVT, the ASH guideline panel *suggests* additional investigations, including serial compression ultrasound or magnetic resonance venography compared with no further investigations after an initial negative ultrasound with imaging of the iliac veins (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Values and preferences

Values and preferences for this guideline were considered from the patient's perspective, with input from all panel members, including patient representatives. The recommendations placed a higher value on avoiding maternal death, VTE, and bleeding as well as on

avoiding fetal complications, including loss and teratogenicity. Equal weight was placed on maternal and fetal well-being.

Explanations and other considerations

Panel members were anonymously polled to select a risk threshold for recommending antepartum and postpartum LMWH prophylaxis. For antepartum prophylaxis, responses ranged from 1% to 4%; however, the majority of respondents selected a 2% VTE risk threshold. For postpartum prophylaxis, responses ranged from 1% to 3%, and the majority selected a 1% VTE risk threshold. These recommendations take into consideration cost and cost-effectiveness, impact on equity, acceptability, and feasibility.

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about diagnosis, prevention, and treatment of VTE in the context of pregnancy**.** The target audience includes patients, hematologists, obstetricians, maternal-fetal medicine specialists, general practitioners, internists, other clinicians, and decision makers. Policy makers who may be interested in these guidelines include those involved in developing local, national, or international programs aiming to reduce the incidence of VTE or to evaluate direct and indirect harms and costs related to VTE. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

VTE complicates ~1.2 of every 1000 deliveries.[1,2] The risk of VTE is spread across all 3 trimesters, although the risk seems highest in the third trimester.[1] A pooled analysis suggests that the absolute incidence of VTE is equal during the antepartum and postpartum periods, at 0.6 per 1000 pregnant women.[1] However, because the postpartum period is much shorter than the antepartum period, the daily risk of VTE is higher postpartum than antepartum.[13] Although an increased risk of VTE may persist for 12 weeks postpartum,[14] women are much more likely to develop DVT or pulmonary embolism during the first 6 weeks after delivery than during the next 6 weeks.[1,14]

Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.[3] Women who develop pregnancy-associated DVT are at substantial risk of postthrombotic syndrome,[1,4-6] which is associated with reduced quality of life.[1]

In addition to the above concerns, the diagnosis, prevention, and treatment of pregnancy-associated VTE are particularly challenging because of the need to consider fetal as well as maternal well-being.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[7-12,15-20] 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 Guideline International Network-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[7-10] An article detailing the methods used to develop these guidelines is forthcoming.

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with that of 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). 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 Schünemann). ASH vetted individuals and appointed them to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process, including the use of the GRADE approach. The membership of the panel and the GRADE Centre team is described in supplement 1.

The panel included hematologists, obstetricians, a specialist in maternal-fetal medicine, internists, a pharmacist with clinical and research expertise on the guideline topic, methodologists with expertise in evidence appraisal and guideline development, and 2 patient representatives. The panel chair was an ASH member and content expert. The vice chair was a critical care physician and internist with experience in guideline development methodology.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was accomplished by using Web-based tools (www.surveymonkey.com and www.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 2 patient representatives received honorariums of $200 each. The panelists received no other payments. Through the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or grant support. 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 Institute of Medicine[21] and the Guidelines International Network.[9] At the time of appointment, a majority of the guideline panel, including the chair

Table 1. Questions included in these guidelines

1. Should antithrombotic therapy (UFH or LMWH) vs no antithrombotics be used for pregnant women with acute VTE?
2. Should anticoagulant intervention vs no anticoagulant intervention be used for pregnant women with proven superficial vein thrombosis?
3. Should LMWH twice per day vs LMWH once per day be used for pregnant women with acute VTE?
4. Should routine anti-FXa monitoring to guide dose adjustment vs no monitoring be used in pregnant women receiving therapeutic-dose LMWH for the treatment of VTE?
5. Should catheter-directed thrombolytic therapy vs no catheter-directed thrombolytic therapy be used in addition to anticoagulant therapy in pregnant women with acute lower-extremity DVT?
6. Should thrombolytic therapy vs no thrombolytic therapy be used in addition to anticoagulant therapy in pregnant women with acute hemodynamically significant pulmonary embolism or pulmonary embolism with significant right ventricular dysfunction?
7. Should outpatient therapy vs hospital admission be used in the initial treatment of pregnant patients with low-risk acute VTE?
8. Should scheduled delivery with discontinuation of LMWH vs cessation of LMWH with spontaneous onset of labor be used for pregnant women receiving therapeutic-dose LMWH?
9. Should scheduled delivery with prior discontinuation of prophylactic-dose LMWH vs cessation of prophylactic LMWH at the onset of spontaneous labor be used for pregnant women receiving prophylactic-dose LMWH?
10. Should one particular anticoagulant vs any other anticoagulant be used for breastfeeding women who have an indication for anticoagulation?
11. Should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used for prevention of VTE in women undergoing assisted reproduction?
12. Should antepartum anticoagulant prophylaxis vs no antepartum anticoagulant prophylaxis be used for pregnant women with prior VTE?
13. Should postpartum anticoagulant prophylaxis vs no postpartum anticoagulant prophylaxis be used for pregnant women with prior VTE?
14. Should antepartum anticoagulant prophylaxis vs no antepartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?
15. Should postpartum anticoagulant prophylaxis vs no postpartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?
16. Should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used for pregnant women with clinical risk factors for VTE?
17. Should intermediate-dose LMWH prophylaxis vs standard-dose LMWH prophylaxis be used for preventing first or recurrent VTE in pregnant women?
18. Should V/Q scanning vs other diagnostic tools be used for diagnosis of pulmonary embolism in pregnant women with suspected pulmonary embolism?
19. Should no further investigations vs additional investigations (serial compression or duplex ultrasound, magnetic resonance imaging, or venography) be used for diagnosis of DVT in pregnant women with suspected DVT and initial negative compression or duplex ultrasound with imaging of the iliac veins?

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, but the balance of the majority was maintained.

Before appointment to the panel, individuals disclosed both 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-interest forms for all panel members. In part A of the forms, individuals disclosed material interests for 2 years before being appointed. In part B, they disclosed interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after being appointed.

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.[9,22-24] The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

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 for researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradepro.org)[25] and SurveyMonkey (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.[26] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach.[26] During this rating process, the panel used definitions of the outcomes (marker states) that were developed for these guidelines. Outcomes were rated to help focus attention on those considered most important and to help resolve or clarify potential disagreements. The highly rated outcomes and those identified as important based on the literature reviews were further refined. The panel rated the following outcomes as critical for decision making across questions: mortality, pulmonary embolism, proximal deep venous thrombosis, major bleeding, and neonatal bleeding. For questions related to treatment and prevention of VTE, heparin-induced thrombocytopenia, chronic thromboembolic pulmonary hypertension, postthrombotic syndrome, pregnancy loss, and congenital malformation were also included. Maternal plasma anticoagulant drug level and burden of therapy were included for questions about once-per-day vs twice-per-day LMWH dosing and the role of anti-FXa LMWH-level monitoring. For questions about the diagnosis of DVT or pulmonary embolism, the panel considered the frequency of false-negative results, the frequency of inconclusive results, fetal and maternal radiation exposure, and adverse maternal experiences related to the test technique to be

critical outcomes. In some studies, outcomes were reported differently from what the panel determined to be critical or important for decision making. Reporting was also inconsistent across studies. This affected the degree of certainty panel members had in the decisions (potentially leading to indirectness), so explicit assumptions were made about the meaning to patients, rather than leaving them implicit, and they were included in the EtD framework for each question.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[17,27,28] The EtD table summarized the results of retrieved studies, as well as systematic reviews of the literature that were updated or performed specifically for these guidelines. The EtD table addressed effects of interventions, test accuracy, resource use, values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, and after the guideline panel meeting, made suggestions for corrections, and identified missing evidence.

The panel considered systematic literature from both the pregnant and nonpregnant populations. For questions on acute VTE treatment and diagnosis, for which much less direct evidence was available, outcome literature was considered from both populations. For questions on prophylaxis, outcome literature was considered specifically from the pregnant patient population. Literature was included in a step-wise approach that was based on study design hierarchy starting with available systematic reviews, individual randomized trials, and then observational studies (eg, cohort, case series) from pregnant populations to inform outcomes. Similarly, to supplement either minimal or absent data from the pregnant population, literature sources from nonpregnant populations were also considered to indirectly inform outcomes.

Literature was excluded that related to nonpharmacologic treatments (eg, mechanical prophylaxis); pharmacologic treatments that may cross the placenta such as fondaparinux as first-line treatment, vitamin K antagonists, oral direct thrombin, and FXa inhibitors (ie, dabigatran, apixaban, edoxaban, and rivaroxaban) outside of use in breastfeeding; dose adjustment methods other than anti-FXa monitoring (eg, according to changes in weight), safety of and optimal management of subcutaneous therapeutic-dose UFH around the time of delivery, conversion to prophylactic UFH close to term, and literature addressed by other ASH guideline chapter publications for management of heparin-induced thrombocytopenia (HIT), optimal management of anti-FXa monitoring in extremes of body weight or with renal dysfunction and diagnosis through D-dimer testing.

To ensure that recent studies were not missed, searches (those for questions 1 through 19 are presented in supplement 4: https://www.dropbox.com/sh/is1c0zj91ixczzx/AACImbnAUcr2zDUZ5qIHjLRYa?dl=0) were updated during October and November 2016, and panel members were asked for studies that were missed and that fulfilled the inclusion criteria for the individual questions.

Under the direction of the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either accepted and randomly checked for accuracy or conducted de novo. For individual studies and new reviews, risk of bias was assessed at the outcome level using the Cochrane Collaboration's risk-of-bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values and preferences, and costs, and these findings were summarized within the EtD frameworks.[17,27,28] Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each of the effect estimates of the outcomes of interest, test accuracy, and the importance of outcomes following the GRADE approach. The GRADE approach is 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 dose-effect relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[11,15,18]

During a 2-day in-person meeting followed by online and telephone discussions, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and agreed on the following: the certainty in the evidence, the balance of benefits and harms of the available management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The guideline panel agreed on the recommendations (including direction and strength), and remarks and qualifications were decided by consensus or, in rare instances, by voting, on the basis of the balance of all desirable and undesirable consequences. The final guidelines, which included recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

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

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online between 1 September and 2 October 2017, for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Eleven individuals and 2 organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 30 July 2018, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality verified that the defined guideline development process was followed, and on 3 August 2018, the officers of the ASH Executive Committee approved submission of the guidelines for

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 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.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their 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.	Policy making 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 adaption) 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 identify possible research gaps.

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 as 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 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, and 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 its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. 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

Treatment of acute VTE and superficial vein thrombosis

Question 1: Should antithrombotic therapy (UFH or LMWH) vs no antithrombotic therapy be used in pregnant women with acute VTE?

Recommendation 1

For pregnant women with acute VTE, the ASH guideline panel *recommends* antithrombotic therapy compared with no antithrombotic therapy (strong recommendation, high certainty in evidence about effects ⊕⊕⊕⊕).

Recommendation 2

For pregnant women with acute VTE, the ASH guideline panel *recommends* LMWH over UFH (strong recommendation, moderate certainty in evidence about effects ⊕⊕⊕◯).

Summary of the evidence. We found 1 randomized trial[29] that reported on outcomes with and without antithrombotic therapy in nonpregnant patients with clinically diagnosed pulmonary embolism and 1 narrative review[30] that described outcomes in pregnant patients with VTE.

One systematic review and meta-analysis examining the risks of recurrent VTE and bleeding events in patients receiving LMWH or UFH for the treatment of pregnancy-related VTE was identified,[31] along with 2 others that compared the safety and efficacy of initial treatment with LMWH with UFH for acute DVT[32] and pulmonary embolism[33] in the nonpregnant population. We found no systematic reviews that undertook the same comparison in pregnant patients with VTE. We retrieved 1 observational study that reported on the risk of osteoporotic fracture in pregnant women receiving higher-than-prophylactic doses of UFH[34] and another that reported on bone mineral density 4 to 7 years after delivery in women who had received extended courses of either prophylactic, intermediate, or therapeutic doses of LMWH during pregnancy.[35] One randomized trial that reported on the risk of spinal fracture after extended intermediate-dose LMWH and UFH in the nonpregnant population was included.[36] We also retrieved a randomized trial that compared

risks of heparin-induced thrombocytopenia in nonpregnant patients receiving prophylactic doses of LMWH compared with prophylactic UFH.[37] The EtD framework is shown online at: https://dbep.gradepro.org/profile/FC27E96F-2A38-D41D-9C2D-0E39F7EBBE93.

Benefits. Antithrombotic therapy markedly reduces mortality in nonpregnant and pregnant patients with acute VTE.[29,30] Treatment also reduces the risk of recurrent VTE.[29,30] In a systematic review and meta-analysis, treatment of pregnancy-associated VTE with LMWH or UFH was associated with an estimated antepartum weighted mean recurrence incidence of 1.97% (95% confidence interval [CI], 0.88% to 3.49%).[31] Results were not provided according to type of heparin. For the nonpregnant population, initial treatment of DVT and pulmonary embolism with LMWH was reported to be at least as effective as therapy with UFH with respect to recurrent VTE and mortality.[32,33]

Harms and burden. In the above-noted meta-analysis examining treatment of pregnancy-associated VTE with LMWH or UFH, the overall risk of major bleeding with treatment during the antepartum period was 1.41% (95% CI, 0.62%-2.41%), whereas that during the first 24 hours after delivery was 1.20% (95% CI, 0.3%-2.50%).[31] In 2 meta-analyses comparing the safety and efficacy of LMWH and UFH for the initial treatment of DVT and pulmonary embolism in the nonpregnant population, the risks of bleeding were similar with both treatments.[32,33]

Extended use of greater-than-standard prophylactic doses of UFH during pregnancy was associated with a risk of osteoporotic fracture of 2.2%.[34] In a study of nonpregnant patients with a mean age of 68 years receiving 3 to 6 months of intermediate-dose anticoagulation after a short course of full-dose UFH for the treatment of VTE, the risk of spinal fracture was 15.0% in those allocated to UFH and 2.5% in those randomly assigned to LMWH (relative risk [RR], 5.88; 95% CI, 0.76-50.00; 122 more per 1000, from 6 fewer to 1000 more).[36] Only limited data were available on the impact of therapeutic-dose LMWH during pregnancy on bone mineral density.[35]

The risk of heparin-induced thrombocytopenia during pregnancy seems low.[31] However, in a randomized trial in the nonpregnant population, the reported risk of this complication was greater with UFH prophylaxis than with LMWH prophylaxis after hip surgery (2.7% vs 0%; RR not estimable).[37]

Other EtD criteria and considerations. The panel did not consider fondaparinux for first-line therapy of VTE in pregnancy, because this drug has been reported to cross the placenta in small amounts, and experience with fondaparinux in pregnancy is very limited (especially during the first trimester).[38,39] Vitamin K antagonists were not considered acceptable therapy for pregnancy-associated VTE, because it is known that these drugs cross the placenta and have the potential to cause teratogenicity, pregnancy loss, fetal bleeding, and neurodevelopmental deficits.[40-44] Similarly, the oral direct thrombin and FXa inhibitors (ie, dabigatran, apixaban, edoxaban, and rivaroxaban) are likely to cross the placenta, and their reproductive effects in humans are unknown.[45-49]

LMWHs are eliminated by the kidneys and may accumulate in patients with significant renal dysfunction. It has been suggested for the nonpregnant population that therapeutic doses of LMWH should not be used in patients with a glomerular filtration rate of <30 mL/min.[50] UFH with activated partial thromboplastin time monitoring would be preferred in pregnant women with significant renal dysfunction who require therapeutic anticoagulation for treatment of VTE.

The management of nonpregnant patients with heparin-induced thrombocytopenia or a history of this condition is addressed by *American Society of Hematology 2018 Guidelines for Venous Thromboembolism: Heparin-Induced Thrombocytopenia* (Cuker A et al, *Blood Advances,* in press). Danaparoid, a heparinoid, does not cross the placenta and has been used to treat heparin-induced thrombocytopenia.[51-53] The use of fondaparinux (with the cautions noted above) is an option where danaparoid is not available (including in the United States).

Conclusions and research needs for these recommendations. The guideline panel determined that there is clear evidence for a net health benefit with antithrombotic therapy for acute VTE in pregnancy and that LMWH has a better safety profile than UFH in this setting. Data on the use of fondaparinux in pregnancy remain limited, and the use of oral anticoagulants (including vitamin K antagonists and the direct-acting oral anticoagulants) during pregnancy is constrained by concerns about increased risks of pregnancy loss and teratogenicity.

The panel identified the following additional research need: more data are required regarding the safety of fondaparinux and the direct oral anticoagulants during pregnancy.

Question 2: Should anticoagulant intervention vs no anticoagulant intervention be used for pregnant women with proven superficial vein thrombosis?

Recommendation 3

For pregnant women with proven acute superficial vein thrombosis, the ASH guideline panel *suggests* that LMWH be used over not using any anticoagulant (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 1 systematic review addressing this question in a general population[54] and none focused specifically on pregnant patients. We identified 2 additional observational studies[35,55] and 2 randomized trials[56,57] that measured other outcomes relevant to this context (eg, potential adverse effects associated with LMWH, including heparin-induced thrombocytopenia and decreased bone mineral density). Altogether, there were 10 randomized trials that addressed this question,[54] although all were in the nonpregnant population. There were no direct data from either randomized trials or observational studies that examined the effect of treatment of acute superficial vein thrombosis specifically in pregnant patients.

In the nonpregnant population, 1 large randomized controlled trial examined the role of fondaparinux in acute superficial vein thrombosis,[58] whereas the others studied the effect of LMWH.[54] No studies reported the risk of neonatal bleeding or congenital malformation specifically in the population of pregnant women with superficial vein thrombosis. The EtD framework is shown online at https://dbep.gradepro.org/profile/FE58248F-F061-EE36-A7B9-956174FA88F4.

Benefits. Fondaparinux 2.5 mg subcutaneously once per day for 45 days in nonpregnant patients with acute, symptomatic lower-limb superficial vein thrombosis at least 5 cm in length reduced the

risk of developing VTE to 0.2% from 1.3% (RR, 0.15; 95% CI, 0.04-0.50; 11 fewer per 1000, from 7 fewer to 13 fewer) and of recurrent superficial vein thrombosis to 0.3% from 1.6% (RR, 0.21; 95% CI, 0.08-0.54; 13 fewer per 1000, from 7 fewer to 15 fewer).[58] LMWH at various doses and for various durations (maximum of 30 days) seemed to reduce the risk of VTE to 2.9% from 4.4% (RR, 0.68; 95% CI, 0.45-1.03; 14 fewer per 1000, from 1 more to 24 fewer) in the nonpregnant population, but this was pooled across various comparators, including placebo, aspirin, nonsteroidal anti-inflammatory agents, and compression stockings.[54] Overall, the certainty of these estimated effects is low, owing to indirectness (various populations studied with exclusion of pregnant patients and different comparators) and imprecision of the estimates.

Harms and burden. Multiple studies reported adverse effects, including major bleeding, heparin-induced thrombocytopenia, and osteopenia as assessed with bone mineral density.[35,54-57] The risk of major bleeding was not different in the nonpregnant population receiving fondaparinux than in the population receiving placebo (RR, 0.99; 95% CI, 0.06-15.90; 0 fewer per 1000, from 1 fewer to 10 more).[58] Major bleeding in pregnant patients is rare, and studies suggest that there is no significant increase with exposure to prophylactic-dose[57,59] (see questions 12 and 14) or therapeutic-dose[31] (see question 1) LMWH. Although it is possible that higher-than-prophylactic doses of LMWH may lead to more osteopenia when used in pregnant patients, the data are limited to observational studies and are limited by confounding and a high degree of imprecision. There is low certainty in the estimate of the risk of adverse effects as a result of these factors. However, given the available evidence, the guideline panel considered the risk of adverse effects most likely to be small.

Other EtD criteria and considerations. The panel considered that the only intervention in the context of pregnancy that was suitable for consideration was LMWH, given that fondaparinux has been shown to cross the placenta[39] and that experience with this medication is limited, especially regarding its use in the first trimester.[38] The panel discussed the observation that although superficial vein thrombosis is often diagnosed clinically, the diagnosis should be confirmed by compression ultrasound whenever possible. The benefits of treating with LMWH were thought to outweigh the potential harms, which in this situation consist mostly of bleeding and the burden of injections, especially for very symptomatic superficial vein thrombosis and superficial vein thrombosis at risk of extension into the deep venous system. No issues related to the feasibility of implementing or acceptability of recommending this intervention were raised. The panel noted that there were no data on LMWH dosing or duration for this indication specific to pregnancy. There was general agreement among panel members that they would treat for the remainder of pregnancy and for 6 weeks postpartum. There was no agreement on LMWH dosing with options of prophylactic dose, intermediate dose, or intermediate dose decreasing to prophylactic dose once symptom resolution advanced.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a low certainty in evidence for a net health benefit from using anticoagulant interventions for acute superficial vein thrombosis. For more distal or less symptomatic superficial vein thrombosis and for patients who are needle averse, the benefits of intervening may be less. On the basis of the body of available evidence, it is likely that anticoagulant interventions reduce the risk of developing VTE. There is low certainty that there is an effect of these interventions on other outcomes. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that such an effect does not exist and does not allow firm conclusions.

The panel identified the following additional research need: more data are required regarding the dose and duration of LMWH if used in this context.

Question 3: Should LMWH twice per day vs LMWH once per day be used for pregnant women with acute VTE?

Recommendation 4

For pregnant women with acute VTE treated with LMWH, the ASH guideline panel *suggests* either once-per-day or twice-per-day dosing regimens (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We found 1 systematic review of randomized controlled trials addressing this question in the general population[60] and none focused specifically on pregnant patients. We were unable to find any randomized trial data that examined this question in pregnant patients; however, there were observational studies that reported on the incidence of recurrent VTE and bleeding in pregnant women receiving twice-per-day or once-per-day dosing regimens.[61,62] We were unable to find any studies that reported on postthrombotic syndrome, chronic thromboembolic pulmonary hypertension, or neonatal bleeding according to dosing regimen. The EtD framework is shown online at: https://dbep.gradepro.org/profile/E6630722-09BB-6950-9272-E88D93F723FF.

Benefits. A 2013 Cochrane review examined the effect of once-per-day compared with twice-per-day LMWH dosing in a nonpregnant population with acute proven VTE and found no difference in the risk of developing recurrent VTE (5.0% with twice-per-day dosing and 4.2% with once-per-day dosing; odds ratio [OR], 1.22; 95% CI, 0.72-2.04; 9 more per 1000, from 11 fewer to 40 more).[60] It is possible that these results are not generalizable to pregnant women, given the changes in pharmacokinetics that occur during pregnancy. Two observational studies in pregnant women with proven VTE treated with either twice-per-day or once-per-day LMWH dosing found an overall low incidence of recurrent pulmonary embolism or DVT, with no difference demonstrated between dosing schedules.[61,62] Overall, the certainty of these estimated effects is very low or low, owing to either significant indirectness or the risk of confounding in the studies and imprecision of the estimates.

Harms and burden. The Cochrane review demonstrated no significant difference in bleeding between twice-per-day and once-per-day dosing of LMWH in nonpregnant patients (2.9% for once-per-day dosing and 2.2% for twice-per-day dosing; OR, 1.30; 95% CI, 0.69-2.50; 6 more per 1000, from 7 fewer to 31 more).[60] Similarly, observational studies in pregnant women demonstrated an overall low risk of bleeding with LMWH therapy and no clear difference between those who received twice-per-day dosing and those who received once-per-day dosing.[61-63] Small observational studies report that only a minority of pregnant women receiving

weight-adjusted therapeutic doses of LMWH-required dose escalation to attain target anti-FXa levels, regardless of whether once-per-day or twice-per-day dosing was used.[64-68] There is low or very low certainty in the estimate of the risk of adverse effects because of indirectness and imprecision. However, given the available evidence, the guideline panel considered that the risk of adverse effects with twice-per-day injections was most likely to be small.

Other EtD criteria and considerations. It is probable that women would consider twice-per-day injections a burden compared with once-per-day injections, although this may not be consistent for all. The costing differential between twice-per-day and once-per-day LMWH is variable. Some panel members noted that any concerns about the effectiveness of once-per-day LMWH would likely be less after initial acute therapy was complete. Current practice is varied and often depends on the preferences of the practitioner or center.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in evidence, which leads to an unclear net health benefit for using twice-per-day dosing of LMWH compared with once-per-day dosing. It is difficult to draw any significant conclusions regarding a balance of benefits or harms on the basis of the limited body of available evidence. Therefore, the panel was unable to make a recommendation for either the intervention or the comparator and instead considered that either is a reasonable option and that individual treatment decisions should be made using a shared decision-making model between the patient and clinician. The smaller number of injections required with once-per-day LMWH might increase feasibility and acceptability of VTE treatment in pregnancy. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that such an effect does not exist and does not allow firm conclusions.

The panel identified the following additional research needs: further evidence regarding the risks, benefits, and acceptability of once-per-day vs twice-per-day LMWH dosing for treatment of acute VTE, specifically in the pregnant patient population, should be sought. Investigations should be performed to determine whether there is any benefit to twice-per-day dosing of LMWH for the treatment of VTE in the acute (ie, first month) setting, followed by de-escalation to once-per-day dosing for the remainder of the treatment period.

Question 4: Should routine anti-FXa monitoring to guide dose adjustment vs no monitoring be used in pregnant women receiving therapeutic-dose LMWH for the treatment of VTE?

Recommendation 5

For pregnant women receiving therapeutic LMWH for the treatment of VTE, the ASH guideline panel *suggests against* routine monitoring of anti-FXa levels to guide dosing (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found no systematic reviews addressing this question. We identified 1 single-center case series that compared outcomes in 2 consecutive groups of pregnant women receiving therapeutic LMWH therapy for acute VTE with and without anti-FXa level monitoring.[69] There were several observational studies that examined the frequency of dosing alterations in pregnant women on anti-FXa–targeted LMWH therapy.[64-68,70,71] There were no direct data, either randomized control trial or observational, that examined the effect of dose-adjusted treatment on mortality, postthrombotic syndrome, or chronic thromboembolic pulmonary hypertension specifically in pregnant patients. The EtD framework is shown online at: https://dbep.gradepro.org/profile/A66232F8-025C-BFD2-98B2-211CA1046A0A.

Benefits. One observational study (n = 26) that examined outcomes in 11 pregnant women receiving treatment for VTE with LMWH with anti-FXa monitoring and 15 without anti-FXa monitoring reported no episodes of recurrent VTE in either group. Mean blood loss at delivery was similar in both groups.[69] Some, but not all, observational studies reported a need for dose adjustments when anti-FXa levels were used to guide therapy[64-68,70,71]; however, none demonstrated a clear clinical benefit related to these adjustments.

Harms and burden. Limited available data suggest that there is no difference in blood loss at the time of delivery between those receiving LMWH therapy that is adjusted according to anti-FXa levels and those whose treatment is not similarly monitored.[69] There is low or very low certainty in the estimate of the risk of adverse effects as a result of study design, imprecision, and risk of bias. However, given the available evidence, the guideline panel considered the risk of adverse effects with anti-FXa monitoring to most likely be small.

Other EtD criteria and considerations. The lack of reliability of these tests[72,73] and the absence of a validated therapeutic range for LMWH in this population were noted. There was significant debate among the panel regarding the impact on patients of anti-FXa level monitoring and dose adjustments. It is likely that some patients will value the increased clinical attention that is associated with more frequent monitoring. However, given the lack of a clear benefit seen with dose adjustments based on the currently available evidence, it is also possible that the burden of clinic visits and frequent blood-taking will be onerous for many. There may be an impact on health equity if anti-FXa level monitoring is recommended, because this testing is costly and is not available in all centers. Until there is evidence that dosing adjusted to target anti-FXa levels leads to improved patient outcomes, it is difficult to justify recommending a resource (time and money)-intensive intervention.

The panel did not address monitoring of anti-FXa levels in patients at extremes of body weight or with renal dysfunction or nor did it address other methods of dose adjustment during pregnancy (eg, according to changes in weight). The role of anti-FXa monitoring in nonpregnant patients at extremes of body weight or with renal dysfunction receiving LMWH is addressed by the *American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Optimal Management of Anticoagulation Therapy* (Witt DM et al, *Blood Advances,* in press).

Conclusions and research needs for this recommendation. The guideline panel determined that there is a low certainty in evidence for a lack of benefit to using anti-FXa level monitoring to guide routine management of pregnant patients receiving therapeutic-dose LMWH for treatment of VTE. Given the lack of benefit and

the costs of increased monitoring and dose adjustments, the panel decided to make a conditional recommendation against monitoring. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that such an effect does not exist and does not allow firm conclusions.

The panel identified the following additional research needs: larger and higher-quality studies examining the role of anti-FXa monitoring in this patient population are required to obtain more precise estimates of effect. Studies evaluating the role of anti-FXa level monitoring in the acute treatment period followed by a standard weight-based dosing approach should be performed.

Question 5: Should catheter-directed thrombolytic therapy vs no catheter-directed thrombolytic therapy be used in addition to anticoagulant therapy in pregnant women with acute lower-extremity DVT?

Recommendation 6

For pregnant women with acute lower-extremity DVT, the ASH guideline panel *suggests against* the addition of catheter-directed thrombolysis therapy to anticoagulation (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 1 meta-analysis,[74] 1 additional randomized trial,[75] and 1 additional observational study[76] that addressed this question in the nonpregnant population. We identified 5 observational studies that examined the role of catheter-directed thrombolysis specifically in pregnant women.[77-81] Two observational studies reported fetal radiation exposure and adverse maternal outcomes with this intervention.[82,83] The EtD framework is shown online at: https://dbep.gradepro.org/profile/76DD6628-F96A-93C7-AB00-87B3AA8A4BA2.

Benefits. A meta-analysis of both randomized and nonrandomized trials in the nonpregnant population demonstrated a reduction in recurrent DVT in those treated with catheter-directed thrombolysis with or without adjunctive endovascular treatment and anticoagulation compared with anticoagulation alone (OR, 0.56; 95% CI, 0.25-1.22; 64 fewer per 1000, from 29 more to 115 fewer); however, results were of very low certainty and were limited by indirectness and imprecision.[74] This same review showed a reduction in the risk of developing postthrombotic syndrome with catheter-directed thrombolysis (OR, 0.42; 95% CI, 0.19-0.96; 210 fewer per 1000, from 10 fewer to 359 fewer).[74]

In contrast to the above results, the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study (n = 692), which was not included in the above meta-analysis and which randomized patients with iliofemoral or femoropopliteal DVT to pharmacomechanical catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone, found that thrombolysis may increase the risk of recurrent VTE over 24 months (12.5% vs 8.5%; RR, 1.48; 95% CI, 0.95-2.31).[75] In this study, there was no difference between the 2 study arms with respect to overall risk of developing postthrombotic syndrome (46.7% in those who received interventional therapy vs 48.2% in those who received anticoagulation alone; RR, 0.97; 95% CI, 0.83-1.14); however, further analysis suggested a reduction in the risk of developing moderate or severe postthrombotic syndrome in those with iliofemoral DVT who received catheter-directed thrombolysis. Pregnancy-specific data were limited to noncontrolled case series with very low certainty in evidence, making it difficult to draw any substantive conclusions regarding benefit.[77-81] Given the overall evidence, the guideline panel considered the desirable effects of the intervention to be small.

Harms and burden. A large observational study of 7188 hospitalized nonpregnant patients demonstrated an increased risk of pulmonary embolism with lower-extremity catheter-directed thrombolysis with or without mechanical thrombectomy and anticoagulation compared with anticoagulation alone (OR, 1.69; 95% CI, 1.49-1.94; 64 more per 1000, from 47 more to 85 more).[76] The ATTRACT randomized trial demonstrated an increase in major bleeding over the first 10 days in the group randomized to catheter-directed thrombolysis (1.7% vs 0.3%; RR, 6.34; 95% CI, 0.77-52.38), although there was no fatal bleeding or any episodes of intracranial bleeding in either study arm.[75] Major bleeding was also increased with thrombolysis compared with anticoagulation alone in a meta-analysis of observational and randomized studies (pooled OR, 2.06; 95% CI, 1.66-2.66; 71 more per 1000, from 46 more to 107 more).[74] In the large observational study described above, those receiving catheter-directed thrombolysis also had a higher risk of intracranial hemorrhage (OR, 2.72; 95% CI, 1.40-5.30; 6 more per 1000, from 1 more to 14 more) and death (OR, 1.41; 95% CI, 0.88-2.55; 4 more per 1000, from 1 fewer to 13 more).[76]

Small case series of pregnant women receiving catheter-directed thrombolysis for lower-extremity DVT did not demonstrate any episodes of major bleeding, although certainty in the results is significantly limited by the very low quality of the evidence.[78-80] Reported estimated fetal radiation exposure with catheter-directed thrombolysis varied, although 1 study showed exposure to be greater than the quoted limit for major organ malformation.[82,83] This risk may be partially alleviated with appropriate lead shielding. Given the available evidence, the guideline panel considered the risk of adverse effects most likely to be large.

Other EtD criteria and considerations. Research to date has not shown a consistent benefit to the nonpregnant population of the addition of catheter-directed thrombolysis to standard therapy with respect to the development of postthrombotic syndrome. The methodologically strongest data from the ATTRACT study suggest that for most patients, the addition of catheter-directed thrombolysis does not prevent the development of this complication. Although severe postthrombotic syndrome may be associated with significant morbidity and there may be relevant values and preferences to consider in this setting, these findings, along with the potential for important harm and the absence of direct evidence for benefit in the pregnant population, resulted in a conditional recommendation against this intervention. The panel also considered the costs associated with catheter-directed thrombolysis and the feasibility of providing this intervention on a wider scale, especially in resource-poor settings. The balance between desirable and undesirable outcomes may favor providing catheter-directed thrombolysis in those with limb-threatening DVT.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a low certainty in evidence for a net health benefit from not providing catheter-directed thrombolysis for DVT in pregnant women. On the basis of the body of available evidence, the addition of catheter-directed

thrombolysis to standard therapy does not seem to reduce the risk of postthrombotic syndrome, although there may be a benefit in certain subsets of patients. This intervention does, however, increase the risk of recurrent DVT, pulmonary embolism, and major bleeding and is also costly and unlikely to be feasible in resource-poor settings.

The panel identified the following additional research needs: more information from high-quality research on the safety and efficacy of catheter-directed thrombolysis in the pregnant population, including in those with limb-threatening DVT, is required. More data regarding patient values and preferences for the potential benefits and drawbacks of this intervention are required. More data on estimated fetal radiation exposure and associated potential harms would be useful.

Question 6: Should thrombolytic therapy vs no thrombolytic therapy be used in addition to anticoagulant therapy in pregnant women with acute hemodynamically significant pulmonary embolism or pulmonary embolism with significant right ventricular dysfunction?

Recommendation 7

In pregnant women with acute pulmonary embolism and right ventricular dysfunction in the absence of hemodynamic instability, the ASH guideline panel *suggests against* the addition of systemic thrombolytic therapy to anticoagulation, compared with anticoagulation alone (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 8

In pregnant women with acute pulmonary embolism and life-threatening hemodynamic instability, the ASH guideline panel *suggests* administering systemic thrombolytic therapy in addition to anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We found 1 meta-analysis of randomized trials addressing this question in the nonpregnant population that also examined outcomes in subgroups of patients, including those with massive pulmonary embolism (defined as sustained arterial hypotension) and those with submassive pulmonary embolism (defined as evidence of right ventricular dysfunction or elevated cardiac biomarkers in the absence of arterial hypotension).[84] We identified 2 summaries of observational studies that examined the role of systemic thrombolysis specifically in pregnant women.[85,86] The EtD framework is shown online at: https://dbep.gradepro.org/profile/576D1522-365C-38E1-9CBA-951F5513E91D.

Benefits. Systemic thrombolysis decreased mortality in the nonpregnant population in both submassive (OR, 0.42; 95% CI, 0.17-1.03; 15 fewer per 1000, from 1 more to 22 fewer) and massive (OR, 0.48; 95% CI, 0.20-1.15; 66 fewer per 1000, from 17 more to 107 fewer) pulmonary embolism; however, certainty in the pooled results was limited by indirectness and imprecision.[84] The same meta-analysis demonstrated a decrease in pulmonary embolism recurrence with thrombolysis; however, this was seen only in the submassive pulmonary embolism group (OR, 0.25; 95% CI, 0.06-1.03; 12 fewer per 1000, from 0 fewer to 15 fewer) and not in the massive pulmonary embolism group (OR, 0.97; 95% CI, 0.31-2.98; 2 fewer per 1000, from 43 fewer to 105 more). Again, limitations in the available data led to very low quality of evidence and residual uncertainty in the results.

Evidence for the use of thrombolysis in pregnant women with pulmonary embolism is limited to case reports and case series.[85,86] Thus, this evidence focuses more on safety and potential for harm rather than on demonstrable benefit of the intervention. Overall, the potential desirable effects of thrombolysis were judged by the panel to be small, although they could be larger in the massive pulmonary embolism subgroup.

Harms and burden. Pooled analysis in a nonpregnant population suggests an increased risk of major bleeding (OR, 2.91; 95% CI, 1.95-4.36; 63 more per 1000, from 32 more to 105 more) and an increased risk of intracranial hemorrhage or related fatality in those receiving thrombolysis in addition to anticoagulation for massive or submassive pulmonary embolism (OR, 3.18; 95% CI, 1.24 to −8.11; 7 more per 1000, from 1 more to 22 more), although this is based on low quality of evidence.[84]

A similar risk of bleeding was demonstrated in the observational studies of pregnant women receiving systemic thrombolysis. One report of 14 patients (7 of whom received tissue plasminogen activator and 7 of whom received streptokinase) found 5 major bleeds (all in those receiving streptokinase) and 3 minor bleeds.[86] Of note, in the 2 summaries of observational studies reporting on systemic thrombolysis in pregnancy (n = 31 total), there were no episodes of maternal mortality, and of the 5 neonatal deaths, none were felt to be related to hemorrhage or thrombolytic therapy.[85,86] Given the available evidence, the guideline panel considered the risk of adverse effects most likely to be large.

Other EtD criteria and considerations. The panel considered the risk of bleeding in pregnant women outweighed the potential benefit in the setting of submassive pulmonary embolism with evidence of right ventricular dysfunction alone. Although patients with life-threatening hemodynamic instability would most likely have been excluded from the relevant studies, the panel was of the opinion that this population would be most likely to benefit from systemic thrombolysis, and hence, a subgroup recommendation was made. The panel also considered relevant cost considerations, including those related to administration of thrombolysis and the resultant monitoring after administration (usually in intensive care units).

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty evidence for a net health benefit from withholding systemic thrombolysis for pregnant women with acute pulmonary embolism unless there is evidence of life-threatening hemodynamic instability. Other EtD criteria also favored withholding systemic thrombolysis, except in those with life-threatening hemodynamic instability.

The panel identified the following additional research needs: more information is required from high-quality direct studies on the safety and efficacy of thrombolysis for pulmonary embolism in the pregnant population, including in those with submassive pulmonary

embolism and right ventricular dysfunction alone. More data on patient values and preferences for potential benefits and drawbacks of this intervention are required.

Question 7: Should outpatient therapy vs hospital admission be used in the initial treatment of pregnant women with low-risk acute VTE?

Recommendation 9

In pregnant women with low-risk acute VTE, the ASH guideline panel *suggests* initial outpatient therapy over hospital admission (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 3 systematic reviews addressing this question in a general population,[87-89] but none focused specifically on pregnant patients. Altogether, there were 7 randomized trials in patients with DVT and 3 in patients with pulmonary embolism that compared inpatient therapy with either home treatment or early discharge, although all were in the nonpregnant population. Twelve additional cohort studies that enrolled pulmonary embolism patients were included in 1 of the systematic reviews.[89] We identified 1 multicenter observational study that examined the antenatal management of VTE in pregnant patients, some of whom were treated initially as outpatients,[62] as well as another small retrospective cohort study published in abstract form that described outcomes in 16 pregnant women with new VTE who were treated on an outpatient basis.[90] The EtD framework is shown online at: https://dbep.gradepro.org/profile/51FC85A1-29DB-1FE7-A662-0B03D80062CA.

The indirect data reported on mortality, recurrent VTE, and major bleeding. The observational studies in pregnancy described mortality, major bleeding, recurrent VTE, postthrombotic syndrome, and pregnancy loss. No studies reported the risk of chronic thromboembolic pulmonary hypertension in either the general or pregnancy-specific populations.

Benefits. Although investigators have reported a high degree of patient satisfaction,[91] better patient social functioning,[92] and reduced expenditures for health care systems[93-95] with outpatient treatment of VTE in the general population, no such data are available for the pregnant population. The panel considered that similar potential benefits might exist for outpatient therapy of low-risk pregnant patients with VTE. Outpatient therapy would also result in less exposure to hospital-based harms (eg, iatrogenic infection).

Harms and burden. Evidence from the nonpregnant patient population with DVT demonstrates no increased risk of mortality (RR, 0.72; 95% CI, 0.45 to 1.15; 13 fewer deaths per 1000, from 7 more to 25 fewer deaths) in those either treated as outpatients or discharged early compared with those treated in the hospital.[88] The risk of major bleeding may have been slightly lower in patients randomly assigned to outpatient management or early discharge (RR, 0.67; 95% CI, 0.33-1.36; 7 fewer per 1000, from 8 more to 14 fewer); however, this was based on very low certainty in evidence.[88] The risk of recurrent VTE seemed to be reduced in nonpregnant patients randomly assigned to outpatient treatment or early discharge (RR, 0.65; 95% CI, 0.44-0.94; 17 fewer episodes per 1000, from 3 fewer to 27 fewer).[87] In 2 randomized trials that included 471 nonpregnant patients with low-risk pulmonary embolism, early discharge or outpatient therapy was not associated with a higher risk of mortality (RR, 0.58, 95% CI, 0.17-1.97; 11 fewer per 1000, from 22 fewer to 26 more), recurrent VTE (RR, 1.23, 95% CI, 0.25-6.03; 2 more per 1000, from 7 fewer to 44 more), or major bleeding (RR, 2.74, 95% CI, 0.45-16.71; 8 more per 1000, from 2 fewer to 69 more).[87] In a systematic review of both cohort and randomized trials that included 15 studies with 2296 low-risk nonpregnant patients with pulmonary embolism (1657 treated as outpatients, 256 discharged early, and 383 treated in hospital), the pooled incidences of mortality, recurrent VTE, and major bleeding were similar in these 3 groups.[89]

The multicenter observational cohort of pregnant patients with VTE reported on 126 patients, 16 of whom were treated entirely as outpatients.[62] There were no maternal deaths or episodes of recurrent VTE in any of the enrolled patients. Details on the location and extent of thrombosis were not provided for patients who were managed as outpatients. Bleeding in pregnant patients is rare, and no episodes of major antenatal bleeding were reported. Major secondary postpartum hemorrhage occurred in 3 of 126 patients (2%; 95% CI, 0.8%-6.8%), although it was not reported whether the affected patients had received initial inpatient or outpatient therapy. Rates of postthrombotic syndrome and pregnancy loss were also not reported separately based on inpatient or outpatient management status. Another small single-center retrospective cohort of 16 pregnant women with VTE managed entirely as outpatients reported no cases of recurrent VTE (0%; 95% CI, 0%-20%).[90] Again, no details on the extent or location of thrombosis in these patients were provided. There was 1 instance of major bleeding in the early postpartum period and no deaths. Given the issues with indirectness and imprecision, the overall certainty in the evidence regarding adverse effects was considered low; however, the guideline panel considered that the risk of initial outpatient anticoagulation therapy for appropriately selected patients was likely to be small.

Other EtD criteria and considerations. The panel considered that requirements for safe outpatient therapy would include appropriate patient selection, patient education, adequate follow-up, and availability of an on-call service. Where the expertise for patient training and outpatient monitoring of therapy does not exist, even low-risk patients may benefit more from initial hospitalization.

This recommendation applies only to low-risk pregnant patients with VTE. For those with any high-risk features, the benefit-harm balance would likely favor hospital admission. Although a number of clinical prediction rules have been developed to help select low-risk patients in the general population,[89] these do not exist for pregnant patients with DVT or pulmonary embolism. Vital sign abnormalities, severe pain requiring analgesia, extensive VTE, advanced gestational age, maternal comorbidities that limit tolerance of recurrent VTE or are associated with increased risk of bleeding, contraindications to LMWH, and lack of adequate support at home are all indicators for initial hospitalization.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a low certainty in evidence for a net health benefit from using outpatient therapy for initial management of acute VTE in pregnancy. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that

such an effect does not exist and does not allow firm conclusions. On the basis of the body of available evidence and other EtD criteria, it is likely that outpatient therapy is as beneficial as hospital-based treatment with improved acceptability and resource use and with no appreciable increase in harm for low-risk patients.

The panel identified the following additional research needs: Studies should be performed that will provide pregnancy-specific data for stratifying risk for complications associated with treatment of VTE, and clinical prediction rules should be developed to identify pregnant patients who require hospital admission for initial management of DVT and pulmonary embolism. Studies examining rates of hospital admission after initiation of outpatient therapy in pregnant patients should be undertaken.

Management of anticoagulants around the time of delivery

Question 8: Should scheduled delivery with discontinuation of LMWH vs cessation of LMWH with spontaneous onset of labor be used for pregnant women receiving therapeutic-dose LMWH?

Recommendation 10

For pregnant women receiving therapeutic-dose LMWH for the management of VTE, the ASH guideline panel *suggests* scheduled delivery with prior discontinuation of anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We were unable to find any systematic reviews or randomized trials specifically addressing this question. We identified 2 retrospective observational studies that examined bleeding risks in women receiving antenatal therapeutic-dose LMWH who stopped their anticoagulants at the start of labor or membrane rupture or the morning of the day before induction of labor or planned cesarean delivery and in controls not receiving LMWH.[96,97] We also identified another observational study that compared wound and bleeding complications in women receiving anticoagulants before and after cesarean delivery with those in women not receiving anticoagulants,[98] a multinational hospital audit of outcomes in pregnant women receiving tinzaparin,[99] and a systematic review of 18 observational studies that reported on outcomes in women receiving therapeutic anticoagulation during pregnancy for the management of acute VTE.[31] A cross-sectional analysis of administrative hospital discharge data supplemented with medical record information from 15 US hospitals,[100] 3 systematic reviews of randomized trials that reported maternal and neonatal outcomes in varied clinical situations with induction of labor at term compared with expectant management,[101-103] and 2 subsequently published randomized trials[104,105] were retrieved. Of the latter studies, the most relevant to our population was a systematic review of 31 randomized studies evaluating outcomes associated with induction of labor in women with intact membranes.[103] No studies were retrieved that reported the risk of VTE or epidural hematoma in pregnant women who were receiving therapeutic LMWH and undergoing induction of labor or spontaneous delivery. The EtD framework is shown online at: https://dbep.gradepro.org/profile/0287B397-3095-8360-8630-729BF9D31158.

Benefits. In the systematic review of outcomes in pregnant women receiving therapeutic anticoagulation for treatment of VTE, the incidence of major hemorrhage within 24 hours of delivery was 1.2% (95% CI, 0.3%-2.5%).[31] The risk of blood loss at delivery >500 mL but ≤1000 mL was 13.5%, and loss >1000 mL but ≤1,500 mL was 0.4% in a multicenter hospital audit of 254 women who received therapeutic doses of tinzaparin.[99] The risks were similar in the subgroup of patients who received tinzaparin within 24 hours of delivery. In a single-center retrospective study in which therapeutic-dose LMWH was switched to twice-per-day dosing at 37 weeks and stopped at the beginning of spontaneous or induced labor (after adjusting for parity, maternal age, and birth weight higher than 4000 g), women with spontaneous onset of labor had a 1.9-fold (95% CI, 0.6-fold to 5.8-fold) increase in the risk of postpartum hemorrhage (≥500 mL) compared with those who had planned induction of labor.[96] Postpartum hemorrhage occurred in 21 (29.6%) of 71 women receiving LMWH who had a vaginal delivery compared with 50 (17.6%) of 284 control women not receiving anticoagulants (OR, 1.9; 95% CI, 1.1-3.5; 113 more per 1000, from 14 more to 252 more). There was no difference in the risk of postpartum hemorrhage after vaginal delivery in women whose last dose of therapeutic LMWH was less than 24 hours previously compared with those with a >24-hour time interval (OR, 1.3; 95% CI, 0.4-4.8). There was no difference in the risk of postpartum hemorrhage (≥1000 mL) after cesarean delivery in women receiving LMWH compared with controls (OR, 2.9; 95% CI, 0.5-19.4; 74 more per 1000, from 22 fewer to 428 more). In another single-center retrospective study, severe postpartum hemorrhage (≥1000 mL) occurred in 6 (6.3%) of 95 women receiving therapeutic-dose LMWH stopped at the beginning of labor or rupture of membranes or the morning of the day before induction of labor or planned cesarean delivery compared with 29 (5.5%) of 524 women not receiving anticoagulants (RR, 1.2; 95% CI, 0.5-2.9; 11 more bleeding episodes, from 28 fewer to 105 more).[97] In a small study of women receiving anticoagulants around the time of cesarean delivery, bleeding outcomes were not different in women who did and did not receive anticoagulant therapy.[98] Of the 77 women in that study receiving anticoagulant therapy, 30 were receiving therapeutic doses and 47 were receiving prophylactic doses. Adverse outcomes were not provided according to dosing category. Although the included evidence suggests that spontaneous delivery in women receiving therapeutic LMWH might be associated with an increased risk of postpartum hemorrhage, this is based on very low certainty in evidence because of issues related to observational study design and imprecision.

Harms and burden. None of the included studies reported on the competing risks of recurrent VTE or complications of VTE or missed access to epidural analgesia with anticoagulant interruption before a scheduled delivery or at the onset of spontaneous labor.

Potential drawbacks of scheduled delivery include maternal and neonatal complications, as well as increased medicalization of delivery associated with induction of labor. In the cross-sectional analysis of administrative hospital discharge data and medical record information, induction of labor increased the risk of cesarean delivery in all weeks of gestation (RR range by week, 1.06 to 1.52) except week 39 (RR, 0.89) on crude modeling; however, after matching on propensity scores, the risk of cesarean delivery was significantly decreased with labor induction during weeks 35 through 39 (RR range, 0.77-0.92) but was significantly elevated

at weeks 40 (RR, 1.22) and 41 (RR, 1.39).[100] A systematic review examining the impact of induction of labor at term on maternal and neonatal outcomes in women with intact membranes reported no increase in the frequency of cesarean delivery, instrumental vaginal delivery, maternal adverse outcomes, perinatal death, or requirement for admission to the neonatal intensive care unit in those randomly assigned to induction.[103] Systematic reviews that evaluated outcomes after induction in other clinical situations and subsequently published randomized trials described similar findings.[101-105] These findings have been further confirmed in the recently published ARRIVE (A Randomized Trial of Induction Versus Expectant Management) randomized controlled study, which demonstrated reductions in perinatal death, neonatal complications, and cesarean delivery in low-risk nulliparous women who were induced at 39 weeks compared with those who were managed expectantly.[106] In 1 study, 512 of 619 women completed a childbirth experience questionnaire.[104] There were no differences between the women undergoing induction and those with unscheduled delivery with respect to satisfaction with the childbirth experience.

Other EtD criteria and considerations. The panel considered the benefits of scheduled delivery, including the decreased risk for maternal bleeding. Access to neuraxial analgesia and anesthesia is another important consideration. The panel agreed that a multidisciplinary, individualized approach should be used when decisions are made about delivery plans and anesthetic options for women receiving anticoagulants. Shared decision making is required when peridelivery management in women receiving therapeutic anticoagulation and its potential impact on access to neuraxial analgesia and anesthesia are considered.

The panel recognized that the main causes of primary postpartum hemorrhage (the loss of ≥500 mL of blood from the genital tract within 24 hours of delivery) are uterine atony and trauma (although problems such as coagulation defects are also associated with excessive blood loss). Because the primary physiologic mechanism to stem bleeding from the placental bed after separation of the placenta is not the hemostatic system but sustained myometrial contraction leading to occlusion of uterine blood vessels,[107] it is presumed that anticoagulants like LMWH do not predispose the patient to atonic uterine bleeding. In contrast, traumatic bleeding from vaginal tears, episiotomy, and cesarean delivery can be adversely affected by agents that impair the hemostatic system. Therefore, careful attention should be paid to minimization of trauma and active management of the third stage of labor (with uterotonics such as oxytocin to enhance uterine contraction and promote placental separation) in women who might be receiving anticoagulants at the time of delivery to reduce the risk of bleeding.[107,108]

Current North American and European anesthetic guidelines call for at least a 24-hour interval between the last dose of greater-than-prophylactic-dose LMWH and placement of an epidural catheter.[109,110] The required time interval between the last dose of therapeutic LMWH and neuraxial analgesia or anesthesia could limit access to regional analgesia in these women; this is also important in women at increased likelihood of cesarean delivery, because the availability of regional anesthesia reduces the need to expose women and babies to the risks of general anesthesia. The panel also considered that the potential for maternal and neonatal harm with scheduled delivery for women receiving therapeutic anticoagulation was likely to be small. Scheduled delivery may remove an element of uncertainty around the peripartum period for women receiving therapeutic anticoagulation for both the clinician and patient.

The panel noted that other options for anticoagulant management, including conversion to intravenous UFH with cessation 4 to 6 hours before delivery or anticipated need for epidural insertion with a repeat activated partial thromboplastin time drawn after 4 hours to confirm normalization would be appropriate in patients considered at high risk for recurrent VTE with prolonged anticoagulant interruption (eg, those with proximal DVT or pulmonary embolism diagnosed 2 to 4 weeks before delivery). The panel did not review the safety of and optimal management of subcutaneous therapeutic-dose UFH around the time of delivery.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty in evidence for a net health benefit from using scheduled delivery with prior discontinuation of anticoagulants at the time of delivery. Because of very low certainty in evidence or no published information about outcomes of mortality or recurrent VTE, lack of better evidence does not imply that an effect does not exist and does not allow firm conclusions. The data informing this recommendation are of very low certainty, and this clinical scenario is likely to be heavily influenced by patient and clinician preferences. Not all panel members agreed with this conditional recommendation in favor of discontinuation of therapeutic anticoagulation before scheduled delivery, and 1 member specifically advocated a conditional recommendation for allowing for spontaneous labor, even with the potential for limiting access to neuraxial analgesia and anesthesia and increasing the risk of major bleeding. The panel noted an element of geographical variation in practice which seems to correlate with rates and acceptance of epidural analgesia during childbirth.

The panel identified the following additional research needs: more outcome data that examines different anticoagulant regimens at the time of delivery, including transitioning to intravenous UFH, would be helpful. Data should be obtained that assess other critical outcomes for pregnant women with therapeutic anticoagulation interruption around the time of delivery (including access to epidural analgesia and frequency of epidural hematomas, cesarean delivery, and maternal and neonatal morbidity and mortality).

Question 9: Should scheduled delivery with prior discontinuation of prophylactic-dose LMWH vs cessation of prophylactic LMWH at the onset of spontaneous labor be used for pregnant women receiving prophylactic-dose LMWH?

Recommendation 11

In pregnant women receiving prophylactic-dose LMWH, the ASH guideline panel *suggests against* scheduled delivery with discontinuation of prophylactic anticoagulation compared with allowing spontaneous labor (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We were unable to find any randomized trials specifically addressing this question. We identified 3 observational studies that examined the peripartum bleeding risk in women receiving prophylactic anticoagulation. One study used data from Swedish national registries to examine venous thromboembolic

and bleeding risks in women receiving prophylactic LMWH for prevention of recurrent thrombosis and compared those risks to those reported in 3000 control women.[111] The second study compared wound and bleeding complications in women receiving anticoagulants before and after cesarean delivery with those in women not receiving anticoagulants,[98] and the third was a multinational hospital audit of outcomes in pregnant women receiving tinzaparin.[99] A systematic review of observational studies and case studies that examined the risks of prophylactic anticoagulation when administered during pregnancy was also included.[112] A cross-sectional analysis of administrative hospital discharge data supplemented with medical record information from 15 US hospitals,[100] 3 systematic reviews of randomized trials that reported maternal and neonatal outcomes in varied clinical situations with induction of labor at term compared with expectant management,[101-103] and 2 subsequently published randomized trials were retrieved.[104,105] Of the latter studies, the most relevant to our population was a systematic review of 31 randomized studies that evaluated outcomes associated with induction of labor in women with intact membranes.[103] No studies were retrieved that reported the risk of VTE or epidural hematoma in women receiving prophylactic LMWH who were undergoing induction of labor or spontaneous delivery. The EtD framework is shown online at: https://dbep.gradepro.org/profile/3C599E02-AC83-5592-A4F6-C43590ED18B1.

Benefits. Allowing spontaneous labor may minimize the need for medical intervention in labor and potentially avoid maternal and neonatal complications as well as increased medicalization of delivery that may be associated with induction of labor. In the cross-sectional analysis of administrative hospital discharge data and medical record information, induction of labor increased the risk of cesarean delivery in all weeks of gestation (RR range, 1.06-1.52), except at 39 weeks (RR, 0.89), on crude modeling; however, after matching on propensity scores, the risk of cesarean delivery was significantly decreased with labor induction during weeks 35 through 39 (RR range, 0.77-0.92) but was significantly increased at weeks 40 (RR, 1.22) and 41 (RR, 1.39).[100] Of note, a systematic review examining the impact of induction of labor at term on maternal and neonatal outcomes in women with intact membranes reported no increase in the frequency of cesarean delivery, instrumental vaginal delivery, maternal adverse outcomes, perinatal death, or requirement for admission to the neonatal intensive care unit in those randomly assigned to induction.[103] Systematic reviews that evaluated outcomes after induction in other clinical situations and subsequently published randomized trials described similar findings.[101,102,104,105] In 1 study, 512 of 619 women completed a childbirth experience questionnaire[104]; there were no differences between women undergoing induction and those with unplanned delivery with respect to satisfaction with the childbirth experience.

Harms and burden. The included evidence does not demonstrate a consistent effect of prophylactic anticoagulation on bleeding risk. A systematic review of observational studies and case reports reported an incidence of postpartum hemorrhage exceeding 500 mL of 0.92% (24 of 2603) and found zero episodes of postpartum wound hematoma in 2603 women receiving prophylactic anticoagulation antepartum.[112] Swedish registry data suggest overall higher risks. The incidence of postpartum hemorrhage exceeding 1000 mL was higher in women receiving prophylaxis (6.1% [20 of 326]) than in controls (1.8% [55 of 3000]; RR, 3.35; 95% CI, 2.03-5.51; 43 more per 1000, from 19 more to 81 more).[111] The risk of developing a hematoma was also increased in women receiving prophylaxis (2.5% [8 of 326]) compared with 0.4% (12 of 3000; RR, 6.17; 95% CI, 2.54-14.99). In a small study of women receiving anticoagulants around the time of cesarean delivery, bleeding outcomes were not different in women who did and did not receive anticoagulants; however, there was a greater risk of wound complications in those receiving anticoagulants (29.9% [23 of 77] compared with 7.8% [6 of 77] in those not receiving anticoagulants [RR, 3.83; 95% CI, 1.65-8.89]).[98] Of the 77 women in that study who received anticoagulants, 30 were receiving therapeutic doses and 47 prophylactic doses. Adverse outcomes were not provided according to dosing category. An observational study that examined 1013 pregnancies in women receiving prophylactic tinzaparin found 10.4% (95% CI, 8.6%-12.4%) had hemorrhage of >500 mL at the time of delivery.[99] The incidence of bleeding was only slightly higher if patients had received a prophylactic dose within 24 hours before delivery (11.1%; 95% CI, 8.2%-14.8%). However, this is based on low certainty in evidence because of issues related to observational study design.

Allowing spontaneous onset of labor may have an impact on access to neuraxial analgesia or anesthesia (eg, epidural analgesia or spinal anesthesia). Current North American and European anesthetic guidelines call for at least a 12-hour interval between the last dose of prophylactic LMWH and placement of an epidural catheter.[109,110] For patients receiving intermediate-dose prophylaxis, that interval is increased to 24 hours.

Other EtD criteria and considerations. In all cases, a multidisciplinary, individualized approach should be used when decisions about delivery plans and anesthetic options for women receiving anticoagulants are being made. Shared decision making is required when peridelivery management in women receiving prophylactic anticoagulation and its potential impact on access to neuraxial analgesia and anesthesia are being considered.

In general, the panel considered that the 12-hour recommended interval between the last dose of standard prophylactic-dose LMWH and placement of a catheter for neuraxial analgesia or anesthesia would allow most women receiving standard prophylactic-dose LMWH the option of neuraxial analgesia or anesthesia, regardless of whether delivery was scheduled or spontaneous. In addition, advising women that they can forgo a dose of prophylactic LMWH until their case has been reviewed if they think they have entered labor spontaneously may improve their access to neuraxial analgesia or anesthesia.

The panel recognized that the main causes of primary postpartum hemorrhage (the loss of ≥500 mL of blood from the genital tract within 24 hours of delivery) are uterine atony and trauma (although problems such as coagulation defects are also associated with excessive blood loss) and that bleeding secondary to the latter (eg, vaginal tears, episiotomy, and cesarean delivery) can be adversely affected by agents like LMWH that impair the hemostatic system. Because the primary physiologic mechanism to stem bleeding from the placental bed after separation of the placenta is not the hemostatic system but instead is sustained myometrial contractions leading to occlusion of uterine blood vessels,[107] it is presumed that anticoagulants do not predispose the patient to

atonic uterine bleeding. For women who might be receiving anticoagulants at the time of delivery, careful attention should be paid to minimization of trauma and active management of the third stage of labor (eg, with uterotonics such as oxytocin to enhance uterine contraction and promote placental separation) to reduce the risk of bleeding.[107,108] The panel did not review data regarding the conversion to prophylactic UFH close to term.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty in evidence for a net health benefit from allowing for spontaneous onset of labor in women receiving prophylactic anticoagulation. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that such an effect does not exist and does not allow firm conclusions. Other EtD criteria were generally in favor of allowing for spontaneous labor. The data informing this recommendation are of very low certainty, and this clinical scenario is likely to be heavily influenced by patient and clinician preference. Scheduled delivery may be preferable for women and their caregivers who place a very high priority on access to an epidural for analgesia or when there is a high risk of birth by cesarean delivery, so that general anesthesia can be avoided.

The panel identified the following additional research need: data should be obtained that examine other critical outcomes for pregnant women with prophylactic anticoagulation interruption around the time of delivery.

Anticoagulant use in breastfeeding women

Question 10: Should one particular anticoagulant vs any other anticoagulant be used for breastfeeding women who have an indication for anticoagulation?

Recommendation 12

In breastfeeding women who have an indication for anticoagulation, the ASH guideline panel *recommends* using UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 13

In breastfeeding women who have an indication for anticoagulation, the ASH guideline panel *recommends against* using direct-acting oral anticoagulants (strong recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We did not find any systematic reviews or randomized controlled trials directly investigating the safety of different anticoagulants in women who are actively breastfeeding. We did identify multiple observational studies that examined anticoagulant drug levels in the breast milk of lactating women or in the plasma of their breastfed infants.[113-124] There were no direct data, from either randomized controlled trials or observational studies, examining the effect of different treatments on neonatal bleeding. The EtD framework is shown online at: https://dbep.gradepro.org/profile/44015A14-C2B5-FE55-B8FD-BB65BBAF839F.

Benefits. Because this question is focused on the safety of various anticoagulants for breastfed infants of women taking anticoagulant therapy, we do not present the comparative efficacy of each agent by indication. For these data, please see the relevant sections related to Recommendations 18 and 22 through 26.

Harms and burden. UFH does not pass into breast milk because of its large size and negative charge.[124] Although LMWH is excreted into breast milk in small amounts, a study of 15 lactating women showed either undetectable or very low anti-FXa LMWH levels in breast milk (range, 0.006-0.037 IU/mL).[120] LMWH has limited oral bioavailability and is unlikely to be absorbed in the newborn; therefore, its use in lactating women is unlikely to be associated with any clinically relevant neonatal bleeding.

Warfarin is polar, nonlipophilic, and highly protein bound and is therefore unlikely to be excreted into breast milk. A study of 13 women receiving anticoagulants found no detectable drug levels in either breast milk (to a level of 0.08 μmol/L) or infant plasma.[119] Two observational studies of women taking warfarin whose infants were breastfeeding failed to identify a single case of infant bleeding.[118,119] Acenocoumarol, another vitamin K antagonist with pharmacologic properties similar to those of warfarin, is also likely safe during breastfeeding, because similar studies have shown undetectable drug levels in breast milk and normal coagulation profiles in infants of lactating women taking acenocoumarol.[114,115] However, phenprocoumon, a vitamin K antagonist with a long half-life, is more lipophilic than warfarin and can be excreted into breast milk. But because it is highly protein bound, detectable drug levels are low (much lower than the average amount for maintenance required for anticoagulation) in breast milk of lactating women taking phenprocoumon.[121,123]

A small number of case reports have reported no or very low anti-FXa activity (<0.07 IU/mL) in the breast milk of women receiving danaparoid.[116] Because danaparoid is not orally absorbed, risks to breastfeeding infants are likely negligible. There are no published data on the excretion of fondaparinux into breast milk. However, significant absorption by breastfeeding infants is again unlikely, because orally ingested heparins have low availability.[120]

A case report suggests that rivaroxaban is excreted into breast milk, although at low levels (estimated relative infant dose, <2%).[122] Data on the other direct-acting oral anticoagulants are lacking.

Other EtD criteria and considerations. The panel heavily weighted avoiding harm in the infants of women who are breastfeeding, especially given that safe options for anticoagulation exist in this setting. The agents with greatest experience in this patient population and the best evidence for safety were warfarin, acenocoumarol, and LMWH. Choosing between these safe agents should involve shared decision making between clinicians and patients that incorporates drug efficacy for the specific indication, strength of evidence for safety, and other factors, such as tolerability of subcutaneous injection and the patients' ability to visit the laboratory for regular testing of the international normalized ratio if warfarin or acenocoumarol is chosen. The panel agreed that phenprocoumon is best reserved for women who are unstable on short-acting acenocoumarol in regions where warfarin is not available.[121] It is possible that the direct-acting oral anticoagulants are safe, but until further evidence and experience are available, clinicians should avoid prescribing these agents to women who are breastfeeding.

Conclusions and research needs for these recommendations. The guideline panel determined that there is low certainty in evidence for the safety of using warfarin, acenocoumarol, LMWH,

fondaparinux, or danaparoid while breastfeeding. There is very low certainty in evidence against using direct-acting oral anticoagulants. This recommendation strongly valued avoiding adverse bleeding outcomes in infants of breastfeeding mothers.

The panel identified the following additional research need: more data are required regarding the safety of the direct-acting oral anticoagulants in this population.

Prevention of VTE

Question 11: Should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used for prevention of VTE in women undergoing assisted reproduction?

Recommendation 14

In unselected women undergoing assisted reproductive therapy, the ASH guideline panel *suggests against* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 15

For women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome, the ASH guideline panel *suggests* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We identified 4 registry-based population studies[125-128] and 3 retrospective studies[129-131] that reported on the risk of VTE with assisted reproduction. We found no systematic reviews examining antithrombotic therapy for prevention of VTE in women using assisted reproduction. A prospective cohort of 234 women undergoing assisted reproductive therapy, 23 of whom received prophylactic LMWH with or without low-dose aspirin, was identified.[132] We retrieved 5 systematic reviews examining the impact of antithrombotic therapy to improve pregnancy outcomes in this patient population: 2 focused on aspirin therapy,[133,134] and 3 investigated LMWH.[135-137] The EtD framework is shown online at: https://dbep.gradepro.org/profile/51D4F0AC-CF1C-CE5C-9825-E98ED4D774EC.

Benefits. Assisted reproduction is associated with an increased risk of VTE; however, in unselected patients, the absolute incidence of symptomatic VTE seems low at less than 1%.[125,126,128,132] Higher risks ranging from 2.5% to 6.6% have been reported in patients with severe ovarian hyperstimulation syndrome and in patients with ovarian hyperstimulation syndrome requiring hospitalization (1.6%).[127,129-131] VTE risk was not addressed in other groups of interest undergoing assisted reproduction, including those with prior VTE or with known thrombophilias. In a single-center prospective cohort of 234 women undergoing assisted reproduction, those receiving no antithrombotic therapy did not have an increased risk of DVT or pulmonary embolism compared with those who received LMWH with or without low-dose aspirin (0.5% vs 0%; OR, 2.99; 95% CI, 0.12-75.40; 9 more per 1000, from 4 fewer to 259 more).[132]

The inclusion and exclusion criteria and analytic methods differed in the 2 meta-analyses that examined the impact of aspirin on pregnancy rate with assisted reproduction.[133,134] In 1, aspirin use was not associated with an increase in pregnancy rate (31.8% and 30.8% in the aspirin and control arms, respectively; RR, 1.03; 95% CI, 0.91-1.17; 38 more per 1000, from 2 more to 74 more).[134] In the other, a small but statistically significant increase in pregnancy rate was seen in women randomly assigned to aspirin therapy (32.5% and 29.3% in the aspirin and control arms, respectively; OR, 1.19; 95% CI, 1.01-1.39), but that effect was lost when only studies with a low risk of bias were analyzed (OR, 1.13; 95% CI, 0.86-1.47).[133] In 2 other meta-analyses, LMWH was also not associated with an increase in pregnancy rate (34.7% and 25.0% in the LMWH and control arms, respectively (RR, 1.66; 95% CI, 0.94-2.90; 165 more per 1000, from 15 fewer to 475 more).[135,136] A third meta-analysis that included only women with at least 3 implantation failures showed a statistically nonsignificant improvement in implantation frequency with LMWH (21.8% with LMWH and 12.7% without (RR, 1.73; 95% CI, 0.98-3.03; 93 more per 1000, from 3 fewer to 258 more).[137] Overall, the certainty of these estimated effects is low because of imprecision and risk of bias in the included trials.

Harms and burden. None of the meta-analyses conducted a formal comparison of the frequency of adverse events such as bruising at injection sites, bleeding, thrombocytopenia, or allergic reactions between patients who received antithrombotic therapy and those who did not.[133-136] One systematic review commented that adverse effects were comparable in women randomly assigned to the LMWH and the control groups.[137] There was no difference in the frequency of vaginal bleeding in the aspirin and control arms in 1 small randomized trial (3.8% and 3.6% in aspirin and control arms, respectively; RR, 1.02; 95% CI, 0.15-6.97; 1 more per 1000, from 31 fewer to 217 more).[138] One placebo-controlled randomized trial reported any bleeding in 7.1% of those randomly assigned to prophylactic LMWH.[139] The frequency in the control patients was not noted, although the authors stated there was no difference between the 2 groups. Given the limited data, there is low certainty in the estimate of the risk of adverse effects with antithrombotic therapy; however, on the basis of more extensive data in pregnant women receiving prophylaxis for other indications, the guideline panel considered the risk of adverse effects with antithrombotic therapy most likely to be small (see questions 12, 14, 16, and 17).

Other EtD criteria and considerations. There were no studies that examined the duration of anticoagulant prophylaxis for patients with severe ovarian hyperstimulation syndrome. If used, prophylaxis could be extended over the time range during which most reported events develop (range, 2 days-11 weeks).[127,130,140]

The panel noted the absence of data specific to women with a history of VTE or thrombophilia. It was agreed that most panel members would consider provision of prophylaxis during assisted reproduction to women who would qualify for antepartum prophylaxis on the basis of their VTE history or high-risk thrombophilia; however, in the absence of data, the panel was not able to make an evidence-based recommendation for these subgroups.

Conclusions and research needs for these recommendations. The guideline panel determined that there is no evidence for a net health benefit from using antithrombotic interventions for prevention of VTE in unselected women using assisted reproductive technologies. On the basis of the body of available evidence, it is likely that the overall risk of VTE is sufficiently low in unselected patients

that antithrombotic interventions to reduce the risk of developing symptomatic VTE are not warranted; undesirable consequences would outweigh desirable consequences if prophylaxis were provided to all women undergoing assisted reproduction. The VTE risk, however, seems sufficiently high in women with severe ovarian hyperstimulation syndrome and those with ovarian hyperstimulation syndrome requiring hospitalization to suggest that the desirable consequences of prophylaxis would outweigh undesirable consequences, even though direct data showing a benefit to intervention in these women are lacking. The absence of published information about VTE risks and benefit to the use of antithrombotic therapy in other specific patient subpopulations does not imply that these risks and effects do not exist. There is no evidence of a benefit with antithrombotic interventions (aspirin or heparins) on other outcomes (eg, implantation, pregnancy, live births).

The panel identified the following additional research needs: more data are required regarding the baseline risk of VTE with assisted reproductive technology in specific patient populations, including those with prior VTE, thrombophilia, and other risk factors for VTE. More data are also required regarding the potential benefits and risks of antithrombotic therapy in reducing the risk of VTE in women using assisted reproductive technologies.

Question 12: Should antepartum anticoagulant prophylaxis vs no antepartum anticoagulant prophylaxis be used for pregnant women with prior VTE?

Recommendation 16

For women not already receiving long-term anticoagulant therapy who have a history of VTE that was unprovoked or was associated with a hormonal risk factor, the ASH guideline panel *recommends* antepartum anticoagulant prophylaxis over no anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Recommendation 17

For women not already receiving long-term anticoagulant therapy who have a history of prior VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors, the ASH guideline panel *suggests against* antepartum anticoagulant prophylaxis (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 1 narrative review[2] and 1 systematic review and meta-analysis[1] that provided baseline risks of antepartum VTE in the general population. A retrospective study (using observational administrative data from the entire state of California) that provided information on the risk of antepartum recurrent VTE[141] and a pooled analysis of cohort and randomized trials[142] that estimated the risk of recurrent VTE and major bleeding during pregnancy with and without LMWH (using information predominantly drawn from observational studies) were also retrieved. We identified 1 meta-analysis of individual patient data from randomized trials of prophylactic LMWH (with or without aspirin) in women with a history of placenta-mediated pregnancy complications,[59] 2 randomized trials,[56,57] and 1 observational study[35] that provided additional information on the safety of prophylactic-dose LMWH in this setting. A study that explored patient values and preferences in this population[143] and another that examined the cost-effectiveness of prophylactic LMWH in pregnant women with a history of VTE[144] were also informative. The EtD framework is shown online at: https://dbep.gradepro.org/profile/01618857-BE05-A8CA-8C89-E76E69C5FDD3.

Benefits. A history of VTE increases the risk of antepartum VTE from ~0.6 of every 1000 deliveries[1,2] to 4.2% (95% CI, 0.3%-6.0%).[142] The risk of recurrent antepartum VTE varied according to risk factors present at the time of the first event. In a pooled analysis of 4 cohort studies, the risk of antepartum recurrence was 3.6% (95% CI, 1.4%-8.9%), 6.4% (95% CI, 3.9%-10.4%), and 1.1% (95% CI, 0.2%-5.8%) in women with prior unprovoked, hormonal-associated, and provoked (nonhormonal temporary risk factor [ie, surgery, trauma, immobilization or bedrest, active cancer]) VTE, respectively.[142] When data from an administrative database were analyzed, the incidence of recurrent VTE with subsequent pregnancies was higher in women with a prior pregnancy-associated VTE (21 [4.5%] of 465 deliveries) than in those whose initial event was unprovoked (37 [2.7%] of 1353 deliveries) (RR, 1.7; 95% CI, 1.0-2.8).[141] Of these recurrent venous thromboembolic events, 15 (71%) of 21 and 20 (54%) of 37 occurred antepartum in the groups with pregnancy-associated and unprovoked VTE, respectively.

In studies in which women with a history of VTE were provided with LMWH or UFH prophylaxis, the risk of antepartum VTE was 0.9% (95% CI, 0.5%-1.8%) compared with 4.2% in studies in which antepartum prophylaxis was not provided (95% CI, 0.3%-6.0%),[142] suggesting that prophylaxis reduces the risk of recurrent VTE by ~75%, which is similar to what was seen with extended LMWH prophylaxis following high-risk orthopedic procedures.[145] Overall, the certainty of these estimated effects is low because of the lack of randomized controlled trials and imprecision of the overall estimates.

Harms and burden. LMWH prophylaxis was not associated with an increased risk of major antepartum (0.2% with and 0.6% without LMWH; RR, 0.34; 95% CI, 0.04-3.21; 4 fewer per 1000, from 6 fewer to 14 more) or peripartum hemorrhage (2.5% with and 3.0% without LMWH; RR, 0.82; 95% CI, 0.36-1.86; 5 fewer per 1000, from 19 fewer to 26 more).[59] The likelihood of developing osteopenia (bone mineral density measured 6 weeks postpartum was 2.16 g/cm^2 [standard deviation, 0.35 g/cm^2] with prophylactic LMWH and 2.23 g/cm^2 [standard deviation, 0.42 g/cm^2] without LMWH prophylaxis [mean difference, 0.07 cm^2; 95% CI, −0.02 to 1.6 cm^2]) or osteoporotic fractures (0% with and without LMWH prophylaxis) was not increased in women receiving antepartum prophylaxis.[57] In 1 small randomized trial, bone mineral density measured after delivery was lower in those who had received antepartum UFH prophylaxis than in those managed with LMWH prophylaxis and in a group of untreated controls (repeated measures analysis of variance [ANOVA], $P = .02$).[56] Thrombocytopenia was not more common with LMWH prophylaxis than without (3.0% vs 1.3%, respectively; RR, 2.37; 95% CI, 0.92-6.11; 17 more per 1000, from 1 fewer to 64 more; no cases of heparin-induced thrombocytopenia were reported in either group).[59] Given the

limited data, there is low certainty in the estimate of the risk of adverse effects with antepartum anticoagulant prophylaxis, although the guideline panel considered it most likely to be small.

Other EtD criteria and considerations. The requirement for daily injections throughout the duration of pregnancy and costs of this intervention may pose a significant burden for some. A cross-sectional international multicenter study of 123 women found that although the majority of women with previous VTE who were pregnant or planning pregnancy would choose to take LMWH prophylaxis during pregnancy (79%), an important minority (40% of low-risk women [those with a prior venous thromboembolic event associated with a transient nonhormonal risk factor and no known thrombophilia who had an estimated risk of antepartum recurrence <5%]) would not,[143] highlighting the need for individualized shared decision making in this setting.

Panel members were anonymously polled to select a risk threshold for recommending antepartum LMWH prophylaxis. Responses ranged from 1% to 4%; however, the majority of respondents selected a 2% VTE risk threshold for recommending LMWH prophylaxis throughout pregnancy.

A cost-effectiveness analysis that used a lifetime time horizon and societal perspective, along with US costs, reported that for low-risk women (those with no known thrombophilia and a prior venous thromboembolic event associated with a transient risk factor; estimated recurrence risk, 0.5%), expectant management was both more effective and less costly than antepartum prophylaxis but that for high-risk women (those with an unprovoked event or a known thrombophilia; estimated recurrence risk, 5.9%), LMWH prophylaxis during pregnancy was associated with a reasonable cost-effectiveness (US$38 700 per quality-adjusted life-year), given a risk of bleeding complications of <1%.[144]

The studies examining the efficacy and safety of antepartum prophylaxis used different anticoagulant drugs and dosing regimens. Some have reported failures of standard-dose LMWH and have suggested that higher doses should be used in the pregnant population,[146] although the proportion of such failures seems similar to that seen in other settings.[145] The issue of the optimal dosing strategy for prophylaxis is addressed in recommendation 28. The panel noted that a trial (NCT01828697; Comparison of Low and Intermediate Dose Low-molecular-weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy) comparing higher doses of LMWH with usual fixed-dose prophylaxis is currently recruiting.

The panel did not consider fondaparinux for first-line prophylaxis of VTE in pregnancy, because this drug has been reported to cross the placenta in small amounts, and experience with fondaparinux in pregnancy is very limited (especially during the first trimester).[38,39] Vitamin K antagonists were not considered acceptable for prevention of pregnancy-associated VTE because it is known that these drugs cross the placenta and have the potential to cause teratogenicity, pregnancy loss, fetal bleeding, and neurodevelopmental deficits.[40-44] Similarly, the oral direct thrombin and FXa inhibitors (ie, dabigatran, apixaban, edoxaban, and rivaroxaban) cross the placenta and have the potential to cause reproductive toxicity.[45-49]

Conclusions and research needs for these recommendations. The guideline panel determined that there is evidence for a net health benefit from using antepartum prophylaxis for the prevention of recurrent VTE, with the exception of women who had a temporary nonhormonal risk factor at the time of their prior event. All but the latter group of women had a risk of antepartum VTE greater than the risk threshold set by the panel for prophylaxis. There was debate about the strength of the data and appropriate strength of the recommendation. Eight of 10 panel members voted for a strong recommendation for the intervention.

The panel identified the following additional research needs: more data are required regarding optimal intensity of LMWH prophylaxis in this setting. Additional information would be helpful regarding the impact of thrombophilia status and precipitating risk factors with prior venous thromboembolic events on the risk of antepartum recurrent VTE.

Question 13: Should postpartum anticoagulant prophylaxis vs no postpartum anticoagulant prophylaxis be used for pregnant women with prior VTE?

Recommendation 18

For women not already receiving long-term anticoagulant therapy who have a history of VTE, the ASH guideline panel *recommends* postpartum anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We used 1 narrative review,[2] 1 systematic review and meta-analysis,[1] and 2 additional studies that used health claims data[14,147] to identify a baseline risk of postpartum VTE in the general population. A pooled analysis of cohort and randomized trials that provided information on the risk of recurrent postpartum VTE and the efficacy and safety of prophylaxis during this time frame was retrieved,[142] along with a meta-analysis of individual patient data from randomized trials of prophylactic LMWH (with or without aspirin) in women with a history of placenta-mediated pregnancy complications.[59] The latter was used to provide additional safety information about prophylactic-dose LMWH. No randomized trials comparing different types, intensities, or durations of postpartum anticoagulation were identified. The EtD framework is shown online at: https://dbep.gradepro.org/profile/FBF1F9D6-70FE-2C87-8A45-75A457592E9B.

Benefits. Postpartum VTE affects 6.5% of pregnancies in women with a history of VTE (95% CI, 4.3%-9.7%),[142] compared with a risk of approximately 0.6 of every 1000 deliveries in the general population.[1,2,14,147] There was no information on risk of postpartum VTE in subgroups of women according to risk factors present at the time of their incident venous thromboembolic event (eg, unprovoked, associated with a hormonal risk factor, or provoked with a nonhormonal risk factor). In women with a history of VTE who were treated with postpartum prophylaxis (LMWH, UFH, or warfarin), the risk of postpartum VTE was substantially lower at 1.8% (95% CI, 1.2%-2.7%), representing a decrement in risk similar to that seen with extended LMWH prophylaxis after high-risk orthopedic procedures.[145] Overall, the certainty of these benefits is low because of the lack of randomized controlled studies.

Harms and burden. The risks of major peripartum and postpartum bleeding with LMWH prophylaxis were similar to the

risks in those not receiving prophylaxis (10 [2.5%] of 404 and 12 [3.0%] of 395, respectively, for major peripartum hemorrhage [RR, 0.82; 95% CI, 0.36-1.86; 5 fewer per 1000, from 19 fewer to 26 more][59] and 2 [0.3%] of 767 and 0 [0.0%] of 108, respectively for postpartum prophylaxis).[142] Because of the shorter time frame involved, the panel considered the burden of postpartum prophylaxis to be substantially less than that of antepartum prophylaxis. Given the limited data and the fact that most of what is available is derived from studies examining LMWH prophylaxis for a different indication, there is low certainty in the estimate of the risk of adverse effects postpartum anticoagulant prophylaxis; however, the guideline panel considered it most likely to be small. Considerations regarding the safety of prophylactic anticoagulants while breastfeeding are addressed in recommendations 12 and 13.

Other EtD criteria and considerations. Panel members were anonymously polled to select a risk threshold for recommending postpartum LMWH prophylaxis. Responses ranged from 1% to 3%; however, the majority of respondents selected a 1% VTE risk threshold for recommending LMWH prophylaxis.

The studies examining the efficacy and safety of postpartum prophylaxis used different anticoagulant drugs and intensity of prophylaxis. Most of the available data are for LMWH prophylaxis, although some studies reported using warfarin, with a target international normalized ratio of 2.0 to 3.0. Some have noted failures of standard-dose LMWH. However, in the absence of direct comparisons of different dosing strategies, an evidence-based recommendation for a preferred prophylactic regimen is not possible.

There have been no studies comparing different durations of postpartum prophylaxis. Although the risk of thrombotic events is highest within 3 to 6 weeks after delivery, it is particularly high in the peripartum period with a continuous decrease in the risk until 12 weeks postpartum. Although a small relative increase in risk persists to 12 weeks after delivery, the absolute risk after 6 weeks is $<$1 of 10 000,[14,147] and prophylaxis between weeks 6 and 12 is unlikely to be of significant benefit in most patients.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in evidence for a net health benefit from using postpartum prophylaxis for the prevention of recurrent VTE. However, based on the available evidence in this population and extrapolating from other populations, the panel's VTE risk threshold, and other EtD criteria, it is likely that prophylactic anticoagulation reduces the risk of developing postpartum VTE with a low risk of harm, and therefore, the panel chose to make a strong recommendation in this situation. The issue of the optimal dosing strategy for prophylaxis is addressed in recommendation 29.

The panel identified the following additional research needs: more data are required regarding optimal intensity of LMWH prophylaxis in this setting. More information regarding optimal duration of postpartum prophylaxis should be gathered. Investigators should explore whether there are certain subgroups of patients more likely to derive benefit from postpartum prophylaxis.

Question 14: Should antepartum anticoagulant prophylaxis vs no antepartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?

Recommendation 19

For women who are heterozygous for the factor V Leiden or prothrombin mutation and in those who have protein C or protein S deficiency, regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 20

For women who have no family history of VTE but have antithrombin deficiency or are homozygous for the prothrombin gene mutation, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 21

For women with antithrombin deficiency who have a family history of VTE and in those who are homozygous for the factor V Leiden mutation or who have combined thrombophilias, regardless of family history of VTE, the ASH guideline panel *suggests* antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We found 1 narrative review[2] and 1 systematic review and meta-analysis[1] that provided baseline risks of antepartum VTE in the general population. Three systematic reviews that used case-control studies to examine the risk of pregnancy-related VTE in women with hereditary thrombophilias were retrieved,[1,148-150] along with a subsequently published case-control study[151] and a pooled analysis of data from women with thrombophilias (predominantly low risk) enrolled in 6 randomized trials examining the role of prophylactic LMWH in the prevention of recurrent placental-mediated pregnancy complications.[142] Information from the systematic reviews and the subsequent case-control study was used to provide RRs of VTE in affected women without a positive family history, whereas data from the systematic review mentioned above[1] provided the baseline risk of antepartum VTE in the general population. This allowed modeling of the data to best approximate absolute effects in those with a thrombophilia but no family history of VTE.

Data from 13 family cohort studies that excluded probands from their analysis, did not include superficial thrombophlebitis in their outcome measure, and used acceptable criteria for the diagnosis of a first venous thromboembolic event (objective confirmation or treatment with anticoagulant therapy for at least 2 to 3 months) were used to provide absolute risk estimates in thrombophilic women with a family history of VTE.[152-164] Where possible, data on women who did not receive prophylaxis were extracted from these studies; otherwise, the data were used as presented. Data from 1 otherwise well-conducted family study were not used because the number of pregnancy risk periods per individual thrombophilia could not

be reliably extracted.[165] When events were not presented separately for the antepartum and postpartum periods, they were presumed to occur in equal proportion in each (with any extra events being assigned to the antepartum period). Data were pooled using a random effects model with Freeman-Tukey double arcsine transformation.[166] The results of a study that included only 1 woman with protein C deficiency and 4 women with protein S deficiency[157] were excluded from pooling because their inclusion resulted in uninterpretable risk estimates.

A meta-analysis of individual patient data from randomized trials of prophylactic LMWH (with or without aspirin) in women with a history of placenta-mediated pregnancy complications,[59] 2 randomized trials,[56,57] and 2 observational studies[35,167] that provided additional information on the safety of prophylactic-dose LMWH in this setting were identified. The EtD framework is shown online at: https://dbep.gradepro.org/profile/19ED27FD-6AA0-F63E-8C49-378C0C283BC2.

Benefits. Thrombophilic women have a higher risk of antepartum VTE than that reported for the general population (approximately 0.6 of every 1000 deliveries).[1,2] The magnitude of the risk increase depends on the thrombophilia and the presence or absence of a family history of VTE.[142,148-164] The absolute risk seems to be low (less than 1%) in those with no family history of VTE who are heterozygous for the factor V Leiden or prothrombin gene mutations and in those who have antithrombin, protein C, or protein S deficiency.[142,148-150] In thrombophilic women with a family history of VTE, pooled risks of antepartum VTE remained low in women with heterozygosity for the factor V Leiden mutation (0.50%; 95% CI, 0.06%-1.21%),[154,159,161-163] heterozygosity for the prothrombin gene mutation (0%; 95% CI, 0%-0.73%),[152,153] protein C deficiency (1.63%; 95% CI, 0%-5.02%),[155,156] and protein S deficiency (0%; 95% CI, 0%-1.46%).[155-157] Pooled risks were substantially higher in women with antithrombin deficiency and a family history of VTE (2.70%; 95% CI, 0%-8.53%).[155-157,164] Risks ranged from 1.0% to 7.0% for women homozygous for the factor V Leiden mutation, depending on study design[151,158,160,163]; our meta-analysis of family studies suggests an antepartum risk of 6.86% (95% CI, 1.04%-15.83%) in these patients. Limited data extrapolated from case-control studies suggest an antepartum risk of VTE of 1.6% for individuals homozygous for the prothrombin gene mutation[149]; we were unable to find any data from family studies on antepartum venous thromboembolic risks in these women. In women with combined thrombophilias, the estimated antepartum risk of VTE from case-control studies was 2.82%,[149,151] whereas that pooled from 2 very small family studies was 0% (95% CI, 0%-2.35%)[158,163]; however, the panel considered it unlikely that the risk of VTE would be substantially lower in those with a family history than in those without a family history of VTE. In the pooled analysis examining the efficacy of LMWH prophylaxis (with or without aspirin) for prevention of placenta-mediated pregnancy complications, none of the women with thrombophilias (predominantly low-risk heterozygosity for the factor V Leiden or prothrombin gene mutations) in the control arm were diagnosed with VTE.[59]

In the absence of randomized studies examining the efficacy of antepartum thrombosis prophylaxis in this population, we are left to assume that the risk reduction with prophylaxis would be ~75%, as reported in other settings, including extended LMWH prophylaxis after high-risk orthopedic procedures.[145] Overall, the certainty of these benefits is low because of the lack of appropriate randomized studies and imprecision of the risk estimates.

Harms and burden. LMWH prophylaxis was not associated with an increased risk of major antepartum bleeding. Only 0.2% of women with and 0.6% of those without LMWH prophylaxis had antepartum bleeding in an individual patient data meta-analysis of trials examining LMWH with or without aspirin for the prevention of placenta-mediated pregnancy complications (RR, 0.34; 95% CI, 0.04-3.21; 4 fewer per 1000, from 6 fewer to 14 more)[59] and 0% in a cohort study of thrombophilic women receiving LMWH prophylaxis either in standard doses or doses adjusted to attain specific anti-FXa levels.[167] The same individual patient data meta-analysis demonstrated no increase in peripartum hemorrhage with LMWH prophylaxis; the incidence was 2.5% with LMWH and 3.0% with no LMWH (RR, 0.81; 95% CI, 0.36-1.86; 5 fewer per 1000, from 19 fewer to 26 more).[59] The likelihood of developing osteopenia (bone mineral density measured 6 weeks postpartum was 2.16 g/cm^2 [standard deviation, 0.35 g/cm^2] with prophylactic LMWH and 2.23 g/cm^2 [standard deviation, 0.42 g/cm^2] without LMWH prophylaxis [mean difference, 0.07 cm^2; 95% CI, −0.02 to 1.6]) or osteoporotic fractures (0% with and without LMWH prophylaxis) was not increased in women receiving antepartum prophylaxis.[57] In 1 small randomized trial, bone mineral density measured after delivery was lower in those who had received antepartum UFH prophylaxis than in those who had received LMWH prophylaxis and in a group of untreated controls (repeated measures ANOVA $P = .02$).[56] No cases of heparin-induced thrombocytopenia were seen in the cohort study of thrombophilic women receiving either standard or anti-FXa level-adjusted LMWH prophylaxis[167] or in either the LMWH prophylaxis or no prophylaxis arm of a randomized trial examining the efficacy of LMWH prophylaxis for recurrent pregnancy complications in thrombophilic women.[57] Given the limited data, there is low certainty in the estimate of the risk of adverse effects antepartum anticoagulant prophylaxis, although the guideline panel considered it most likely to be small.

Other EtD criteria and considerations. Panel members were anonymously polled to select a risk threshold for recommending antepartum LMWH prophylaxis. Responses ranged from 1% to 4%; however, the majority of respondents selected a 2% VTE risk threshold for recommending LMWH prophylaxis throughout pregnancy. Table 3 summarizes our guideline recommendations.

In the absence of any relevant data, the panel was unable to make an evidence-based recommendation regarding antepartum prophylaxis in women homozygous for the prothrombin gene mutation with a family history of VTE. However, given that risk estimates for those with this thrombophilia and no family history of VTE are close to our threshold of 2%, VTE risks are likely to be higher in those with a positive family history, and corresponding data for those homozygous for the factor V Leiden mutation shows a risk greater than our threshold; thus, panel members favored antepartum prophylaxis.

The requirement for daily injections throughout the duration of pregnancy and costs of this intervention may pose a significant burden for some. It was noted that the need for prophylaxis should be considered within the totality of the patient risk profile, and patients with low-risk thrombophilias might benefit from LMWH prophylaxis in the setting of additional risk factors. For patients with deficiencies of 1 of the natural anticoagulants, the severity of the deficiency might also be considered when decisions about prophylaxis are made.

The panel did not consider fondaparinux for first-line prophylaxis of VTE in pregnancy because this drug has been reported to cross the placenta in small amounts, and experience with fondaparinux in pregnancy (especially during the first trimester) is very limited.[38,39] Vitamin K antagonists were not considered acceptable for prevention of pregnancy-associated VTE because it is known that these drugs

Table 3. Guideline summary: prevention of first VTE in pregnant women with hereditary thrombophilia

American Society of Hematology (ASH)	Society of Obstetricians and Gynecologists of Canada (SOGC)*,[235]	Royal College of Obstetricians and Gynecologists (RCOG)†,[240]	American College of Obstetricians and Gynecologists (ACOG)‡,[239]	American College of Chest Physicians (ACCP)§,[237]
Heterozygosity for factor V Leiden or prothrombin gene mutation				
Antepartum: Regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Clinical surveillance (no grade).	Antepartum: Clinical surveillance unless additional risk factors are present; with a weighted score of at least 3,‖ thrombosis prophylaxis throughout the antepartum period should be considered; if the weighted score is only 2,‖ prophylaxis should be considered from 28 weeks (D).	Antepartum: Either clinical surveillance or prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are heterozygous for factor V Leiden mutation or prothrombin gene mutation, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).
Postpartum: For women without a family history of VTE, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a VTE (conditional recommendation, very low certainty in evidence about effects). For women with a family history of VTE, the ASH guideline panel *suggests against* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Postpartum: Clinical surveillance or prophylaxis if present in combination with any 2 of the following risk factors (each with an absolute risk of VTE <1% in isolation): BMI ≥30 kg/m^2 at first antepartum visit (II-2B), smoking >10 cigarettes per day antepartum (II-2B), preeclampsia (II-2B), intrauterine growth restriction (II-2B), placenta previa (II-2B), emergency cesarean section (II-2B), peripartum or postpartum blood loss of >1 L or need for blood product replacement (II-2B), preterm delivery (III-B), stillbirth (III-B), or maternal disease (cardiac disease, systemic lupus erythematosus, sickle cell disease, inflammatory disease, varicose veins, gestational diabetes) (III-B). If prescribed, prophylaxis should be given for 6 weeks (II-3B).	Postpartum: Consider thrombosis prophylaxis for at least 10 days after delivery if additional risk factors are present with a weighted score of at least 1‖; if there is a family history of VTE in a first-degree relative, thrombosis prophylaxis should be extended to 6 weeks (D).	Postpartum: Either clinical surveillance or anticoagulation if there are additional risk factors (first-degree relative with thrombotic episode before age 50 years or other major thrombotic risk factor (eg, obesity, prolonged immobility) (no grade).	Postpartum: For pregnant women who are heterozygous for factor V Leiden or prothrombin gene mutation, suggest postpartum clinical surveillance if there is no family history of VTE and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH, or vitamin K antagonists targeted at an INR of 2.0 to 3.0 for 6 weeks if there is a family history of VTE rather than routine care (grade 2C).
Protein C deficiency				
Antepartum: Regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Clinical surveillance (no grade).	Antepartum: Advice of a local expert should be sought and antepartum LMWH should be considered (D).	Antepartum: Either clinical surveillance or prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are protein C deficient, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).
Postpartum: For women without a family history of VTE, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects). For women with a family history of VTE, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects)	Postpartum: Clinical surveillance or prophylaxis if in combination with any 2 of the following risk factors (each with an absolute risk of VTE <1% in isolation): BMI ≥30 kg/m^2 at first antepartum visit (II-2B), smoking >10 cigarettes per day antepartum (II-2B), preeclampsia (II-2B), intrauterine growth restriction (II-2B), placenta previa (II-2B), emergency cesarean section (II-2B), peripartum or postpartum blood loss of >1 L or need for blood product replacement (II-2B), preterm delivery (III-B), stillbirth (III-B), or maternal disease (cardiac disease, systemic lupus erythematosus, sickle cell disease, inflammatory disease, varicose veins, gestational diabetes) (III-B). If prescribed, prophylaxis should be given for 6 weeks postpartum (II-3B).	Postpartum: Recommend LMWH for 6 weeks postpartum (D).	Postpartum: Either clinical surveillance or anticoagulation if there are additional risk factors (first-degree relative with thrombotic episode before age 50 years or other major thrombotic risk factor [eg, obesity, prolonged immobility]) (no grade).	Postpartum: For pregnant women who are protein C deficient, suggest postpartum clinical surveillance if there is no family history and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH for 6 weeks if there is a family history of VTE rather than routine care (grade 2C).
Protein S deficiency				
Antepartum: Regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Clinical surveillance (no grade).	Antepartum: Advice of a local expert should be sought and antepartum LMWH should be considered (D).	Antepartum: Either clinical surveillance or prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are protein S deficient, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).

Table 3. (continued)

American Society of Hematology (ASH)	Society of Obstetricians and Gynecologists of Canada (SOGC)*,[235]	Royal College of Obstetricians and Gynecologists (RCOG)†,[240]	American College of Obstetricians and Gynecologists (ACOG)‡,[239]	American College of Chest Physicians (ACCP)§,[237]
Postpartum: For women without a family history of VTE, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects). For women with a family history of VTE, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Postpartum: Clinical surveillance or prophylaxis if in combination with any 2 of the following risk factors (each with an absolute risk of VTE <1% in isolation): BMI ≥30 kg/m^2 at first antepartum visit (II-2B), smoking >10 cigarettes per day antepartum (II-2B), preeclampsia (II-2B), intrauterine growth restriction (II-2B), placenta previa (II-2B), emergency cesarean section (II-2B), peripartum or postpartum blood loss of >1 L or need for blood product replacement (II-2B), preterm delivery (III-B), stillbirth (III-B), or maternal disease (cardiac disease, systemic lupus erythematosus, sickle cell disease, inflammatory disease, varicose veins, gestational diabetes) (III-B). If prescribed, prophylaxis should be given for 6 weeks postpartum (II-3B).	Postpartum: Recommend LMWH for 6 weeks postpartum (D).	Postpartum: Either clinical surveillance or anticoagulation if there are additional risk factors (first-degree relative with thrombotic episode before age 50 years or other major thrombotic risk factor [eg, obesity, prolonged immobility]) (no grade).	Postpartum: For pregnant women who are protein S deficient, suggest postpartum clinical surveillance if there is no family history and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH for 6 weeks rather than routine care if there is a family history of VTE (grade 2C).
Compound heterozygosity				
Antepartum: Regardless of family history, the ASH guideline panel *suggests* antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Prophylactic LMWH (IIIB).	Antepartum: Advice of a local expert should be sought and antepartum LMWH should be considered (D).	Antepartum: Prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are compound heterozygotes, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).
Postpartum: Regardless of family history of VTE, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Postpartum: Prophylactic LMWH (II-2B). Prophylaxis should be given for 6 weeks postpartum (II-3B).	Postpartum: Recommend LMWH for 6 weeks postpartum (D).	Postpartum: Anticoagulation (no grade).	Postpartum: For pregnant women who are compound heterozygotes, suggest postpartum clinical surveillance if there is no family history and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH, or vitamin K antagonists targeted at an INR of 2.0 to 3.0 for 6 weeks rather than routine care of a family history of VTE (grade 2C).
Homozygosity for factor V Leiden or prothrombin gene mutation				
Antepartum: For women who are homozygous for the factor V Leiden mutation, regardless of family history, the ASH guideline panel *suggests* antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects). For women homozygous for the prothrombin gene mutation who have no family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects). The ASH guideline panel was unable to make an evidence-based recommendation for women homozygous for the prothrombin gene mutation with a family history of VTE; however, panel members generally favored prophylaxis.	Antepartum: Prophylactic LMWH (II-2A for factor V Leiden; IIIB for prothrombin gene mutation).	Antepartum: Advice of a local expert should be sought, and antepartum LMWH should be considered (D).	Antepartum: Prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are homozygous for factor V Leiden or the prothrombin gene mutation and have no family history of VTE, suggest antepartum clinical vigilance (grade 2B). In the presence of a positive family history of VTE, suggest antepartum prophylactic- or intermediate-dose LMWH (grade 2B).
Postpartum: For women who are homozygous for the factor V Leiden mutation or for the prothrombin gene mutation, regardless of family history of VTE, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects)	Postpartum: Prophylactic LMWH (II-2B). Prophylaxis should be given for 6 weeks postpartum (II-3B).	Postpartum: Recommend LMWH for 6 weeks postpartum (D).	Postpartum: Anticoagulation (no grade).	Postpartum: For pregnant women who are homozygous for either factor V Leiden or the prothrombin gene mutation, suggest postpartum prophylaxis with prophylactic- or intermediate-dose LMWH, or vitamin K antagonists targeted at an INR of 2.0 to 3.0 for 6 weeks rather than routine care (regardless of family history) (grade 2B).

Table 3. (continued)

American Society of Hematology (ASH)	Society of Obstetricians and Gynecologists of Canada (SOGC)*,[235]	Royal College of Obstetricians and Gynecologists (RCOG)†,[240]	American College of Obstetricians and Gynecologists (ACOG)‡,[239]	American College of Chest Physicians (ACCP)§,[237]
Antithrombin deficiency				
Antepartum: For women who have no family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects). For women who have a family history of VTE, the ASH guideline panel *suggests* antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Prophylactic LMWH (IIIB).	Antepartum: These women require specialist management by experts in hemostasis, and pregnancy antepartum prophylaxis should be provided from at least 28 weeks; if additional risk factors with a weighted score of at least 1‖ are present, then prophylaxis should be provided from the first trimester (D).	Antepartum: Prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are antithrombin deficient, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).
Postpartum: For women without a family history of VTE, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects) For women with a family history of VTE, the ASH guideline panel *recommends* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (strong recommendation, moderate certainty in evidence about effects).	Postpartum: Prophylactic LMWH (II-2B). Prophylaxis should be given for 6 weeks postpartum (II-3B).	Postpartum: Recommend LMWH for at least 6 weeks after delivery (D).	Postpartum: Anticoagulation (no grade).	Postpartum: For pregnant women who are antithrombin deficient, suggest postpartum clinical surveillance if there is no family history of VTE and postpartum prophylaxis with prophylactic-or intermediate-dose LMWH or vitamin K antagonists targeted at an INR of 2.0 to 3.0 for 6 weeks rather than routine care if there is a family history of VTE (grade 2C).

BMI, body mass index; INR, international normalized ratio.

*SOGC quality of evidence assessment.

I: Evidence obtained from at least 1 properly randomized controlled trial.

II-1: Evidence from well-designed controlled trials without randomization.

II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than 1 center or research group.

II-3: Evidence obtained from comparisons between times or places with or without the intervention.

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Recommendation grading.

A: There is good evidence to recommend the clinical preventative action.

B: There is fair evidence to recommend the clinical preventative action.

C: The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventative action; however, other factors may influence decision making.

D: There is fair evidence to recommend against the clinical preventative action.

E: There is good evidence to recommend against the clinical preventative action.

L: There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making.

†RCOG recommendation grading.

A: At least 1 meta-analysis, systematic review, or randomized controlled trial rated as 1++ (well conducted with a very low risk of bias) directly applicable to the target population, or a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+ (well-conducted meta-analysis, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias) directly applicable to the target population and demonstrating overall consistency of results.

B: A body of evidence including studies rated as 2++ (high-quality systematic reviews of case-control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding bias or chance and high probability that the relationship is causal) directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1++ (well conducted with a very low risk of bias) or 1+ (well-conducted meta-analysis, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias).

C: A body of evidence including studies rated as 2+ (well-conducted case-control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship is causal) directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 2++ (high-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding bias or chance and high probability that the relationship is causal).

D: Evidence is level 3 (nonanalytical studies [eg, case reports or case series]) or 4 (expert opinion), or extrapolated evidence from studies rated as 2+ (well-conducted case-control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship is causal).

‡ACOG recommendation grading.

Level A: based on good and consistent scientific evidence.

Level B: based on limited or inconsistent scientific evidence.

Level C: based primarily on consensus and expert opinion.

§ACCP recommendation grading.

1A: Strong recommendation, high-quality evidence.

1B: Strong recommendation, moderate-quality evidence.

1C: Strong recommendation, low- or very-low-quality evidence.

2A: Weak recommendation, high-quality evidence.

2B: Weak recommendation, moderate-quality evidence.

2C: Weak recommendation, low- or very-low-quality evidence.

‖Risk factor weighting.

+1 (for each risk factor): immobility and/or dehydration; current systemic infection, preeclampsia in current pregnancy, assisted reproduction (antepartum only), multiple pregnancy, elective cesarean delivery, midcavity or rotational operative delivery, prolonged labor (>24 h), postpartum hemorrhage (>1 L or transfusion), preterm birth <37 weeks in current pregnancy, gross varicose veins, smoker, parity ≥3, obesity with BMI ≥30, age >35 years, family history of unprovoked or estrogen-related VTE in first-degree relative.

+2 (for each risk factor): cesarean delivery in labor, obesity with BMI ≥40.

+3 (for each risk factor): hyperemesis, any surgical procedure except immediate repair of the perineum, medical comorbidity (eg, cancer, heart failure, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease, nephrotic syndrome, type I diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug use.

+4 (for each risk factor): ovarian hyperstimulation syndrome (first trimester only).

cross the placenta and have the potential to cause teratogenicity, pregnancy loss, fetal bleeding, and neurodevelopmental deficits.[40-44] Similarly, the oral direct thrombin and FXa inhibitors (ie, dabigatran, apixaban, edoxaban, and rivaroxaban) are likely to cross the placenta, and their reproductive toxicity in humans is unknown.[45-48]

Conclusions and research needs for these recommendations. The guideline panel determined that there is a very low certainty in evidence for a net health benefit from using antepartum prophylaxis for the prevention of VTE in women with inherited thrombophilias. However, based on the available evidence in this population and extrapolating from other populations, the panel's VTE risk threshold, and other EtD criteria, it is likely that prophylactic anticoagulation reduces the risk of developing antepartum VTE with a low risk of harm and likely benefits those at higher risk of VTE.

The panel identified the following additional research needs: more data are required on patient values and preferences in this setting. Studies examining the risks and benefits of antepartum prophylaxis in women with thrombophilia and a family history of VTE are needed.

Question 15: Should postpartum anticoagulant prophylaxis vs no postpartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?

Recommendation 22

For women without a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 23

For women with a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation, the ASH guideline panel *suggests against* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 24

For women with a family history of VTE who have antithrombin deficiency, the ASH guideline panel *recommends* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (strong recommendation, moderate certainty in evidence about effects ⊕⊕⊕◯).

Recommendation 25

For women with a family history of VTE who have protein C or protein S deficiency, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 26

For women with combined thrombophilias or who are homozygous for the factor V Leiden mutation or prothrombin gene mutation, regardless of family history, the ASH guideline panel *suggests* postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We used 1 narrative review,[2] 1 systematic review and meta-analysis,[1] and 2 additional studies that used health claims data[14,147] to identify a baseline risk of postpartum VTE in the general population. Three systematic reviews that used case-control studies to examine the risk of pregnancy-related VTE in women with hereditary thrombophilias were retrieved,[148-150] along with a subsequently published case-control study.[151] Information from these studies was used to provide RRs of VTE in affected women without a positive family history, whereas data from the systematic review mentioned above[1] provided the baseline risk of postpartum VTE in the general population. This allowed modeling of the data to best approximate absolute effects in those with a thrombophilia but no family history of VTE.

Data from 13 family cohort studies that excluded probands from their analysis did not include superficial thrombophlebitis in their outcome measure and used acceptable criteria for the diagnosis of a first venous thromboembolic event (objective confirmation or treatment with anticoagulant therapy for at least 2 to 3 months) were used to provide absolute risk estimates in thrombophilic women with a family history of VTE.[152-164] When possible, data for women who did not receive prophylaxis were extracted from these studies; otherwise, the data as presented were used. Data from 1 otherwise well-conducted family study were not used because pregnancy risk periods by individual thrombophilia could not be reliably extracted.[165] When events were not presented separately for the antepartum and postpartum periods, they were presumed to occur in equal proportion in each period (with any extra events being assigned to the antepartum period). Data were pooled using a random effects model with Freeman-Tukey double arcsine transformation.[166] The results of a study that included only 1 woman with protein C deficiency[157] were excluded from pooling.

No randomized trials comparing prophylaxis to no prophylaxis or different types or intensities of postpartum anticoagulation in this patient population were identified. A pooled analysis of 4 trials that provided information on the risk of VTE in women with predominantly low-risk thrombophilias (heterozygosity for the factor V Leiden and prothrombin gene mutation) who received postpartum LMWH was retrieved,[142] along with a cohort study and subsequent systematic review examining the risk of VTE in women heterozygous for the factor V Leiden mutation and prothrombin mutation with an unspecified family history who did and did not receive postpartum thrombosis prophylaxis.[168] Data from an individual patient data meta-analysis of randomized trials examining prophylactic LMWH (with or without aspirin) in women with a history of placenta-mediated pregnancy complications[59] and from a small cohort study in which women with predominantly low-risk thrombophilias all received 40 mg of enoxaparin for 42 days postpartum[167] were used to provide safety information about prophylactic dose LMWH. The EtD framework is shown online at: https://dbep.gradepro.org/profile/B630AD49-0B51-4541-BA13-479F6E89F061.

Benefits. Thrombophilic women have a higher risk of postpartum VTE than that reported for the general population (approximately 0.6 of every 1000 deliveries),[1,2,14,147] although the magnitude of the risk increase depends on the type of thrombophilia and the presence or absence of a family history of VTE.[142,148-164,168] The risk seems to be low (<1%) in those with no family history of VTE who are heterozygous for the factor V Leiden or prothrombin gene mutations and in those who have antithrombin, protein C, or protein S deficiency.[142,148-150,168] In women with a thrombophilia and family history of VTE, the risks of postpartum VTE were higher, although our meta-analysis suggested that in women heterozygous for the factor V Leiden mutation or prothrombin gene mutation, the postpartum risk of VTE was still <1% for those heterozygous for factor V Leiden (0.62%; 95% CI, 0%-1.90%)[154,159,161-163] or the prothrombin mutation (0.95%; 95% CI, 0-3.26).[152,153] The risk was 4.83% (95% CI, 0%-15.65%) in those with antithrombin deficiency,[155-157,164] 1.76% (95% CI, 0%-5.99%) in those with protein S deficiency,[155-157] and 1.06% (95% CI, 0%-4.09%) in those with protein C deficiency.[155-157] Limited data from case-control studies (no family history of VTE) suggest a postpartum risk of VTE of ~2% (but with broad 95% CIs) in those homozygous for the factor V Leiden or prothrombin gene mutation[149] and ~3% in those with combined thrombophilias.[151] Our meta-analysis of family studies suggests a postpartum risk of 5.87% (95% CI, 0.47%-14.4%) in women homozygous for the factor V Leiden mutation.[158,160,163] The pooled risk from family studies was 3.99% (95% CI, 0.10%-11.12%) in those with combined thrombophilias.[158,163] We found no data from family studies for women homozygous for the prothrombin gene mutation.

In the absence of randomized studies examining the efficacy of postpartum thrombosis prophylaxis in this population, we are left to assume that the risk reduction with prophylaxis would be ~75%, as reported in other settings, including extended LMWH prophylaxis after high-risk orthopedic procedures.[145] Overall, the certainty of these benefits is low because of the lack of randomized studies and imprecision of the risk estimates.

Harms and burden. The risks of major peripartum and postpartum bleeding with LMWH prophylaxis were similar to those in women not receiving prophylaxis (10 [2.5%] of 404 and 12 [3.0%] of 395, respectively, for major peripartum hemorrhage [RR, 0.82; 95% CI, 0.36-1.86; 5 fewer per 1000, from 19 fewer to 26 more][59] and 2 [0.3%] of 767 and 0 [0.0%] of 108, respectively, for postpartum prophylaxis).[142] A higher risk, 3.6%, was reported in a cohort study of women with various thrombophilias who received 42 days of postpartum LMWH prophylaxis.[167] There were no reported cases of heparin-induced thrombocytopenia in this cohort study.[167] The panel considered the burden of postpartum prophylaxis to be substantially less than that of antepartum prophylaxis. Given the limited data and the fact that most of what is available is derived from studies examining LMWH prophylaxis for a different indication, there is low certainty in the estimate of the risk of adverse effects postpartum anticoagulant prophylaxis; however, the guideline panel considered it most likely to be small. Considerations regarding the safety of prophylactic anticoagulants while breastfeeding are addressed in Recommendations 12 and 13.

Other EtD criteria and considerations. Panel members were anonymously polled to select a risk threshold for recommending postpartum LMWH prophylaxis. Responses ranged from 1% to 3%; however, the majority of respondents selected a 1% VTE risk threshold for recommending LMWH prophylaxis. Our guideline recommendations are summarized in Table 3.

In the absence of any relevant data, the panel was unable to make an evidence-based recommendation regarding postpartum prophylaxis in women homozygous for the prothrombin gene mutation with a family history of VTE; however, given that the risk estimates for those with this thrombophilia and no family history of VTE exceed our risk threshold, VTE risks in those with a positive family history of VTE are unlikely to be lower and very likely to be higher, and corresponding data for those homozygous for the factor V Leiden mutation show risks that exceed our threshold; thus, panel members suggested postpartum prophylaxis.

It was noted that the need for prophylaxis should be considered within the totality of the patient risk profile. Patients not requiring prophylaxis solely on the basis of their thrombophilia status might benefit from LMWH prophylaxis in the setting of additional risk factors. For patients with deficiencies of 1 of the natural anticoagulants, the severity of the deficiency might also be considered when decisions about prophylaxis are being made.

Studies examining the efficacy and safety of postpartum prophylaxis used different anticoagulant drugs and intensity of prophylaxis. Some have noted failures of standard-dose LMWH. However, in the absence of direct comparisons of different dosing strategies, an evidence-based recommendation for a preferred prophylactic regimen is not possible.

Conclusions and research needs for these recommendations. The guideline panel determined that there is a very low to low certainty in evidence for a net health benefit from using postpartum prophylaxis for the prevention of VTE in women with inherited thrombophilias. However, on the basis of the available evidence in this population and extrapolating from other populations, the panel's VTE risk threshold, and other EtD criteria, it is likely that prophylactic anticoagulation reduces the risk of developing postpartum VTE with a low risk of harm, and these benefits are further accentuated in those at highest risk of VTE.

The panel identified the following additional research needs: more data are required regarding patient values and preferences in this setting. Studies examining the risks and benefits of postpartum prophylaxis in women with thrombophilia are needed.

Question 16: Should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used for pregnant women with clinical risk factors for VTE?

Recommendation 27

For women with no or 1 clinical risk factor (excluding a known thrombophilia or history of VTE), the ASH guideline panel *suggests against* antepartum or postpartum prophylaxis (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. One narrative review,[2] 1 systematic review and meta-analysis,[1] and 2 additional studies that used health claims data[14,147] provided baseline risks of antepartum and postpartum VTE in the general population. One systematic review that examined the risk of VTE with cesarean delivery,[169] as well as 5 cohort studies[170-174] and 17 case-control studies[61,175-190] that evaluated the impact of other clinical risk factors (eg, increased body mass index, immobilization, medical

comorbidities, and placental-mediated pregnancy complications) were retrieved. A meta-analysis of individual patient data from randomized trials of prophylactic LMWH (with or without aspirin) in women with a history of placenta-mediated pregnancy complications,[59] a pooled analysis exploring the safety and efficacy of prophylactic LMWH,[142] 3 randomized trials,[56,57,167] and 2 observational studies[35,99] that provided additional information on the safety of prophylactic dose LMWH in this setting were identified.

A meta-analysis[191] of 4 randomized trials in women undergoing cesarean delivery[192-195] as well as a subsequently published small randomized trial in this patient population[196] and a retrospective cohort study[98] provided data on the safety and efficacy of anticoagulants in these women.

We retrieved a study that described the performance of a risk prediction model developed through multivariable logistic regression analysis using data from 433 353 deliveries recorded in the England-based Clinical Practice Research Datalink.[197] There were 4 cohort studies that evaluated risk scoring systems that incorporated clinical risk factors (in addition to or other than history of VTE or thrombophilia status).[198,199] Two randomized trials were identified. Both were feasibility pilot studies that enrolled postpartum women judged to be at increased risk of VTE. In the first study, participants received 21 days of either prophylactic dose LMWH or saline placebo injections,[200] whereas in the second study, patients were randomly assigned to receive either prophylactic LMWH for 10 days or no treatment.[201] The EtD framework is shown online at:https://dbep.gradepro.org/profile/52F7A6C0-0C27-03B9-AFF8-52D5C099FED8.

Benefits. Clinical risk factors increase the risk of antepartum and postpartum VTE above the general population risk (~0.6 per 1000 deliveries in the each of the antepartum and postpartum time periods).[1,2,14,147] The magnitude of the risk increase depends on the nature of and number of risk factors.[61,169-195,197] Most clinical factors have only a modest effect on risk, with few increasing the absolute risk to >1%. How combinations of risk factors affect venous thromboembolic risk has not been well studied; for most risk factors, it is unclear whether risks are additive or multiplicative.

Data on the impact of prophylaxis on VTE risk in pregnant or postpartum women with additional clinical risk factors are very limited. In a meta-analysis of 4 randomized trials in which women undergoing cesarean delivery were randomly assigned to heparin (UFH or LMWH) or placebo, prophylaxis did not reduce the risk of VTE (1.2% vs 0.9%, respectively; RR, 1.30; 95% CI, 0.39-4.27; 3 more per 1000, from 6 fewer to 30 more); however, these conclusions are limited by imprecision (small patient numbers).[191] A prediction model for calculation of venous thromboembolic risk in postpartum women developed by using clinical databases in the United Kingdom and validated with Swedish data seemed to have good performance characteristics (C statistic, 0.73; 95% CI, 0.71-0.75).[197] The impact of prospectively applying this model has not been assessed. Risks of VTE were low in 4 cohort studies in which women received thromboprophylaxis based on scoring systems that incorporated clinical risk factors in addition to or other than thrombophilia or prior VTE history.[198,199,202,203] However, in the absence of a comparator arm, the impact of this type of intervention is difficult to assess. Two pilot feasibility studies that randomly assigned women judged to be at increased risk of VTE on the basis of the presence of a known low-risk thrombophilia or antepartum immobilization or 2 other clinical risk factors (postpartum hemorrhage, postpartum infection, prepregnancy body mass index of >25 kg/m^2, emergency cesarean birth, smoking >5 cigarettes per day before becoming pregnant, preeclampsia, or infant birth weight below the third percentile) to either prophylactic LMWH or placebo or no intervention for 21 or 10 days postpartum did not demonstrate a benefit from prophylaxis but were very underpowered to detect important differences.[200,201]

Overall, the certainty of any benefit with provision of prophylaxis to antepartum or postpartum women with clinical risk factors is low or very low because of the lack of appropriate randomized studies and imprecision of the risk estimates.

Harms and burden. Three of 4 randomized studies in the above-mentioned meta-analysis of women undergoing cesarean delivery reported on adverse events. In these studies, there was no increase in the need for transfusion (0.8% with prophylaxis vs 2.3% without prophylaxis; RR, 0.24; 95% CI, 0.03-2.13; 17 fewer per 1000, from 22 fewer to 25 more) or incidence of serious wound complications (0.8% vs 0.8%, respectively; RR,1.03; 95% CI, 0.07-16.13; 0 fewer per 1000, from 7 fewer to 114 more) with prophylaxis.[191] A single-center retrospective study of women undergoing cesarean delivery also showed no increase in risk-estimated mean blood loss or need for transfusion in those receiving anticoagulation; however, there was a greater incidence of wound complications in women receiving prophylaxis (29.9% vs 7.8%; OR, 4.22; 95% CI, 1.60-12.80; 185 more per 1000, from 41 more to 442 more).[98]

There are limited data on the risk of bleeding in pregnant women with other clinical risk factors who receive prophylactic LMWH. However, LMWH prophylaxis was not associated with an increased risk of major antepartum hemorrhage (0.2% with LMWH and 0.6% without LMWH (RR, 0.36; 95% CI, 0.04-3.21; 4 fewer per 1000, from 6 fewer to 14 more) or peripartum hemorrhage (2.5% with LMWH and 3.0% with no LMWH; RR, 0.81; 95% CI, 0.36-1.86; 6 fewer per 1000, from 20 fewer to 26 more) in an individual patient data meta-analysis of trials examining LMWH with or without aspirin for the prevention of placenta-mediated pregnancy complications.[59]

In the first of 2 small randomized pilot feasibility studies described above, postpartum prophylaxis was not associated with an increased risk of major bleeding in patients randomly assigned to dalteparin 5000 units subcutaneously for 21 days vs saline placebo injections (RR, 0.80; 95% CI, 0.02-37.55).[200] In a follow-up study in which patients received dalteparin 5000 units subcutaneously per day for 10 days postpartum or no treatment, major bleeding occurred in 1 (6.3%) of 16 and 0 (0%) of 21 of patients, respectively (RR, 3.53; 95% CI, 0.15-81.11).[201] In a pooled analysis of studies in which women received postpartum prophylaxis as part of either a randomized comparison or a cohort, postpartum bleeding occurred in 2 (0.3%) of 767 of those receiving LMWH prophylaxis vs 0 (0%) of 108 of those not receiving prophylaxis.[142]

The likelihood of developing osteopenia (bone mineral density measured 6 weeks postpartum was 2.16 g/cm^2 [standard deviation, 0.35 g/cm^2] with prophylactic LMWH and 2.23 g/cm^2 [standard deviation, 0.42 g/cm^2] without LMWH prophylaxis [mean difference, 0.07 cm^2; 95% CI, −0.02 to 1.6]) or osteoporotic fractures (0% with and without LMWH prophylaxis) was not

increased in women receiving antepartum prophylaxis for prevention of thrombophilia-associated pregnancy complications.[57] In 1 small randomized trial, bone mineral density measured after delivery was lower in those who had received antepartum UFH prophylaxis than in those receiving LMWH prophylaxis and in a group of untreated controls (repeated measures ANOVA $P = .02$).[56] In a meta-analysis of individual patient data for women with a history of placenta-mediated pregnancy complications, thrombocytopenia was not more common with LMWH prophylaxis than without (3.0% vs 1.3%; RR, 2.32; 95% CI, 0.90-5.98; 17 more per 1000, from 1 fewer to 64 more) and there were no reported cases of heparin-induced thrombocytopenia in either group.[59] The requirement for daily injections throughout the duration of pregnancy or postpartum and costs of this intervention may pose a significant burden.

Given the limited data, there is low certainty in the estimate of the risk of adverse effects associated with antepartum or postpartum anticoagulant prophylaxis, although the guideline panel considered it most likely to be small.

Other EtD criteria and considerations. The panel did not consider fondaparinux for first-line prophylaxis of VTE in pregnancy because this drug has been reported to cross the placenta in small amounts and experience with fondaparinux in pregnancy is very limited (especially during the first trimester).[38,39] Vitamin K antagonists were not considered acceptable for prevention of pregnancy-associated VTE because it is known that these drugs cross the placenta and have the potential to cause teratogenicity, pregnancy loss, fetal bleeding, and neurodevelopmental deficits.[40-44] Similarly, the oral direct thrombin and FXa inhibitors (ie, dabigatran, apixaban, edoxaban, and rivaroxaban) are able to cross the placenta and have the potential to cause reproductive toxicity.[45-49] Considerations regarding the safety of prophylactic anticoagulants while breastfeeding are addressed in Recommendations 12 and 13.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty in evidence for a net health benefit from using prophylaxis for the prevention of VTE in women with clinical risk factors (excluding a known thrombophilia or history of VTE). However, on the basis of the available evidence in this population and extrapolating from other populations as well as other EtD criteria, it is likely that the potential burdens and harms from prophylactic anticoagulation exceed potential health benefits in those with no or only 1 clinical risk factor for VTE.

The panel identified the following additional research needs: more data should be gathered on the absolute risk of VTE with combinations of risk factors. Information on the impact of applying risk scoring systems and predictive models with respect to thrombosis prevention and bleeding risks as assessed by randomized trials would be helpful.

Question 17: Should intermediate-dose LMWH prophylaxis vs standard-dose LMWH prophylaxis be used for preventing first or recurrent VTE in pregnant women?

Recommendation 28

In pregnant women who require prophylaxis, the ASH guideline panel *suggests against* intermediate-dose LMWH prophylaxis compared with standard-dose LMWH prophylaxis during the antepartum period (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Recommendation 29

For women who require prophylaxis, the ASH Guideline panel *suggests* either standard- or intermediate-dose LMWH prophylaxis during the postpartum period (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Summary of the evidence. We found only 1 small randomized trial that directly compared different LMWH prophylaxis dosing regimens in this patient population. In that study, 84 women after cesarean delivery who had a body mass index of at least 35 kg/m^2 were randomly assigned to standard (enoxaparin 40 mg subcutaneously once per day) or weight-based (enoxaparin 0.5 mg/kg subcutaneously twice per day) prophylactic dosing.[204] There were 2 randomized trials that compared standard-dose LMWH prophylaxis to placebo after cesarean delivery,[192,195] a pilot trial that reported on outcomes in women with a history of VTE randomly assigned to antepartum standard-dose LMWH or placebo,[192] and a multicenter study that randomly assigned women with thrombophilia at increased risk of VTE or with previous placenta-mediated pregnancy complications to initial standard-dose LMWH prophylaxis, increasing to an intermediate dose at 20 weeks of gestation, or no prophylaxis.[57] Several observational studies that reported on the incidence of VTE and bleeding in women receiving standard- and intermediate-dose prophylaxis were retrieved, including 1 prospective study that used Swedish registry data to evaluate the efficacy of LMWH thromboprophylaxis in women with a history of VTE, most of whom received standard dose prophylaxis[111]; 2 retrospective cohort studies that reported on the outcomes in women at increased risk of VTE who received standard-dose LMWH prophylaxis[146,205]; 1 cohort study that described outcomes in women who received standard- or intermediate-dose prophylaxis based on a VTE risk assessment score[206]; 1 single-center study that described the incidence of treatment complications in pregnant women receiving initial therapeutic- followed by intermediate-dose LMWH and prophylactic-dose LMWH,[207] 2 single-center observational studies that described bleeding outcomes around the time of delivery in women receiving therapeutic doses of LMWH,[96,97] 1 study using international registry data that described safety outcomes in women receiving prophylactic and therapeutic doses of LMWH,[99] and an observational cohort study that focused on bone mineral density and risk of osteoporotic fracture after prolonged prophylactic or therapeutic dose LMWH exposure during pregnancy.[35] The EtD framework is shown online at: https://dbep.gradepro.org/profile/D6ED324B-12B2-8D29-8873-2B41E8473024.

Benefits. There were no venous thromboembolic events in either group in the randomized trial that compared 2 enoxaparin dosing strategies after cesarean delivery in women with a body mass index of at least 35 kg/m^2.[204] The incidence of first or recurrent VTE in randomized trials or observational studies in which women received standard prophylactic-dose LMWH ranged from 0% to 8.8%.[111,146,192,195,205,206] In the multicenter study that randomly assigned women with thrombophilia at increased risk of VTE or with previous placenta-mediated pregnancy complications to initial standard-dose LMWH prophylaxis with dose escalation at 20 weeks, 1 symptomatic venous thromboembolic event occurred

Table 4. Identified research priorities

Treatment of acute VTE
More data are required regarding the safety of fondaparinux and direct oral anticoagulants during pregnancy.
Further evidence should be sought regarding the risks, benefits, and acceptability of once-per-day vs twice-per-day LMWH dosing for treatment of acute VTE, specifically in the pregnant patient population.
Investigations should be performed to determine whether there is any benefit to twice-per-day dosing of LMWH for the treatment of VTE in the acute (ie, first month) setting, followed by de-escalation to once-per-day dosing for the remainder of the treatment period.
Larger and higher-quality studies that examine the role of anti-FXa monitoring in pregnant women receiving LMWH for treatment of acute VTE are required to obtain more precise estimates of effect.
Studies should be performed that evaluate the role of anti-FXa–level monitoring in the acute VTE treatment period followed by a standard weight-based dosing approach.
Studies should be performed that will provide pregnancy-specific data for stratifying risk for complications associated with treatment of VTE, and clinical prediction rules should be developed to identify pregnant patients who require hospital admission for initial management of DVT and pulmonary embolism.
Studies should be undertaken to examine the rates of hospital admission after outpatient VTE therapy has been initiated in pregnant patients.
More information is required from high-quality research on the safety and efficacy of catheter-directed thrombolysis in the pregnant population, including in those with limb-threatening DVT.
More data are required regarding patient values and preferences for the potential benefits and drawbacks of this catheter-directed thrombolysis for treatment of DVT in the pregnant population.
More data would be useful on estimated fetal radiation exposure and associated potential harms of catheter-directed thrombolysis for treatment of DVT during pregnancy.
More information is required from high-quality direct studies on the safety and efficacy of thrombolysis for pulmonary embolism in the pregnant population, including in those with submassive pulmonary embolism and right ventricular dysfunction alone.
More data are required on patient values and preferences for potential benefits and drawbacks of thrombolysis for pulmonary embolism during pregnancy.
Treatment of acute superficial vein thrombosis
More data are required regarding the dose and duration of LMWH if it is used in this context.
Management of anticoagulant therapy around the time of delivery
More outcome data would be helpful in examining different anticoagulant regimens at the time of delivery, including transitioning to intravenous UFH.
Data should be obtained that examines other critical outcomes for pregnant women with therapeutic anticoagulation interruption or prophylactic anticoagulation interruption around the time of delivery (including access to epidural analgesia and frequency of epidural hematomas, cesarean delivery, and maternal and neonatal morbidity and mortality).
Anticoagulant use in breastfeeding women
More data are required regarding the safety of the direct-acting oral anticoagulants in this population.
Prevention of VTE
More data are required regarding the baseline risk of VTE with assisted reproductive technology in specific patient populations, including those with prior VTE, thrombophilia, and other risk factors for VTE.
More data are required regarding the potential benefits and risks of antithrombotic therapy in reducing the risk of VTE and improving implantation outcomes in women using assisted reproductive technologies.
More data are required regarding optimal intensity of LMWH prophylaxis for the prevention of recurrent VTE during the antepartum and postpartum periods. The panel noted that the ongoing HIGHLOW study (Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy; NCT 01828697) would provide valuable information once completed.
Further investigations should be performed to determine whether there are specific patient subgroups most likely to benefit from higher-dose prophylaxis.
Additional information would be helpful on the impact of thrombophilia status and precipitating risk factors with prior venous thromboembolic events on the risk of antepartum recurrent VTE.
More information should be gathered regarding optimal duration of postpartum prophylaxis.
Investigators should explore whether certain subgroups of patients with prior VTE are more likely to derive benefit from postpartum prophylaxis.
More data are required on patient values and preferences for antepartum and postpartum prophylaxis in women with thrombophilia.
Studies are needed examining the risks and benefits of antepartum and postpartum prophylaxis in women with thrombophilia.
More data should be gathered on the absolute risk of VTE with combinations of clinical risk factors.
Information would be helpful on the impact of applying clinical risk scoring systems and predictive models with respect to thrombosis prevention and bleeding risks as assessed by randomized trials.
Diagnosis of VTE
The role of D-dimer testing and clinical prediction rules in limiting the need for radiologic tests in pregnant women with suspected pulmonary embolism and suspected DVT needs to be evaluated in well-designed management studies.
More data are required on the safety of excluding DVT in pregnant women on the basis of a negative initial whole-leg compression ultrasound with imaging of the iliac veins.

during antepartum prophylaxis (1 of 146; 0.7%; 95% CI, 0.04%-4.3%).[57] That event occurred at 11 weeks during standard prophylaxis in 1 of the 21 women with a history of VTE randomly assigned to prophylaxis (4.8%; 95% CI, 0.3%-25.9%). There were no episodes of VTE during the intermediate-dosing phase of the study. In an observational study in which prophylaxis dosing was based on a risk stratification score, 2 of 116 (1.7%; 95% CI, 3.0% to 6.7%) women judged to be at high risk for VTE and managed with 100 to 200 units/kg/day of dalteparin from enrollment to 6 weeks postpartum suffered a venous thromboembolic event.[206] The available limited data, therefore, do not support a benefit of higher-than-standard-dose prophylaxis in terms of thrombosis prevention.

Harms and burden. There were no differences in the incidence of major bleeding or wound hematoma between the 2 patient groups in the randomized trial that compared 2 enoxaparin dosing strategies after cesarean delivery in women with a body mass index of at least 35 kg/m^2.[204] Although the risk of major antepartum bleeding was not increased in women with thrombophilia randomly assigned to standard-dose followed by intermediate-dose LMWH prophylaxis compared with those allocated to no prophylaxis (3 [2.1%] of 143 vs 2 [1.4%] of 141; RR, 1.48; 95% CI, 0.25-8.72; 7 more per 1000, from 11 fewer to 110 more), the risk of minor antepartum bleeding was higher (28 [19.6%] of 143 vs 13 [9.2%] of 141; RR, 2.12; 95% CI, 1.15-3.93).[57] One single-center observational study reported no episodes of major antepartum bleeding in 89 women receiving initial therapeutic followed by intermediate-dose LMWH or in 101 women receiving standard-dose prophylaxis.[207] The risks of minor or minimal bleeding were similar in the 2 groups of patients (6 [6.7%] of 89 and 3 [3.0%] of 101; RR, 2.27; 95% CI, 0.59-8.81). No data were available on the risks of bleeding around the time of delivery in women receiving intermediate-dose LMWH; however, in 2 small single-center observational studies, the overall risks of postpartum hemorrhage (>500 mL) and severe postpartum hemorrhage (>1000 mL) did not seem to be increased in women receiving antepartum therapeutic-dose LMWH compared with controls.[96,97] A subgroup analysis in 1 study did suggest an increased risk of postpartum hemorrhage after vaginal delivery (29.5% in those receiving therapeutic-dose LMWH and 17.8% in controls; OR, 1.9; 95% CI, 1.1-3.5) or emergency cesarean delivery (22.2% in those receiving therapeutic-dose LMWH and 2.8% in controls; OR, 11.3; 95% CI, 1.0-145.5).[96] Blood loss at delivery did not seem greater in those receiving treatment doses of LMWH in a retrospective hospital audit at 28 centers in 8 countries that included 265 pregnant women receiving treatment doses of LMWH and 1013 women receiving prophylactic doses.[99]

In an observational cohort study in which bone mineral density was measured by dual-energy X-ray absorptiometry 4 to 7 years after last delivery in 75 women who had received prolonged exposure to prophylactic-dose LMWH during pregnancy and 17 who had received treatment doses of LMWH, multivariate regression analysis performed separately for those with prophylactic-dose LMWH compared with controls and for those with weight-adjusted treatment or intermediate-dose LMWH compared with controls showed that, after adjustment for potential confounding factors, LMWH exposure during pregnancy was not significantly associated with decreased lumbar spine bone mineral density.[35] There were no cases of osteoporotic fracture or heparin-induced thrombocytopenia in 143 thrombophilic women randomly assigned to antepartum initial standard-dose LMWH prophylaxis with dose escalation at 20 weeks of gestation to intermediate-dose LMWH.[57]

Although there may be a higher risk of antepartum bleeding and bleeding around the time of delivery in women receiving higher-dose antepartum LMWH, the certainty of these estimated effects is very low, owing to the lack of direct comparisons, indirectness, and imprecision of the estimates. Overall, there is very low certainty in the estimate of the risk of adverse effects in women receiving intermediate-dose LMWH prophylaxis.

Other EtD criteria and considerations. The guideline panel agreed that for the purposes of this analysis, in the absence of a standard definition, any dose greater than the standard dose of LMWH prophylaxis and less than the therapeutic dose would be considered intermediate. It was acknowledged that conclusions drawn from comparisons between nonrandomized studies of different dosing regimens are limited by possible confounding because of the use of differing strategies to prevent bleeding in women who are receiving higher doses of prophylaxis and by lack of data regarding compliance.

The costs of intermediate-dose LMWH were considered likely to be greater than those of standard-dose prophylaxis. Current anesthetic guidelines from North American and Europe call for at least a 24-hour interval between the last greater-than-prophylactic dose of LMWH and placement of an epidural catheter.[109,110] The required time interval between the last greater-than-prophylactic dose of LMWH and placement of an epidural catheter could limit access to epidural analgesia in women receiving intermediate-dose prophylaxis. The panel noted a lack of direct evidence for making recommendations about groups of women who might benefit most from intermediate-dose LMWH prophylaxis.

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty in evidence, which leads to an unclear net health benefit for using intermediate dosing of LMWH compared with standard dosing. However, because of very low certainty in evidence or no published information about other outcomes, lack of better evidence is not proof that such an effect does not exist and does not allow firm conclusions. There were some concerns about an increased risk of bleeding and reduced access to epidural analgesia with higher-dose antepartum prophylaxis; therefore, the panel agreed that a conditional recommendation in favor of standard prophylactic dosing of LMWH before delivery was warranted. The panel considered that both options would lead to net desirable consequences after delivery, given the increased thrombotic risk during this time period.

The panel identified the following additional research needs: further evidence is required regarding the risks and benefits of intermediate- vs standard-dose LMWH prophylaxis. The panel noted that the ongoing Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy (NCT01828697) trial will provide valuable information when it is completed. Further investigations should be performed to determine whether there are specific patient subgroups most likely to benefit from higher-dose prophylaxis.

Diagnosis of VTE

Question 18: Should V/Q scanning vs other diagnostic tools be used for diagnosis of pulmonary embolism in pregnant women with suspected pulmonary embolism?

Recommendation 30

In pregnant women with suspected pulmonary embolism, the ASH guideline panel *suggests* V/Q lung scanning over CT pulmonary angiography (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 2 systematic reviews that examined imaging techniques for suspected pulmonary embolism in pregnancy.[208,209] One review found no studies that examined magnetic resonance angiography in this population and focused on the accuracy of V/Q scanning compared to that of CT pulmonary angiography.[209] There were no true accuracy studies that had comparison with a reference standard. Because all of the studies used clinical follow-up to confirm the absence of pulmonary embolism as established on initial scanning, no conclusions regarding the ability of these 2 tests to establish the diagnosis of pulmonary embolism could be drawn. The second review, published only in abstract form, focused solely on the proportion of nondiagnostic test results with these 2 diagnostic modalities.[208] A randomized trial comparing the performance of V/Q scanning and CT pulmonary angiography in nonpregnant patients suspected of having pulmonary embolism was retrieved.[210] Several studies describing the potential impact of maternal and fetal radiation and contrast exposure were also included.[211-226] The EtD framework is shown online at: https://dbep.gradepro.org/profile/75D4DCB7-7A8E-00D4-9D65-9BE485BE581F.

Benefits. When evaluated in clinical follow-up studies in which anticoagulants were withheld in patients with negative tests, V/Q scanning and CT pulmonary angiography had a low and similar frequency of false-negative results (0.5% [95% CI, 0.2%-1.3%] and 0.4% [95% CI, 0.2%-1.3%], respectively) when used to evaluate suspected pulmonary embolism during pregnancy.[209] For every 1000 women scanned, 5 (95% CI, 2-13) pulmonary emboli would be incorrectly ruled out with V/Q scanning and 4 (95% CI, 2-13) would be incorrectly ruled out with CT pulmonary angiography. In pregnant women, unlike in the nonpregnant population, the number of inconclusive or nondiagnostic scans was not appreciably higher with VQ scanning than with CT pulmonary angiography.[208,209] The randomized trial in the nonpregnant population suggested that the proportion of patients diagnosed with pulmonary embolism at presentation was higher with CT pulmonary angiography than with V/Q scanning; however, in those in whom pulmonary embolism was considered excluded at presentation, the rate of venous thromboembolic events during 3-month follow-up was low and similar with both techniques, suggesting that at least some of the events detected by CT pulmonary angiography at presentation may have been of questionable significance.[210] Overall, the certainty of the estimated effects is low or very low because of risk of bias, indirectness, and imprecision.

Harms and burden. Based on modeling data, V/Q scanning seems safer for the mother than CT pulmonary angiography with respect to breast-absorbed radiation dose and potential risk of future breast cancer.[211,214,217,225] Maternal risks from contrast exposure with CT pulmonary angiography and radiopharmaceutical exposure with V/Q scanning are small.[216,219,223,224] Although the fetal radiation dose may be greater with V/Q scanning than with CT pulmonary angiography (with the difference being dependent on the type of protocol used for both techniques and gestational age with CT pulmonary angiography), typical fetal radiation doses from V/Q scanning and CT pulmonary angiography are far below the suggested accepted maximal cumulative threshold for fetal radiation exposure,[215,220,224,226] and any potential absolute increase in the risk of childhood cancer is likely to be very small, as is the risk for fetal hypothyroidism secondary to contrast-associated iodine exposure with CT pulmonary angiography.[212,213,218,221]

Other EtD criteria and considerations. No good-quality studies with acceptable reference standards assessing the accuracy of CT pulmonary angiography, V/Q scanning, and magnetic resonance imaging for the evaluation of suspected pulmonary embolism in the pregnant population were found. It was noted that V/Q lung scanning is likely not as readily available as CT pulmonary angiography at all centers, and in instances where it is not available, CT pulmonary angiography would be acceptable. In addition, CT pulmonary angiography might be preferred in patients with abnormal chest radiographs.

Conclusions and research needs for this recommendation. The guideline panel determined that given the otherwise similar anticipated desirable health consequences and fetal safety of V/Q scanning and CT pulmonary angiography, the former technique should be favored, if available, given concerns about increased maternal breast cancer risks with CT pulmonary angiography.

The panel identified the following additional research need: the role of D-dimer testing and clinical prediction rules in limiting the need for radiologic tests in pregnant women with suspected pulmonary embolism needs to be evaluated in well-designed management studies.

Question 19: Should no further investigations vs additional investigations (serial compression or duplex ultrasound, magnetic resonance imaging, or venography) be used for diagnosis of DVT in pregnant women with suspected DVT and initial negative compression or duplex ultrasound with imaging of the iliac veins?

Recommendation 31

In pregnant women with suspected DVT, the ASH guideline panel *suggests* additional investigations, including serial compression ultrasound or magnetic resonance venography compared with no further investigations after an initial negative ultrasound with imaging of the iliac veins (conditional recommendation, low certainty in evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 5 cohort studies (3 studies assessing serial proximal ultrasonography with imaging of the iliac veins,[227-229] 1 evaluating a single whole-leg ultrasound [including the calf veins] with iliac vein imaging,[230] and 1 evaluating

serial whole-leg ultrasounds with iliac vein imaging except in those judged to have a high clinical probability of DVT who underwent magnetic resonance venography[231]) and 1 cross-sectional study (comparing proximal ultrasonography with imaging of the pelvic veins and inferior vena cava with magnetic resonance imaging)[232] that addressed this question specifically in pregnant patients. The cohort studies assessing serial proximal ultrasonography seemed to be at least partially overlapping.[227-229] No accuracy studies with comparison with a reference standard in this patient population were identified. Several narrative reviews[215,220,224,233] and 1 large population database study[234] describing potential fetal harms (eg, teratogenicity, increased risk of childhood cancer) associated with various diagnostic imaging studies were also included. The EtD framework is shown online at: https://dbep.gradepro.org/profile/EDF9BCA4-0B5B-1B56-A6BF-CEF85A75328E.

Benefits. In the largest prospective cohort study, proximal ultrasonography with iliac vein imaging and follow-up tests on days 2 to 4 and 6 to 8 in patients with an initial negative result was associated with a low frequency of symptomatic VTE during follow-up (1 of 205 false-negative results [0.5%; 95% CI, 0.2%-2.5%]).[229] In other words, of 1000 women with initial negative serial ultrasounds, only 5 (95% CI, 2-25) would later be found to have a symptomatic DVT during follow-up. Although most deep vein thromboses were diagnosed at presentation (the first ultrasound), up to 24% were detected during serial ultrasound examinations in other cohorts.[227,228] The frequency of subsequent positive ultrasounds after an initial negative result during follow-up in pregnant women undergoing a single whole-leg ultrasound with imaging of the iliac veins was 2 of 145 (1.4%; 95% CI, 0.3%-4.9%).[230] There were limited data to suggest that magnetic resonance imaging of the pelvic veins might detect pelvic thrombosis not imaged with Doppler ultrasonography.[232] Overall, the certainty of the estimated effects is low because of study design and imprecision of overall estimates.

Harms and burden. Typical fetal radiation doses from standard radiologic tests that might be performed in addition to ultrasonography are far below the suggested accepted maximal cumulative threshold for fetal radiation exposure.[215,220,224,233] Tests that could potentially be associated with an increase in the risk of childhood cancer secondary to ionizing radiation (eg, venography and CT venography) are not usually performed in this patient population. Performance of magnetic resonance imaging during the first trimester of pregnancy does not seem to be associated with an increased risk of harm to the fetus; the addition of gadolinium at any time during pregnancy may be associated with a small absolute increase in adverse fetal and neonatal outcomes.[234]

Other EtD criteria and considerations. No good-quality studies with acceptable reference standards that assess the accuracy of magnetic resonance imaging vs ultrasonographic imaging of the pelvic veins were found. No data were available to allow risk stratification of patients most likely to benefit from additional testing. It was noted that magnetic resonance imaging is more costly than repeat ultrasonography and is not readily available at all centers.

Conclusions and research needs for this recommendation. The guideline panel determined that a strategy of serial testing seem safe in pregnant women with suspected DVT who have a negative initial proximal ultrasound with iliac vein imaging. However, with the low certainty in evidence, a single ultrasound at presentation should not be considered sufficient to rule out disease in pregnant women presenting with suspected DVT. In the absence of well-designed clinical management studies using magnetic resonance imaging and comparative studies of that technique with serial ultrasonographic imaging including the iliac veins, the panel was not able to recommend one additional test over another.

The panel identified the following additional research needs: more data are required on the safety of excluding DVT in pregnant women on the basis of a negative initial whole-leg compression ultrasound with imaging of the iliac veins. The role of D-dimer testing and clinical prediction rules in the management of pregnant women with suspected DVT needs to be evaluated in well-designed management studies.

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

Several of the recommendations contained in this guideline are consistent with those from other organizations. Guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC),[235] the Royal College of Obstetricians and Gynecologists (RCOG),[236] the American College of Chest Physicians (ACCP),[237] and clinicians from Australia/New Zealand[238] favor LMWH over other anticoagulants for the treatment of VTE. The American College of Obstetricians and Gynecologists (ACOG),[239] RCOG,[236] and ACCP[237] recommend warfarin, UFH, and LMWH as safe anticoagulants during breastfeeding. The ACCP guidelines also include acenocoumarol and danaparoid in their list of safe anticoagulants but recommend alternatives to fondaparinux in this population.[237] The SOGC,[235] RCOG,[236] and Australia/New Zealand[238] guidelines also recommend either once-per-day or twice-per-day dosing of therapeutic LMWH used for the treatment of VTE. The RCOG,[236] Australia/New Zealand,[238] and ACCP[237] guidelines do not recommend routine anti-FXa level monitoring in pregnant women receiving therapeutic doses of LMWH to treat VTE; however, the RCOG guidelines[236] do recommend monitoring in women at extremes of body weight, with renal impairment, or with recurrent VTE. Thrombolytic therapy is recommended for massive or life-threatening pulmonary embolism by the SOGC,[235] RCOG,[236] ACCP,[237] and Australia/New Zealand[238] guidelines. Restriction of this therapy to DVT that is limb threatening is recommended by the SOGC[235] and Australia/New Zealand[238] guidelines. The SOGC,[235] RCOG,[240] ACCP,[237] Australia/New Zealand,[241] and ACOG[239] guidelines also recommend antepartum prophylaxis for women with a history of unprovoked or hormone-associated VTE and postpartum prophylaxis for all women with a DVT or pulmonary embolism. The SOGC guidelines[235] favor V/Q lung scanning for the investigation of suspected pulmonary embolism in pregnant women and recommend serial lower-extremity ultrasounds with imaging of the iliac veins in pregnant women with suspected DVT. Serial compression ultrasonography, venography, or magnetic resonance direct imaging is recommended by the Australia/New Zealand guidelines for pregnant women with suspected DVT and a normal initial compression ultrasound.[238] The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology[242] and the Australia/New Zealand guidelines[238] recommend perfusion scintigraphy for pregnant women with suspected pulmonary embolism and a normal chest radiography

and CT pulmonary angiography if the chest radiograph is abnormal or lung scintigraphy is not readily available.

There is inconsistency among available guidelines for several recommendations. The Australia/New Zealand guidelines recommend initial inpatient observation and treatment of all pregnant women with newly diagnosed pulmonary embolism,[238] whereas the recommendation from the ACOG guidelines for hospitalization in cases of hemodynamic instability, large VTE, or maternal comorbidity is more consistent with the recommendations in these guidelines.[239] The SOGC,[235] ACCP,[237] Australia/New Zealand,[241] and ACOG[239] guidelines generally recommend against antepartum prophylaxis in women with a history of VTE related to a temporary nonhormonal risk factor, whereas the RCOG[240] recommends introduction of prophylaxis at 28 weeks in these women. Guidelines from the SOGC,[235] the RCOG,[240] Australia/New Zealand clinicians,[241] and the ACOG,[239] however, favor prophylaxis throughout the antepartum period if the affected woman is known to carry a thrombophilia. Recommendations for prophylaxis differ greatly between the various guidelines for pregnant and postpartum women with clinical risk factors for VTE; however, the SOGC,[235] RCOG,[240] and ACCP[237] also recommend against routine prophylaxis in women undergoing assisted reproduction but favor prophylaxis in those with severe ovarian hyperstimulation syndrome.

The SOGC[235] recommendation for prophylactic- or intermediate-dose LMWH for 1 to 6 weeks in pregnant women with bilateral or very symptomatic superficial vein thrombosis and for superficial vein thrombosis located ≤5 cm from junctions with the deep venous system or affecting at least 5 cm of a vein differs from the recommendation in these guidelines. These guidelines also differ from guidelines from the ACOG,[239] SOGC,[235] and RCOG[240] in recommending against antepartum prophylaxis to prevent a first VTE in women who have no family history of VTE but have antithrombin deficiency. They also differ from the ACCP guidelines[237] in recommending antepartum prophylaxis to prevent a first venous thromboembolic event in women who are homozygous for the factor V Leiden mutation or who have combined thrombophilias regardless of family history (Table 3). The recommendation against postpartum prophylaxis to prevent a first venous thromboembolic event in women with a family history of VTE and heterozygosity for either the factor V Leiden mutation or prothrombin gene mutation differs from that advanced by the RCOG[240] and ACCP[237] guidelines. The SOCG[235] and ACCP[237] recommend a multidisciplinary discussion about delivery options for women receiving antepartum anticoagulants; neither these guidelines nor the RCOG,[236] ACOG,[239] or Australia/New Zealand[238] guidelines express a preference for scheduled or unscheduled delivery in these patients.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions. Much of this uncertainty is because of a lack of pregnancy-specific evidence, resulting in the need, in some instances, to rely on generalizations from studies examining nonpregnant patients. Despite efforts to consider implications of these recommendations across geographical regions, it is possible that certain countries, especially low-resource ones, will have additional considerations that we do not address that may affect uptake of these recommendations.

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.[243]

Priorities for research

On the basis of gaps in evidence identified during the guideline development process, the panel identified several areas for further research. These have been listed with each question and recommendation and are also summarized in Table 4.

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Authorship

Contribution: S.M.B. and B.R. wrote the first draft of the manuscript and revised the manuscript on the basis of authors' suggestions; guideline panel members (A.R., S.M., C.M., M.A.R., A.H.J., S.R.V., I.A.G., J.J.R., D.B., and A.L.) critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (J.J.R., M.B., and N.S.) contributed evidence summaries to the guidelines; these were reviewed by the guideline panel members who provided suggestions for improvement (S.M.B., B.R., A.R., S.M., C.M., M.A.R., A.H.J., S.R.V., I.A.G., D.B., and A.L.); J.J.R. checked the manuscript for accuracy and helped coordinate the systematic review team; all authors approved the manuscript and evidence summaries content; and S.M.B. was the chair and B.R. was the vice chair of the panel, and they led the panel meeting.

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