CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

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Background: Venous thromboembolism (VTE) is the third most common vascular disease. Medical inpatients, long-term care residents, persons with minor injuries, and long-distance travelers are at increased risk.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support patients, clinicians, and others in decisions about preventing VTE in these groups.

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 adult patients. The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 19 recommendations for acutely ill and critically ill medical inpatients, people in long-term care facilities, outpatients with minor injuries, and long-distance travelers.

Conclusions: Strong recommendations included provision of pharmacological VTE prophylaxis in acutely or critically ill inpatients at acceptable bleeding risk, use of mechanical prophylaxis when bleeding risk is unacceptable, against the use of direct oral anticoagulants during hospitalization, and against extending pharmacological prophylaxis after hospital discharge. Conditional recommendations included not to use VTE prophylaxis routinely in long-term care patients or outpatients with minor VTE risk factors. The panel conditionally recommended use of graduated compression stockings or low-molecular-weight heparin in long-distance travelers only if they are at high risk for VTE.

Summary of recommendations

Background

Venous thromboembolism (VTE) is the third most common cardiovascular diagnosis, with an incidence rate of ~1 in 1000 annually in middle age and increasing to nearly 1% annually in nonagenarians.[1] About 50% of all VTE events occur as a result of a current or recent hospital admission for surgery or acute medical illness.[2,3] Hospital-acquired VTE is preventable, with interventions including anticoagulants and mechanical measures, including compression stockings and intermittent pneumatic compression.

Submitted 27 June 2018; accepted 19 September 2018. DOI 10.1182/bloodadvances.2018022954.

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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.

Other nonhospitalized medical populations that are at increased risk for VTE include long-term care residents, frail persons, those with minor injuries, and long-distance travelers, particularly those with preexisting VTE risk factors.[2-7] These guidelines addressed methods to prevent VTE in these adult in-hospital and outpatient medical populations who are not on chronic anticoagulants for other indications.

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 practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[8-11] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[12-18] to assess the certainty in the evidence and formulate recommendations.

Interpretation of Strong and Conditional Recommendations

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

Strong recommendation

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

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's 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 to identify possible research gaps.

We defined acutely ill medical patients as patients hospitalized for a medical illness. Critically ill patients were defined as suffering from an immediately life-threatening condition admitted to an intensive or critical care unit. Chronically ill medical patients were defined as those with medical conditions who may be cared for in long-term care facilities. Interventions evaluated include anticoagulants ("parenterals," defined as unfractionated heparin [UFH], low-molecular-weight heparin [LMWH] or fondaparinux, and direct oral anticoagulants [DOACs]), aspirin, and mechanical methods.

Recommendations

Acutely ill medical patients: pharmacological VTE prophylaxis

Recommendations 1, 2, and 3. In acutely ill medical patients, the American Society of Hematology (ASH) guideline panel *suggests* using UFH, LMWH, or fondaparinux rather than no parenteral anticoagulant (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯). Among these anticoagulants, the panel *suggests* using LMWH (low certainty in the evidence of effects ⊕⊕◯◯) or fondaparinux (very low certainty in the evidence of effects ⊕⊕◯◯) rather than UFH (conditional recommendation). **Remark**: These recommendations also apply to patients with stroke who receive VTE prophylaxis.

Critically ill medical patients: pharmacological VTE prophylaxis

Recommendations 4 and 5. In critically ill medical patients, the ASH guideline panel *recommends* using UFH or LMWH over no UFH or LMWH (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯) and *suggests* using LMWH over UFH (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Acutely or critically ill medical patients: mechanical VTE prophylaxis vs a combination of pharmacological and mechanical or pharmacological VTE prophylaxis alone

Recommendation 6. In acutely or critically ill medical patients, the ASH guideline panel *suggests* using pharmacological VTE prophylaxis over mechanical VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 7. In acutely or critically ill medical patients who do not receive pharmacological VTE prophylaxis, the ASH guideline panel *suggests* using mechanical VTE prophylaxis over no VTE prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 8 and 9. In acutely or critically ill medical patients, the ASH guideline panel *suggests* pharmacological or mechanical VTE prophylaxis alone over mechanical combined with pharmacological VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 10. In acutely or critically ill medical patients who are receiving mechanical VTE prophylaxis, the ASH guideline panel *suggests* using pneumatic compression devices or graduated compression stockings for VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

DOAC vs LMWH in acutely ill medical patients

Recommendation 11. In acutely ill hospitalized medical patients, the ASH guideline panel *recommends* using LMWH over DOACs for VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 12. In acutely ill hospitalized medical patients, the ASH guideline panel *recommends* inpatient VTE prophylaxis with LMWH only, rather than inpatient and extended-duration outpatient VTE prophylaxis with DOACs (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). **Remark:** If patients are on a DOAC for other reasons, this recommendation may not apply.

Extended-duration outpatient prophylaxis vs inpatient-only prophylaxis

Recommendation 13. In acutely ill medical patients, the ASH guideline panel *recommends* inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Extended-duration outpatient prophylaxis vs inpatient-only UFH or LMWH

Recommendation 14. In critically ill medical patients, the ASH guideline panel *recommends* inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Chronically ill medical patients or nursing home patients

Recommendation 15. In chronically ill medical patients, including nursing home patients, the ASH guideline panel *suggests* not using VTE prophylaxis compared with using any VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** If a patient's status changes to acute, other recommendations would apply.

Medical outpatients with minor provoking risk factors for VTE

Recommendation 16. In medical outpatients with minor provoking risk factors for VTE (eg, immobility, minor injury, illness, infection), the ASH guideline panel *suggests* not using VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Long-distance travelers

Recommendation 17. In long-distance (>4 hours) travelers without risk factors for VTE, the ASH guideline panel *suggests* not using graduated compression stockings, LMWH, or aspirin for VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 18. In people who are at substantially increased VTE risk (eg, recent surgery, prior history of VTE, postpartum women, active malignancy, or ≥2 risk factors, including combinations of the above with hormone replacement therapy, obesity, or pregnancy), the ASH guideline panel *suggests* using graduated compression stockings or prophylactic LMWH for long-distance (>4 hours) travel (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 19. In people who are at substantially increased VTE risk (eg, recent surgery, prior history of VTE, postpartum women, active malignancy, or ≥2 risk factors, including combinations of the above with hormone replacement therapy, obesity, or pregnancy), and in whom LMWH or graduated compression stockings is not feasible (eg, resource-constrained setting or aversion to other indicated anticoagulants), the ASH guideline panel *suggests* using aspirin rather than no VTE prophylaxis (conditional recommendations, very low certainty in the evidence of effects ⊕◯◯◯).

Values and preferences

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

Explanations and other considerations

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

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about prevention of VTE in hospitalized and nonhospitalized medical patients and long-distance travelers. The target audience includes patients, hematologists, general practitioners, internists, hospitalists, other clinicians, pharmacists, and decision makers. Policy makers 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 problems

VTE in hospitalized and nonhospitalized medical patients and long-distance travelers confers an important disease burden and can be fatal. About 50% of all VTE events in the community occur as a result of a current or recent hospital admission, mainly for surgery (24%) or acute medical illness (22%).[2,3] Thus, hospitalization for acute medical illness is an important opportunity for applying prevention efforts. Risk factors for hospital-acquired VTE include acute medical illness, surgery, cancer and cancer therapy, trauma, immobilization, central venous catheters, previous history of VTE, older age, and obesity.[19] Almost all hospitalized patients have ≥1

Table 1. RAMs used in medical inpatients

RAM	Points
Padua VTE RAM: score ≥4 indicates high VTE risk*	
Reduced mobility	3
Active cancer	3
Previous VTE (excluding superficial thrombophlebitis)	3
Known thrombophilic condition	3
Recent trauma and/or surgery (<1 mo)	2
Elderly age (ie, >70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Ongoing hormonal treatment	1
Obesity (body mass index >30)	1
Acute infection and/or rheumatologic disorder	1
IMPROVE VTE RAM: score ≥2 indicates increased VTE risk†	
Previous VTE	3
Known thrombophilia‡	2
Lower limb paralysis§	2
Active cancer	2
Immobilization ≥7 d	1
ICU/CCU stay	1
Age >60 y	1
IMPROVE bleeding RAM: score ≥7 indicates high bleeding risk¶	
Renal failure (GFR 30-59 vs ≥60 mL/min per m^2)	1
Male vs female	1
Age 40-80 vs <40 y	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/Critical Care Unit stay	2.5
Renal failure (GFR <30 vs ≥60 mL/min per square meter)	2.5
Hepatic failure (INR > 1.5)	2.5
Age ≥85 y vs <40 y	3.5
Platelet count $<50 \times 10^9$/L	4
Bleeding in 3 mo before admission	4
Active gastroduodenal ulcer	4. 5

CI, confidence interval; CCU, Coronary Care Unit; GFR, glomerular filtration rate; ICU, Intensive Care Unit; INR, international normalized ratio.

*A total of 60.3% of patients in this study were low risk (Padua score 0-3). VTE prophylaxis was administered by provider choice from among several medications and with or without concomitant compression stockings.[36]
VTE incidence without VTE prophylaxis:
Padua score 0 to 3: 0.3%
Padua score ≥ 4: 11%
Among at-risk patients (Padua score ≥ 4)
Overall VTE hazard ratio (HR), 32 (95% CI, 4.1-251)
Incidence of VTE
No prophylaxis: 11%
With prophylaxis: 2.2%
VTE HR with prophylaxis, 0.13 (95% CI, 0.04-0.4)
Incidence of major or clinically relevant nonmajor bleeding with prophylaxis = 1.6% (95% CI, 0.5-4.6)
Interpretation: among at-risk patients (Padua score ≥ 4), the reduction in VTE appears to outweigh the increased risk of bleeding with pharmacologic prophylaxis.

†Risk level: score of 0 or 1 = low risk, score of 2 or 3 = moderate risk; score ≥ 4 = high risk. For scores ≥ 2, VTE prophylaxis is indicated.
A total of 69% of patients in this study[37] were low risk for VTE (score 0 or 1).
Three-month rate of symptomatic VTE:
IMPROVE VTE score 0 or 1: 0.5%
IMPROVE VTE score 2 or 3: 1.5%
IMPROVE VTE score ≥ 4: 5.7%.

‡Congenital or acquired thrombophilic condition (eg, factor V Leiden, lupus anticoagulant, protein C, or protein S deficiency).

§Leg falls to bed by 5 seconds but has some effort against gravity using the National Institutes of Health stroke scale.

¶About 90% of patients in this study[40] were low risk for bleeding (score < 7).
Incidence of major bleeding/any bleeding:
IMPROVE bleeding score < 7: 0.4%/1.5%
IMPROVE bleeding score ≥ 7: 4.1%/7.9%.

risk factor for VTE, and ~40% have ≥3 risk factors.[20] In a United States population-based study, hospital-acquired DVT and PE occurred in 1.3% and 0.4% of hospital admissions, respectively.[21] The increased risk of VTE persists for 45 to 60 days after hospital discharge.[22] Other medical populations that may be at increased risk for VTE include long-term care residents, frail persons, those with minor injuries, and long-distance travelers, particularly those with preexisting VTE risk factors.[2-7]

Description of the target populations

The panel discussed which acutely ill medical inpatients should be considered in these guidelines. Medical inpatients are a heterogeneous population in terms of VTE risk, but these patients have conventionally been subject to universal, or group-based, VTE-prevention strategies.[20,23-25] We defined acutely ill medical patients as patients hospitalized for a medical illness. Critically ill patients were defined as suffering from an immediately life-threatening condition requiring hospitalization in an intensive or critical care unit. Chronically ill medical patients were defined as those with medical conditions who may be cared for in long-term care facilities. We also considered long-distance travelers, as those traveling by air for >4 hours, and outpatients with minor provoking risk factors for VTE.

Recent studies among hospitalized medically ill patients suggest that a universal approach to prevention has minimal impact on reducing VTE.[26,27] This may be due, in part, to (1) shorter lengths of stay and truncated thromboprophylaxis regimens compared with older studies that showed significant reductions in thromboembolic events with prophylaxis or insufficient duration of follow-up in research studies[28-30]; (2) overprophylaxis of low-risk patients and underprophylaxis of high-risk patients, resulting in an unfavorable risk–harm balance for these patients; or (3) underutilization of appropriate prophylaxis in hospitalized medical patients due to clinician concern for bleeding or perception that patients are not at sufficiently high risk for VTE to warrant prophylaxis.[31]

Based on enhanced understanding of these issues, a paradigm shift in VTE risk assessment and prevention is underway that prompts clinicians to strive for individualized prophylaxis based on VTE and bleeding risk. Over the last decade, several quantitative VTE risk-assessment models (RAMs) were developed for medical inpatients.[32-34] The 2 most extensively studied are the empirically derived Padua score[35] and the database-derived IMPROVE score[36] (Table 1). Both have been externally validated and showed fair discrimination in identifying medical inpatients who are and are not at increased risk for VTE.[32,37,38] The IMPROVE investigators also developed an externally validated bleeding risk RAM (Table 1) that may aid in identifying acutely ill medical inpatients at increased risk for bleeding.[39-41] The footnote of Table 1 provides data on how these RAMs may be applied for clinical decision making.

D-dimer, a by-product of fibrin degradation, is a biomarker for increased VTE risk in medical inpatients.[42,43] A modified version of the IMPROVE VTE risk score, IMPROVEDD, showed improved risk assessment in the APEX clinical trial population.[44]

Although optimal strategies for VTE risk assessment and decision making on prophylaxis are yet to be identified, when clinicians and health care systems use these ASH VTE guidelines, they should integrate VTE and bleeding risk assessments into clinical decision-making processes. Importantly, none of the existing validated quantitative RAMs proposed for clinical use in this setting have undergone extensive impact analyses that shows their use leads to a reduction in clinical outcomes.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[12-18] The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and GIN.[8-11] 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 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 (Dr. Adam Cuker) and vice-chair (H.J.S.). ASH vetted and appointed individuals 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, internists, other physicians, and a pharmacist who all had clinical and research expertise on the guideline topic; methodologists with expertise in evidence appraisal and guideline development; and 1 patient representative. The panel chair was a content expert. The vice-chair was an internist and expert 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 done using Web-based tools (https://www.surveymonkey.com and https://gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

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

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representative was offered, but declined, an honorarium of $200. The panelists received no other payments. Some researchers who contributed to the systematic evidence reviews received salary or grant support through the McMaster GRADE Centre. 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[45] and GIN.[11] At the time of appointment, a majority of the guideline panel, including the chair 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 financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms of all panel members. In Part A of the forms, individuals disclosed material interests for 2 years prior to appointment. In Part B, they disclosed interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was also used to manage conflicts of interest. During all deliberations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines were recused from making judgments about relevant recommendations.[11,46-48] The Evidence-to-Decision framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

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

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (https://gradepro.org)[49] and SurveyMonkey (https://www.surveymonkey.com) to brainstorm and then prioritize the questions described in Table 2.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[50] In brief, the panel brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach.[50] During this rating process, the panel used definitions of the outcomes ("marker states") that were developed for these guidelines. Rating outcomes by their relative importance can help to focus attention on those outcomes that are considered most important for clinicians and patients and help to resolve or clarify potential disagreements. The outcomes rated highly by the panel

Table 2. Patient populations and interventions for the prevention of VTE and the corresponding recommendations

Acutely ill patients: pharmacological prophylaxis addressing the following comparisons
1. Parenteral anticoagulant vs no parenteral anticoagulant
2. LMWH vs unfractionated heparin
3. Fondaparinux vs low molecular weight heparin or unfractionated heparin
Critically ill patients: pharmacological prophylaxis addressing the following comparisons
4. Any heparin vs no heparin
5. LMWH vs unfractionated heparin
Acutely or critically ill patients: mechanical prophylaxis addressing the following comparisons
6. Mechanical vs pharmacological prophylaxis
7. Mechanical vs no prophylaxis
8. Mechanical combined with pharmacological vs mechanical alone
9. Mechanical combined with pharmacological vs pharmacological alone
10. Intermittent pneumatic compression stockings vs graduated compression stockings
DOACs in acutely ill medical patients
11. DOACs vs prophylactic LMWH
12. Extended-duration DOACs vs shorter-duration non-DOAC prophylaxis
Extended-duration outpatient prophylaxis vs inpatient-only prophylaxis
13. Acutely ill medical patients
14. Critically ill medical patients
Chronically ill patients or nursing home patients
15. Pharmacological prophylaxis vs no prophylaxis
Medical outpatients with minor provoking factors for VTE (eg, immobility, minor injury, illness, infection)
16. Prophylaxis vs no prophylaxis
Long-distance travelers: prophylaxis addressing the following comparisons
17. Graduated compression stockings
18. LMWH
19. Aspirin vs no prophylaxis

and those identified as important based on the literature reviews were further refined. The panel rated the following outcomes as critical for clinical decision making across questions: mortality, PE, proximal DVT, distal DVT, major bleeding including gastrointestinal bleeding, and heparin-induced thrombocytopenia (HIT). For several outcomes, the studies reported outcomes differently from what the panel determined to be critical or important for decision making. Typically, outcomes were reported as "any VTE," "any PE," "any DVT," "any proximal DVT," or "any distal DVT," sometimes preceded by "asymptomatic" or "symptomatic," but reporting was inconsistent across studies. This affected the degree of certainty that panel members had in making recommendations, so they made explicit assumptions about the meaning of the outcomes to patients through the use of marker states, rather than leaving them implicit.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE Evidence-to-Decision (EtD) framework, using the GRADEpro Guideline Development Tool (https://gradepro.org).[12,13,18] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for these guidelines. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (presented in Supplement 4) were updated during October and November of 2016, and panel members were asked to suggest any studies that may have been considered missed and 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 for bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk for bias was assessed at the health outcome level using the Cochrane Collaboration's risk for 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, preferences and costs, and summarized findings within the EtD frameworks.[12,13,18] Subsequently, the certainty in the body of evidence (also known as

quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk for bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk for publication bias, presence of large effects, dose–response relationship, and an assessment of the effect of plausible residual and opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[14-16]

During a 2-day in-person meeting, followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table 3 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 17 July 2017 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Thirty-three individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to the recommendations. On 30 April 2018, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline-development process was followed; on 4 May 2018, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared 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

Acutely ill medical patients: pharmacological prophylaxis

Question: Should any parenteral anticoagulant (UFH, LMWH or fondaparinux) vs no parenteral anticoagulant be used in acutely ill medical patients for VTE prophylaxis?

Question: If pharmacologic prophylaxis is used, should LMWH vs UFH be used?

Question: If pharmacologic prophylaxis is used, should fondaparinux vs LMWH or UFH be used?

Recommendation 1, 2, and 3

In acutely ill medical patients, the ASH guideline panel *suggests* using UFH, LMWH, or fondaparinux rather than no parenteral anticoagulant (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯). Among these anticoagulants, the panel *suggests* using LMWH (low certainty in the evidence of effects ⊕⊕◯◯) or fondaparinux (very low certainty in the evidence of effects ⊕◯◯◯) rather than UFH (conditional recommendation). **Remark:** These 3 recommendations also apply to anticoagulant choices when VTE prophylaxis is considered for patients with stroke.

Parenteral anticoagulant vs no parenteral anticoagulant in acutely ill medical patients

Summary of the evidence. We found 17 systematic reviews that addressed this question,[51-67] with 25 studies[29,30,68-89] (H. Vissinger and S. Husted, unpublished data, 1995) in these reviews evaluating outcomes relevant to this question. All studies included acutely ill medical inpatients, with 16 of the trials specifically including stroke patients.[68-82] The panel also considered the randomized controlled trial (RCT) by Cohen et al[28] that compared fondaparinux against no parenteral anticoagulation and felt that the results were similar enough to include fondaparinux with UFH and LMWH. The EtD framework is shown online at https://dbep.gradepro.org/profile/54B577E9-7F80-3A78-B3EA-3850E9A1D432.

Benefits. Parenteral anticoagulants (UFH, LMWH, or fondaparinux) had no impact on mortality based on a meta-analysis of 21

Table 3. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	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 adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

RCTs (relative risk [RR], 0.97; 95% confidence interval [CI], 0.91-1.04; absolute risk reduction [ARR], 2 fewer per 1000; 95% CI, from 6 fewer to 3 more per 1000), but we estimated that heparins reduced the risk for developing PE (RR, 0.59; 95% CI, 0.45-0.78; ARR, 4 fewer per 1000; 95% CI, from 6-2 fewer per 1000), symptomatic proximal DVT (RR, 0.28; 95% CI, 0.06-1.37; ARR, 3 fewer per 1000; 95% CI, from 4 fewer to 1 more per 1000), and symptomatic distal DVT (RR, 0.75; 95% CI, 0.17-3.34; ARR, 1 fewer per 1000; 95% CI, from 2 fewer to 5 more per 1000).

Harms and burden. Sixteen RCTs reported on major bleeding (RR, 1.48; 95% CI, 0.81-2.71; ARR, 3 more per 1000; 95% CI, from 1 fewer to 12 more per 1000). Two RCTs reported an increase in gastrointestinal bleeding (RR, 2.61; 95% CI, 0.36-18.86; ARR, 50 more per 1000; 95% CI, from 20 fewer to 558 more per 1000), and 3 reported little impact on thrombocytopenia (RR, 0.95; 95% CI, 0.47-1.92; ARR, 0 per 1000; 95% CI, from 1 fewer to 2 more per 1000), with 1 of the studies specifically reporting no HIT in either group.

Certainty in the evidence of effects. The certainty in these estimated effects was judged as low owing to the risk of bias and imprecision of the estimates.

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important for decision making to patients. Three reports compared the cost-effectiveness of LMWH compared with no heparin in medical patients and showed favorable cost-effectiveness of enoxaparin.[90-92] Although the panel assumed no impact on health equity, the use of any parenteral anticoagulant (UFH, LMWH, and fondaparinux) was considered acceptable and feasible.

Conclusions and research needs for this recommendation. The panel determined that there is low certainty in the evidence for a net health benefit from using any parenteral anticoagulant in acutely ill medical patients. Other EtD criteria were generally in favor of using any parenteral anticoagulant for VTE prevention so that the desirable consequences were greater than the undesirable consequences.

The panel identified the following additional research questions:

- Better information on baseline risk assessment of thrombosis and bleeding in medical inpatients is needed, in particular whether risk varies over the course of admission; and
- More information on the optimal dosing of parenteral anticoagulation to prevent VTE in medical inpatients is needed. In particular, can lower or higher doses be used in different settings (perhaps dependent on baseline risk), and should dosing be adjusted in obese patients, underweight patients, and patients with renal disease?

LMWH vs UFH in acutely ill medical patients

Summary of the evidence. We found 8 systematic reviews[51,52,54,58,59,63,65,67] that addressed this question and included 11 RCTs.[93-103] We identified 1 additional study[99] published after the search for the systematic reviews was completed. All studies included acutely ill medical patients, with 5 studies in stroke patients.[93-97] The EtD framework is shown at https://dbep.gradepro.org/profile/FA048403-345D-A41B-8147-6657D26C1399.

Benefits, harms, and burden. LMWH compared with UFH had little impact on mortality (RR, 0.99; 95% CI, 0.82-1.19; ARR, 1 fewer per 1000; 95% CI, 9 fewer to 10 more per 1000). LMWH showed reductions in PE, symptomatic DVT, major bleeding, and HIT compared with UFH, but the estimates were imprecise, with small ARRs (see evidence profile in the online EtD framework).

Certainty in the evidence of effects. Overall, the certainty in these estimated effects was rated as very low owing to risk of bias and imprecision of the estimates (see evidence profile in the online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important for decision-making to patients. Eleven reports[91,104-113] compared the cost-effectiveness of LMWH with UFH in hospitalized patients; 1 was a trial-based analysis that the panel considered most informative.[106] All reports concluded that

LMWH was cost-effective for thromboprophylaxis compared with UFH, with 4 reports suggesting that LMWH was more effective and provided net savings compared with UFH.[91,104,105,111] The panel recognized that cost may change or differ widely across settings. In addition, the panel expressed caution about existing cost-effectiveness analyses that differed in their assumptions and input parameters from that used by the panel in the EtD. Although the panel assumed no impact on health equity, the fewer injections required with once-daily LMWH made it feasible and acceptable compared with UFH, which is administered more than once daily.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in the evidence for a net health benefit from using LMWH over UFH in acutely ill medical patients. Other EtD criteria were generally in favor of using LMWH so that the desirable consequences were greater than the undesirable consequences. This recommendation includes stroke patients, despite a slightly higher bleeding risk with LMWH compared with UFH among stroke patients in our systematic review. The panel judged that the consequences from using LMWH were favorable compared with the consequences of using UFH.

There were no future research needs prioritized by the panel.

Fondaparinux vs LMWH or UFH in acutely ill medical patients

Summary of the evidence. We did not identify trials that directly addressed this question. One trial,[28] which was included in 9 identified systematic reviews,[55,56,58-61,63,66,67] addressed the use of fondaparinux compared with no prophylaxis in acutely ill medical patients. This trial was used to indirectly compare the effect of fondaparinux with LMWH and UFH through a calculation of the ratio of risk ratios based on the 25 identified RCTs that compared these agents vs no prophylaxis. The EtD framework is shown at https://dbep.gradepro.org/profile/4F45952B-32AD-43CA-8839-6CB829E4BF3D.

Benefits, harms, and burden. Fondaparinux may reduce several outcomes when indirectly compared with the meta-analysis of RCTs using LMWH or UFH, including mortality (RR, 0.56; 95% CI, 0.30-1.06; ARR, 30 fewer per 1000; 95% CI, from 47 fewer to 4 more per 1000), PE (RR, 0.59; 95% CI, 0.18-1.94; ARR, 3 fewer per 1000; 95% CI, from 5 fewer to 6 more per 1000), distal DVT (RR, 0.82; 95% CI, 0.26-2.55; ARR, 10 fewer per 1000; 95% CI, from 42 fewer to 87 more per 1000), and major bleeding (RR, 0.66; 95% CI, 0.04-11.32; ARR, 7 fewer per 1000; 95% CI, from 19 fewer to 202 more per 1000). However, proximal DVT was increased (RR, 1.75; 95% CI, 0.50-6.12; ARR, 14 more per 1000; 95% CI, from 9 fewer to 93 more per 1000).

Certainty in the evidence of effects. Overall, the certainty in these estimated effects was very low owing to the risk of bias, the indirect comparison, and imprecision of the estimates.

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important for decision making to patients. There were no published cost-effectiveness analyses, and no cost differences between fondaparinux and LMWH were assumed. The panel assumed no impact on health equity and that the use of fondaparinux was acceptable and probably feasible.

Conclusions and research needs for this recommendation. The panel judged that the desirable and undesirable consequences did not favor fondaparinux over LMWH but favored fondaparinux over UFH for similar considerations as for LMWH over UFH. However, this judgment was based on very low certainty in the evidence for the comparison of the health effects exerted by fondaparinux compared with UFH or LMWH in acutely ill medical patients. No specific research needs related to fondaparinux were recommended by the panel.

Critically ill medical patients: pharmacological prophylaxis

Any heparin vs no heparin

Question: Should any heparin (UFH or LMWH) vs no UFH or LMWH be used for venous thrombosis prophylaxis in critically ill patients?

Recommendation 4

In critically ill medical patients, the ASH guideline panel *recommends* using UFH or LMWH over no UFH or LMWH (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Five of 6 panelists without conflicts voted in favor of a strong recommendation over a conditional recommendation.

Summary of the evidence. We identified 1 systematic review that addressed this question in critically ill medical patients.[114] Three RCTs in this review fulfilled our inclusion criteria and measured outcomes relevant to this context (eg, mortality, PE, DVT, major bleeding, and thrombocytopenia).[115-117] Our update of this systematic review did not identify any additional studies that fulfilled the inclusion criteria. All studies included critically ill medical inpatients. We excluded studies that addressed this question in critically ill patients who underwent surgery or those with trauma.

Of the 3 included studies, 2 of them[115,117] assessed the effect of LMWH, whereas 1 study[117] assessed the effect of UFH. Two studies reported the effect of treatment on mortality,[115,117] and all 3 studies reported outcomes of any PE and any DVT (it was not specified whether symptomatic or asymptomatic DVT or whether proximal or distal DVT). One study[117] reported on development of DVT assessed as symptomatic DVT, which was used to extrapolate data for proximal DVT and distal DVT representing the moderate marker state. Two studies[115,117] assessed the risk of major bleeding, and 1 study assessed the risk of thrombocytopenia.[115] No studies reported the outcome of HIT specifically. The EtD framework is shown at https://dbep.gradepro.org/profile/783DCF1B-50FC-72D0-A1E1-3C31011E9471.

Benefits. In absolute and relative terms, pharmacological prophylaxis probably reduces mortality, PE, and DVT. The mortality RR was 0.89 (95% CI, 0.78-1.02), and ARR was 32 fewer per 1000 (95% CI, from 64 fewer to 6 more per 1000). The PE RR was 0.53 (95% CI, 0.28-0.98), and ARR was 2 fewer per 1000 (95% CI, 0-3 fewer per 1000). The DVT RR was 0.86 (95% CI, 0.59-1.25), and ARR was 1 fewer per 1000 (95% CI, 8 fewer to 5 more per 1000) for distal DVT, for a baseline risk of 2.0%.

Harms and burden. Major bleeding is probably not increased with UFH or LMWH (RR, 1.01; 95% CI, 0.40-2.54), and absolute risk increase (ARI) was 7 more per 1000 (95% CI, 30 fewer to 76 more per 1000). Although no studies reported on HIT, 1 study reported an increased risk for thrombocytopenia with heparin

use, with an RR of 1.49 (95% CI, 0.59-3.78) and an ARI of 30 more per 1000 (95% CI, 25 fewer to 171 more per 1000). However, the panel considered thrombocytopenia an important, but not critical, outcome for decision making.

Certainty in the evidence of effects. Overall, the panel judged the certainty in these estimated effects as moderate owing to serious imprecision of the estimates for the critical outcomes (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, DVT, and major bleeding was critical to patients and judged that the benefits clearly favored prophylaxis. The panel judged that costs were negligible, and heparin prophylaxis was acceptable and feasible.

Conclusions and research needs for this recommendation. The guideline panel determined that there was moderate certainty in the evidence that the desirable effects of heparin (UFH or LMWH) outweigh the undesirable effects in critically ill medical patients. The panel made a strong recommendation for using pharmacological prophylaxis, although the exact magnitude of the mortality benefit is still in question. The panel did not identify high-priority future research questions.

LMWH vs UFH

Question. Should LMWH vs UFH be used for VTE prophylaxis in critically ill patients?

Recommendation 5

In critically ill medical patients, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Of 6 panelists without conflicts, 4 (67%) favored a conditional recommendation and 2 (33%) favored a strong recommendation for LMWH over UFH. Considering the ASH criterion for strong recommendations (80% majority required), the panel made a conditional recommendation.

Summary of the evidence. We identified 1 systematic review that addressed this question in critically ill medical patients.[114] Three RCTs in this review fulfilled the inclusion criteria and measured relevant outcomes (eg, mortality, PE, DVT, major bleeding, and thrombocytopenia).[117-119] Our update of this systematic review did not identify any additional studies. All studies included critically ill medical inpatients. We excluded studies that addressed this question in critically ill patients who underwent surgery or had trauma.

All 3 studies[117-119] reported the effect of LMWH compared with UFH on mortality. Two studies[117,118] reported on the development of any PE, and 1 of these studies[118] reported on development of symptomatic PE specifically, which was used to extrapolate data for the outcome of PE representing the moderate marker state. All 3 studies reported on the development of any DVT, and 2 studies[117,118] reported on the development of symptomatic DVT, which was used to extrapolate data for proximal DVT and distal DVT representing the moderate marker state. All 3 studies assessed the risk of major bleeding, and 1 study[118] assessed the risk of HIT. No studies reported on the risk of gastrointestinal bleeding specifically. The EtD framework is shown at https://dbep.gradepro.org/profile/FDD22673-C5BB-8A63-A715-5D225B808EA2.

Benefits. In absolute and relative terms, LMWH compared with UFH appeared to have a moderate impact on mortality and VTE. The mortality RR was 0.90 (95% CI, 0.75-1.08), and ARR was 24 fewer per 1000 (95% CI, from 61 fewer to 19 more per 1000). For PE, the RR was 0.80 (95% CI, 0.44-1.46). With a baseline risk of 0.4%, the ARR for PE was 1 fewer per 1000 (95% CI, from 2 fewer to 2 more per 1000). For DVT, the RR was 0.87 (95% CI, 0.60-1.25). With a baseline risk of 0.5% for proximal DVT, this translated to an ARR of 1 fewer per 1000 (95% CI, 1 fewer to 2 more per 1000). For distal DVT with a baseline risk of 1.4%, the ARR was 2 fewer per 1000 (95% CI, 6 fewer to 4 more per 1000).

Harms and burden. Major bleeding did not appear to differ between LMWH and UFH (RR, 0.98; 95% CI, 0.76-1.27; RR, 1 fewer per 1000; 95% CI, 13 fewer to 14 more per 1000). HIT was probably decreased with LMWH vs UFH, with an RR of 0.42 (95% CI, 0.15-1.18) and an ARR of 3 fewer per 1000 (95% CI, 5 fewer to 1 more per 1000).

Certainty in the evidence of effects. Overall, the panel judged the certainty in these estimated effects as moderate owing to serious imprecision of the estimates, although the certainty was judged as low for mortality and PE. However, the effect estimates all favored LMWH and, thus, the overall certainty was moderate for the critical outcomes.[120]

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, and DVT was critical or important for decision making to patients. The panel judged that the cost or savings were negligible, and LMWH was probably acceptable and feasible given that fewer injections would be required compared with UFH.

Conclusions and research needs for this recommendation. The guideline panel determined that there was moderate certainty in the evidence that the desirable consequences of LMWH outweigh the undesirable consequences compared with UFH in critically ill medical patients. The panel made a conditional recommendation because of remaining uncertainty about the exact magnitude of the effect and because critically ill medical patients with renal failure and hepatic failure may require alternative options. The panel did not prioritize the comparison of fondaparinux against LMWH or UFH in critically ill patients. Future research should address:

- Tools for quantitative risk assessment for VTE and bleeding in critically ill medical patients; and
- Determination of the acceptable balance between bleeding and thrombosis risk in the context of selecting the optimal thromboprophylaxis in critically ill medical patients.

Acutely or critically ill medical patients: mechanical VTE prophylaxis vs a combination of pharmacological and mechanical or pharmacological VTE prophylaxis alone

Question: Should mechanical VTE prophylaxis vs pharmacological VTE prophylaxis be used in acutely or critically ill medical patients?

Question: Should mechanical VTE prophylaxis vs no VTE prophylaxis be used in acutely or critically ill medical patients?

Question: Should mechanical combined with pharmacological vs mechanical VTE prophylaxis alone be used in acutely or critically ill medical patients?

Question: Should mechanical combined with pharmacological vs pharmacological VTE prophylaxis alone be used in acutely or critically ill medical patients?

Question: Should pneumatic compression devices vs graduated compression stockings be used for VTE prophylaxis in acutely or critically ill medical patients?

Recommendation 6

In acutely or critically ill medical patients, the ASH guideline panel *suggests* using pharmacological VTE prophylaxis over mechanical VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 7

In acutely or critically ill medical patients who do not receive pharmacological VTE prophylaxis, the ASH guideline panel *suggests* using mechanical VTE prophylaxis over no VTE prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendations 8 and 9

In acutely or critically ill medical patients, the ASH guideline panel *suggests* pharmacological or mechanical VTE prophylaxis alone over mechanical combined with pharmacological VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 10

In acutely or critically ill medical patients who are receiving mechanical VTE prophylaxis, the ASH guideline panel *suggests* using pneumatic compression devices or graduated compression stockings for VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

For questions addressing mechanical approaches to VTE prophylaxis, we defined mechanical prophylaxis broadly as including pneumatic compression devices or graduated compression stockings. Pneumatic compression devices included intermittent pneumatic compression or sequential pneumatic compression. We used the collective term "mechanical prophylaxis" when mechanical prophylaxis modalities are compared with, or combined with, pharmacological prophylaxis.

Mechanical vs pharmacological prophylaxis

Question: Should mechanical VTE prophylaxis vs pharmacological VTE prophylaxis be used in acutely or critically ill medical patients?

Recommendation 6

In acutely or critically ill medical patients, the ASH guideline panel *suggests* using pharmacological VTE prophylaxis over mechanical VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We did not identify any systematic review that addressed this question, but our comprehensive search for RCTs identified 2 studies[121,122] in acutely or critically ill medical patients that provided limited evidence for this question. Therefore, the guideline panel decided to include indirect evidence from RCTs in trauma patients, for which we identified a systematic review.[123] Our update of that systematic review did not identify any eligible additional studies.

Seven studies reported the effect of mechanical prophylaxis vs pharmacological prophylaxis on risk of mortality.[122,124-129] Seven studies reported the effect of mechanical prophylaxis vs pharmacological prophylaxis on development of symptomatic PE.[121,122,124-127,129] Three studies reported the effect of mechanical prophylaxis vs pharmacological prophylaxis on development of symptomatic DVT.[121,126,127] Seven studies reported the effect of mechanical prophylaxis vs pharmacological prophylaxis on risk of major bleeding.[121,124-128,130] The EtD framework is shown at https://dbep.gradepro.org/profile/95794127-BD67-D33B-BCDA-3FF49A76A6F2.

Benefits. In absolute and relative terms, mechanical prophylaxis compared with pharmacological prophylaxis appeared to have little or no impact on mortality (RR, 0.95; 95% CI, 0.42-1.13; ARR, 1 fewer per 1000; 95% CI, from 11 fewer to 21 more per 1000). For PE, the RR was 1.54 (95% CI, 0.48-4.93), and the ARI was 1 more per 1000 (95% CI, from 1 fewer to 4 more per 1000), for a baseline risk of 0.1%. For symptomatic DVT, the RR was 2.20 (95% CI, 0.22-22.1). Using a baseline risk of 0.2% for proximal DVT, the ARI was 2 more per 1000 (95% CI, 1 fewer to 38 more per 1000), and with a baseline risk of 0.7% for distal DVT, this extrapolated to an ARI of 9 more per 1000 (95% CI, 6 fewer to 152 more per 1000).

Harms and burden. Major bleeding appeared reduced with mechanical vs pharmacological prophylaxis, with a RR of 0.87 (95% CI, 0.25-3.08) and an ARR of 4 fewer per 1000 (95% CI, 21 fewer to 58 more per 1000) (very low certainty in the evidence). No quantitative estimates were available on the risk of falls, ischemia, and limb ulceration.

Certainty in the evidence of effects. Overall, the certainty in these estimated effects was very low owing to very serious imprecision and serious indirectness of the estimates (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, and DVT was critical for decision making for patients. Given the efficacy of pharmacological prophylaxis compared with no prophylaxis, as well as uncertainty about the difference in effects and cost between pharmacological and mechanical prophylaxis, the panel judged that acceptability and feasibility would vary importantly across settings.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the evidence that there are net desirable consequences from pharmacological prophylaxis compared with mechanical prophylaxis in acutely or critically ill medical patients. The panel made a conditional recommendation for using pharmacological prophylaxis over mechanical prophylaxis and determined that the recommendation would not apply to groups in whom the risk of VTE would be too small to justify the downsides or burden of any prophylaxis. The panel felt that the very low certainty about the effect estimates suggests that there is a research gap with regard to effectiveness. Research question identified:

- Better information on bleeding risk in medical inpatients to inform decisions about use of mechanical compared with pharmacological VTE prophylaxis.

Mechanical vs no prophylaxis

Question: Should mechanical VTE prophylaxis vs no VTE prophylaxis be used in acutely or critically ill medical patients?

Recommendation 7

In acutely or critically ill medical patients who do not receive pharmacological VTE prophylaxis, the ASH guideline panel *suggests* using mechanical VTE prophylaxis over no VTE prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Summary of the evidence. We did not identify any systematic review that addressed this question. Our systematic search for RCTs identified 1 study[131] conducted in critically ill medical patients, which provided limited evidence. Due to the scarcity of direct evidence, the guideline panel decided to consider indirect evidence available from systematic reviews of RCTs conducted in trauma and stroke patients. We found 1 systematic review that provided evidence from trauma patients[123] and 1 systematic review that provided evidence from stroke patients.[132] Our update of the systematic reviews identified 1 additional study in stroke patients[133] that fulfilled our inclusion criteria.

In total, 7 studies each reported on the effect of mechanical methods vs no intervention on mortality[126,131,133-137] and on the development of PE.[126,131,133-135,137,138] Five studies reported the effect of mechanical methods vs no intervention on the development of proximal DVT: 2 for symptomatic proximal DVT[133,134] and 3 for any proximal DVT.[131,135,137] Four studies reported the effect of mechanical methods vs no intervention on the development of distal DVT: 2 for symptomatic distal DVT[133,134] and 2 for any distal DVT.[131,137] The EtD framework is shown at https://dbep.gradepro.org/profile/01137182-5DA7-ADF7-B58C-BBAF33FD4DCD.

Benefits. In absolute and relative terms, mechanical prophylaxis appeared to have little or no impact on mortality and VTE (RR, 0.93; 95% CI, 0.77-1.13; ARR, 7 fewer per 1000; 95% CI, from 24 fewer to 14 more per 1000). For PE, the RR was 0.73 (95% CI, 0.51-1.04), translating to an ARR of 0 fewer per 1000 (95% CI, from 0 fewer to 0 fewer per 1000) using a baseline risk of 0.1% per admission for PE; for proximal or distal DVT, the RR was 0.82 (95% CI, 0.61-1.10), translating to an ARR of 0 fewer per 1000 (95% CI, 0-1 fewer per 1000) using a baseline risk of 0.2%.

Harms and burden. The panel rated adverse effects of mechanical prophylaxis, such as risk of falls, ischemia, and limb ulceration, as important, but not critical, for decision making. A study[134] showed 2 events of lower limb ischemia or amputation in 1438 patients receiving pneumatic compression devices compared with 0 events in 1438 patients not receiving pneumatic compression devices. The panel also suggested that pneumatic compression devices might reduce mobility and cause falls in patients who ambulate, although the panel did not review specific evidence for these outcomes, and some evidence suggests no increased risk of falls with pneumatic compression devices.[139]

Certainty in the evidence of effects. Overall, the certainty in the estimated effects was moderate owing to imprecision of the estimates when the small possible benefits are weighed against the less important potential harms or burden (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, and DVT was critical or important for decision making to patients. Mechanical prophylaxis, including pneumatic compression devices, appeared to be cost-effective. For example, 1 study[134] comparing pneumatic compression devices with no devices for immobile stroke patients suggested an additional cost of US $2171 to prevent 1 DVT of any type. In general, mechanical prophylaxis was considered acceptable, and, among options, graduated compression stockings were considered more feasible than pneumatic compression devices.

Conclusions and research needs for this recommendation. The guideline panel determined that there is moderate certainty in the evidence that the desirable consequences of mechanical prophylaxis outweigh the undesirable consequences in acutely or critically ill medical patients. The panel made a conditional recommendation because, prior to applying the intervention to all patients, clinicians should carefully evaluate suitability based on risk factors. For example, patients given mechanical prophylaxis must be observed to reduce the risk of falls and other complications. Patients with peripheral vascular disease may experience higher rates of adverse events, including leg ulceration, ischemia, and amputations. The absolute risk reduction in VTE may be higher in high-risk VTE patients, and the benefits may outweigh the harms among patients at increased risk of bleeding. Some patient groups (eg, those with lower extremity injuries or open wounds) may not be able to use pneumatic compression devices. The cost of the devices for large hospitals may be considerable, and devices require storage space. The panel also felt that more research should be conducted to elucidate:

- Net health benefit of mechanical prophylaxis in a lower-risk medical inpatient population;
- Utility of outpatient use of mechanical prophylaxis in those at risk of VTE;
- Direct comparisons between graduated compression stockings and pneumatic compression devices in medical inpatients; and
- Impact of use of pneumatic compression devices in medical inpatients at high bleeding risk or with active bleeding

Mechanical combined with pharmacological vs mechanical prophylaxis alone

Question: Should mechanical combined with pharmacological VTE prophylaxis vs mechanical VTE prophylaxis alone be used in acutely or critically ill medical patients?

Recommendation 8

In acutely or critically ill medical patients, the ASH guideline panel *suggests* using mechanical alone over mechanical combined with pharmacological VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. No existing systematic review addressed this question, and our systematic search for RCTs

identified 1 study providing direct evidence for this question.[88] This trial reported any confirmed VTE as an outcome. Therefore, we extrapolated the effects to representative baseline risks for PE and proximal and distal VTE to estimate the potential benefits and harms but rated down for indirectness because information for symptomatic VTE was not available.

The EtD framework is shown at https://dbep.gradepro.org/profile/01137182-5DA7-ADF7-B58C-BBAF33FD4DCD.

Benefits. In absolute and relative terms, combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone appeared to have no impact on mortality (RR, 1.0; 95% CI, 0.8-1.2; ARR, 0 fewer per 1000; 95% CI, from 10 fewer to 10 more per 1000). For VTE, the RR was 1.98 (95% CI, 0.60-6.58). For PE, this resulted in an ARI of 1 more per 1000 (95% CI, 0-6 more per 1000) using a baseline risk of 0.1%. For proximal DVT, the ARI was 2 more per 1000 (95% CI, 1 fewer to 10 more per 1000) using a baseline risk of 0.2%. For distal DVT, this extrapolated to an ARI of 7 more per 1000 (95% CI, 3 fewer to 40 more per 1000) using a baseline risk of 0.7%.

Harms and burden. Major bleeding was increased, with an RR of 1.48 (95% CI, 0.7-3.1) and an ARI of 1 more per 1000 (95% CI, from 1 fewer to 6 more per 1000). The panel considered the risk of falls, ischemia, and limb ulceration as important outcomes (as discussed for recommendation 7), but no quantitative estimates were available.

Certainty in the evidence of effects. The panel considered the certainty in these estimated effects as very low owing to very serious imprecision and indirectness (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, and DVT was critical or important to patients for decision making.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the balance between desirable and undesirable health effects of combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone in acutely or critically ill medical patients. The panel felt that applying combined prophylaxis to all patients would mean that the undesirable consequences would likely outweigh the desirable consequences. The panel felt that more research should be conducted to:

- Provide more direct evidence on combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone via clinical trials on efficacy, harms, and adherence to the intervention, particularly in high-risk medical inpatients in whom the balance of potential benefits vs harms might be more favorable than among lower-risk patients;
- Obtain patient preferences for mechanical or pharmacological prophylaxis by studying feasibility, equity, and acceptability;
- Determine current utilization rate of combined mechanical and pharmacological prophylaxis in practice; and
- Compare combined mechanical and pharmacological prophylaxis with mechanical prophylaxis alone utilizing comparative effectiveness research studies.

Mechanical combined with pharmacological vs pharmacological prophylaxis alone

Question: Should mechanical combined with pharmacological VTE prophylaxis vs pharmacological VTE prophylaxis alone be used in acutely or critically ill medical patients?

Recommendation 9

In acutely or critically ill medical patients, the ASH guideline panel *suggests* pharmacological VTE prophylaxis alone over mechanical combined with pharmacological VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We did not identify any systematic review that addressed this question or any RCT addressing this question in acutely or critically ill medical patients. Because of the lack of direct evidence to answer this question, the guideline panel decided to include indirect evidence available from RCTs in trauma and stroke patients. We used 1 systematic review summarizing evidence for patients with trauma[123] and 1 systematic review in patients with stroke.[132] Our update of these systematic reviews did not identify any additional eligible studies. The EtD framework is shown at https://dbep.gradepro.org/profile/DBB3AAE6-C0E9-1F2D-947D-4ED4A2B15E33.

Benefits. In absolute and relative terms, mechanical prophylaxis may reduce mortality, PE, and DVT, but the estimates are very uncertain (for mortality the RR was 0.50; 95% CI, 0.05-5.30; ARR, 4 fewer per 1000; 95% CI, from 8 fewer to 34 more per 1000; for PE the RR was 0.35; 95% CI, 0.05-2.22; ARR, 1 fewer per 1000; 95% CI, from 1 fewer to 1 more per 1000; for proximal DVT the RR was 0.13; 95% CI, 0.04-0.40; ARR, 2 fewer per 1000; 95% CI, 1-2 fewer per 1000; for distal DVT the RR was 0.21; 95% CI, 0.02-1.76; ARR, 6 fewer per 1000; 95% CI, from 7 fewer to 5 more per 1000).

Harms and burden. Major bleeding with mechanical plus pharmacological prophylaxis compared with pharmacological prophylaxis alone may be increased, with an RR of 2.83 (95% CI, 0.30-26.7) and an ARR of 51 more major bleeding events per 1000 (95% CI, 20 fewer to 720 more per 1000). The panel considered risk of falls, ischemia, and limb ulceration with mechanical prophylaxis as important outcomes (as discussed for recommendation 7).

Certainty in the evidence of effects. Overall, the certainty in the estimated effects was very low owing to very serious imprecision and serious indirectness of the estimates (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, DVT, and major bleeding was critical to patients. The panel judged that cost was moderate and cost-effectiveness favored pharmacological prophylaxis alone, but combined prophylaxis was deemed acceptable and feasible (see recommendation 7).

Conclusions and research needs for this recommendation. The guideline panel determined that, in acutely or critically ill medical patients, there is very low certainty in the evidence that, compared with pharmacological prophylaxis the undesirable consequences of mechanical combined with pharmacological

prophylaxis outweigh the desirable consequences of the 2 approaches combined. Thus, the panel made a conditional recommendation for using pharmacological prophylaxis alone. Priorities for research include conducting trials of combined mechanical and pharmacological prophylaxis compared with pharmacological prophylaxis alone among very high risk patient groups. Other research needs are outlined in recommendation 8.

Pneumatic compression devices vs graduated compression stockings

Question: Should pneumatic compression devices vs graduated compression stockings be used for VTE prophylaxis in acutely or critically ill medical patients?

Recommendation 10

In acutely or critically ill medical patients who are not receiving pharmacological VTE prophylaxis, the ASH guideline panel *suggests* using pneumatic compression devices or graduated compression stockings for VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We did not identify any systematic review that addressed this question, but our systematic search for RCTs identified 1 RCT[122] in acutely ill medical patients that provided limited evidence for this question. This study compared intermittent pneumatic compression with graduated compression stockings. The EtD framework is shown at https://dbep.gradepro.org/profile/481D40D6-31CD-153A-BB3F-1CF50F1A7B23.

Benefits, harms, and burden. For this recommendation, there was only 1 RCT with 43 participants and very few events (1 death, 1 PE, 3 DVTs). In comparing these 1 alternatives the panel believed felt it could not judge the balance of health effects based on this RCT.

Certainty in the evidence of effects. The panel rated the certainty in these estimated effects as very low owing to very serious imprecision and serious indirectness of the estimates (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, and DVT was critical or important for decision making to patients.

Conclusions and research needs for this recommendation. The guideline panel determined that there was a paucity of evidence, as well as very low certainty in the evidence. The panel decided to not make a final judgment about which 1 of the 2 options led to more desirable than undesirable consequences. Thus, deducting from other recommendations, the panel made a conditional recommendation for using either option if mechanical prophylaxis is chosen.

With regard to research, the panel felt that:

- A systematic review of observational studies and a large comparative RCT are needed to increase the evidence available comparing pneumatic compression devices to graduated compression stockings in acutely or critically ill medical patients.
- Studies of pneumatic compression devices compared with graduated compression stockings are needed in acutely or critically ill medical patients with contraindications to pharmacological prophylaxis or those at high bleeding risk.

DOACs in acutely ill medical patients

Question: Should any DOAC vs LMWH be used for VTE prophylaxis in acutely ill hospitalized medical patients?

Question: Should any DOAC extended beyond hospital discharge vs standard duration non-DOAC VTE prophylaxis administered in hospital only be used in acutely ill medical patients?

Recommendation 11

In acutely ill hospitalized medical patients, the ASH guideline panel *recommends* using LMWH over DOACs as VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 12

In acutely ill hospitalized medical patients, the ASH guideline panel *recommends* inpatient VTE prophylaxis with LMWH only, rather than inpatient and extended duration outpatient VTE prophylaxis with DOACs (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). **Remark:** If patients are on a DOAC for other reasons, this recommendation may not apply.

Summary of the evidence. We did not find any systematic reviews addressing the questions and, thus, conducted a new systematic review. We made decisions a priori regarding search methods, eligibility criteria, data collection, and data analysis. We included 3 RCTs comparing a standard course inpatient treatment of 6 to 14 days of the LMWH enoxaparin with an extended treatment of 30 to 42 days of the DOAC rivaroxaban,[140] apixaban,[141] or betrixaban.[42] The studies had similar designs. We evaluated outcomes in 2 phases: first, we focused on outcomes at the end of the standard-course inpatient treatment with enoxaparin or oral DOAC (ie, enoxaparin and DOAC for the same period of time), and then we evaluated outcomes separately at the end of the prophylaxis period (ie, standard inpatient duration for enoxaparin vs extended-duration DOAC). Following our public comment period, we received data from the APEX trial investigators to allow us to conduct analyses focusing on the relevant time periods, as described above, and all outcomes. Specifically, we invited the APEX trial investigators to provide information about outcomes including all-cause mortality, PE, symptomatic DVT, and major bleeding at the end of short-term treatment with enoxaparin or oral DOAC. In response, the APEX investigators provided this additional information (Supplement 5).

The 3 RCTs reported the effects of DOAC vs LMWH on mortality, VTE-related mortality, PE, symptomatic DVT, and major bleeding. None of the studies reported whether the symptomatic DVTs were proximal or distal; therefore, we estimated the absolute effect on proximal and distal DVT by applying results to a representative baseline risk. Gastrointestinal bleeding was not reported separately in all trials, but the APEX investigators provided us with information about these events. In our analyses, none of the DOACs had effects that differed importantly or statistically from the others. Therefore, following our prespecified analysis approach, we used the combined analyses of the 3 RCTs to formulate recommendations. The EtD frameworks are shown at https://dbep.gradepro.org/profile/684ECAB2-2D90-B610-94A8-00BED6FC63FE (for Recommendation 11) and

https://dbep.gradepro.org/profile/200AE04A-D3F5-16AC-BEFE-A9E99C2A3900 (for Recommendation 12).

Any DOAC vs LMWH

Question: Should any DOAC vs LMWH be used for VTE prophylaxis in acutely ill hospitalized medical patients?

Benefits. In absolute terms, use of a DOAC compared with LMWH probably had no impact on VTE-related mortality (RR, 0.64; 95% CI, 0.21-1.98; ARR, 0 fewer deaths per 1000; 95% CI, 1 fewer to 1 more per 1000) and little impact on VTE (for nonfatal PE: RR, 1.01; 95% CI, 0.29-3.53; ARR, 0 fewer per 1000; 95% CI, 1 fewer to 3 more per 1000; for symptomatic DVT: RR, 1.03; 95% CI, 0.34-3.08; ARR, 0 fewer per 1000; 95% CI, 1 fewer to 2 more per 1000). We extrapolated these estimates for symptomatic proximal and distal DVT because trials did not report DVT location. For symptomatic proximal DVT, the ARR was 0 fewer per 1000 (95% CI, 1 fewer to 4 more per 1000) estimated for a baseline risk of 0.2%, and for symptomatic distal DVT, the ARR was 0 fewer per 1000 (95% CI, 4 fewer to 12 more per 1000) estimated for a baseline risk of 0.6%.

Harms and burden. In the 3 included trials, use of a DOAC compared with LMWH led to an increased risk for major bleeding (RR, 1.70; 95% CI, 1.02-2.82; ARI, 2 or 8 more hemorrhages per 1000 for 2 representative baseline risks of bleeding [low and high]). The 95% CIs for these absolute effects using baseline risks from Spencer et al were 0 to 4 more per 1000 and 2 to 22 more per 1000, respectively.[142]

Certainty in the evidence of effects. The overall certainty in these estimated effects was moderate owing to imprecision of the estimates for the VTE outcomes (see evidence profile in the online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, VTE-related death, PE, DVT, and bleeding was critical or important to patients for decision making. The panel judged that DOACs would lead to cost savings in hospital because of lower DOAC drug cost compared with LMWH. Compared with LMWH, DOACs are probably acceptable and definitely feasible.

Any DOAC extended beyond hospital discharge vs non-DOAC in hospital only

Question: Should any DOAC extended beyond hospital discharge vs non-DOAC VTE prophylaxis administered in hospital only be used in acutely ill medical patients?

Benefits. In absolute terms, extended use of DOACs appeared to have no impact on mortality (RR, 1.01; 95% CI, 0.89-1.14), with an ARR of 0 fewer per 1000 treated (95% CI, 5 fewer to 7 more per 1000). The relative risk for PE was reduced (RR, 0.67; 95% CI, 0.41-1.09), with an ARR of 1 fewer per 1000 treated (95% CI, 0-2 fewer per 1000). For proximal and distal symptomatic DVT, we applied an RR of 0.62 (95% CI, 0.36-1.05), which was the RR for any symptomatic DVT in the studies. The resulting ARR for symptomatic proximal DVT was 0 fewer per 1000 (95% CI, 0-1 fewer per 1000) for a baseline risk of 0.2%, and the ARR for symptomatic distal DVT was 2 fewer per 1000 (95% CI, 0-4 fewer per 1000) for a baseline risk of 0.6%.

Harms and burden. In the 3 trials, extended use of a DOAC led to an increased risk for major bleeding (RR, 1.99; 95% CI, 1.08-3.65). The ARI for 2 baseline risks based on Spencer et al[142] were 4 or 12 more hemorrhages per 1000 treated (95% CI, 0-10 more and 1-32 more per 1000, respectively).

Certainty in the evidence of effects. The certainty in these estimated effects was moderate owing to imprecision of the estimates when the small possible benefits are balanced against the harms.

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important for decision making to patients. Although the panel judged that extending prophylaxis with a DOAC was probably acceptable and feasible, it could increase inequity because of access to and cost of extended out-of-hospital use.

Conclusions and research needs for these recommendations

The guideline panel determined that there is moderate certainty in the evidence for net health harm given the increased bleeding risk from using a DOAC compared with LMWH in acutely ill medical inpatients, both for inpatient use and extended use. Other EtD criteria generally favored LMWH use in hospital only because the undesirable effects of DOACs were greater than the desirable consequences. The panel considered that the EtDs were formulated using RCTs that tested 3 DOACs, but there was no heterogeneity observed in the systematic review, and the drugs have the same mechanism of action. The panel prioritized symptomatic over asymptomatic VTE, and the latter were included in the trial end points. However, inclusion of asymptomatic VTE in our analysis would not have changed interpretation of the relative effects of treatment. A strong recommendation was warranted given the overall moderate certainty in the evidence and minimal absolute effects on mortality and VTE compared with the increased bleeding risk from DOACs.

The panel suggested that future research should address:

- DOAC use among medical inpatients or for extended prophylaxis after discharge in larger trials assessing symptomatic VTE and bleeding end points, and in more selected patients based on predicted risk of VTE and of bleeding; and
- Evaluation of lower-dose DOAC regimens in medical inpatients or for extended use after discharge, to determine whether this might mitigate bleeding risk while preventing VTE.[143]

Extended-duration outpatient prophylaxis vs inpatient-only prophylaxis in acutely ill medical patients

Question: Should extended-duration pharmacological VTE prophylaxis after discharge (ie, up to 30 or 40 days) vs in-hospital–only pharmacological VTE prophylaxis be used in acutely ill hospitalized medical patients?

Recommendation 13

In acutely ill medical patients, the ASH guideline panel *recommends* inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). **Remark:** This recommendation applies to heparin and DOACs.

Summary of the evidence. We identified 1 systematic review that provided evidence to address this question.[145] Our

update of the systematic review identified 1 additional study.[42] All studies included acutely and critically ill medical patients.

Four studies utilizing enoxaparin (1 study) or a DOAC (3 studies) for extended prophylaxis reported the effect of extended vs in-hospital–only pharmacological prophylaxis on the development of nonfatal PE, symptomatic proximal DVT, major bleeding, and mortality[42,140,141,145]; 3 studies reported the development of symptomatic distal DVT,[42,140,141] and 1 study[145] assessed the risk of developing HIT. These studies also provided evidence for Recommendation 14, addressing extended-duration prophylaxis with DOACs.

The EtD framework is shown at https://dbep.gradepro.org/profile/B7E7908E-FFD0-19C4-862E-16561BEC51FE.

Benefits. Extended duration of pharmacological prophylaxis (LMWH or DOAC) appeared to have no effect on mortality (RR, 1.00; 95% CI, 0.89-1.12; ARR, 0 per 1000; 95% CI, 5 fewer to 5 more per 1000). For VTE, there were important relative effects but small absolute effects. Specifically, for PE the RR was 0.63 (95% CI, 0.39-1.03), and ARR was 1 fewer per 1000 (95% CI, 0-3 fewer per 1000). For proximal DVT, the RR was 0.54 (95% CI, 0.32-0.91), and ARR was 3 fewer per 1000 (95% CI, 1-4 fewer per 1000 based on representative baseline risks).

Harms and burden. In the 4 trials, extended use of pharmacological prophylaxis led to an increased risk for major bleeding (RR, 2.09; 95% CI, 1.33-3.27; ARI, 4-13 more bleeds per 1000; 95% CI, 1-8 more and 4-27 more per 1000 for baseline risks of 0.4% and 1.2%, respectively, based on the trials and Decousus et al[39]).

Certainty in the evidence of effects. Overall, the certainty in these estimated effects was low owing to imprecision of the estimates and indirect comparisons (see evidence profile in the online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important to patients for decision making but that using extended prophylaxis could cause inequity because of concerns about cost and the ability to self-inject. A relevant trial was published after the guideline panel finalized this recommendation and during revision of this manuscript.[146] The study did not find that rivaroxaban was superior to placebo when given to medical patients at increased predicted VTE risk for 45 days after hospital discharge.[146] This finding is consistent with the conclusions of the systematic review conducted for this recommendation. Although this trial adds important information to the body of evidence for this recommendation, the guideline panel agreed that the trial results should not change the recommendation.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in the evidence for net health harm from using extended compared with in-hospital prophylaxis. Other EtD criteria were generally in favor of using in-hospital prophylaxis only, because the undesirable consequences were greater than the desirable consequences in acutely ill medical patients, leading to a recommendation for shorter prophylaxis.

With regard to future research, the panel suggests:

- Studies of risk assessment tools for guidance on defining high-risk status for VTE and bleeding at discharge;
- Trials of pharmacological or nonpharmacological interventions in selected high-risk medical patients for VTE at discharge[143]; and
- Studies that evaluate dose adjustments or lower doses of anticoagulants that might maximize benefit while minimizing harm when used for extended treatment to prevent VTE after hospital discharge.

Extended-duration outpatient prophylaxis vs inpatient-only UFH or LMWH in critically ill medical patients

Question: Should extended-duration (ie, up to 30 or 40 days) vs in-hospital–only UFH or LMWH be used for the thromboprophylaxis of VTE in critically ill hospitalized medical patients?

Recommendation 14

In critically ill medical patients, the ASH guideline panel *recommends* inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Because we did not find evidence addressing this question directly in critically ill hospitalized medical patients, the panel extrapolated the information found in acutely ill patients from recommendation 13 to critically ill patients. The EtD framework that combined acutely and critically ill patients is shown at https://dbep.gradepro.org/profile/627ca9c1-1a6f-4155-bb21-44ffdf6cc197.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in the evidence for net health harm from using extended compared with in-hospital prophylaxis in critically ill patients and that the other EtD criteria were generally in favor of using in-hospital–only prophylaxis so that the undesirable consequences were greater than the desirable consequences in critically ill medical patients. Given that this recommendation was based on indirect data and extrapolation from acutely ill medical patients, further research in critically ill medical patients is required. Research questions are listed in under recommendation 13.

Chronically ill medical patients or nursing home patients

Question: Should pharmacological VTE prophylaxis be used in chronically ill medical patients or nursing home patients?

Recommendation 15

In chronically ill medical patients, including nursing home patients, the ASH guideline panel *suggests* not using VTE prophylaxis compared with using any VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** If a patient's status changes to acute, other recommendations would apply.

Summary of the evidence. We did not identify any systematic review that addressed this question. We identified

1 randomized trial of LMWH vs placebo with 87 patients[147] that fulfilled our inclusion criteria and measured outcomes relevant to this question (mortality, PE, proximal and distal DVT). The study included outpatients with chronic obstructive pulmonary disease requiring home oxygen and who also had restricted physical activity. The study did not report the risk of major bleeding, gastrointestinal bleeding, or HIT specifically. The EtD framework is shown at https://dbep.gradepro.org/profile/92523320-6D45-1BCA-9311-C750EB428BCB.

Benefits. In absolute and relative terms, LMWH appeared to have a moderate impact on mortality and no impact on VTE, but these effects were considered very uncertain. For mortality, the RR was 0.43 (95% CI, 0.14-1.31), and the ARR was 119 fewer per 1000 (180 fewer to 65 more per 1000). For PE, the RR could not be calculated, because there were no events in the intervention and control groups. For proximal DVT, the RR was 0.98 (95% CI, 0.06-15.1), with an ARR of 0 fewer per 1000 (95% CI, 22 fewer to 329 more per 1000 using the study baseline risk of 2.3%). Reardon et al reported an incidence of 3.7% per year of any VTE in 2144 nursing home residents,[149] which was the basis of modeling of assumptions of a 3% VTE risk in a high-risk population, as well as a 1% VTE risk in a low-risk population. Based on the modeling of low- and high-risk populations, the ARR for proximal DVT was 0 fewer per 1000 (95% CI, 0 fewer to 5 more per 1000) and 0 fewer per 1000 (95% CI, 1 fewer to 15 more per 1000), respectively. The same RR was used for distal DVT, resulting in an ARR of 0 fewer per 1000 (95% CI, 1 fewer to 20 more per 1000) for a low-risk population and 0 fewer per 1000 (95% CI, 4 fewer to 61 more per 1000) for a high-risk population.

Harms and burden. The study did not report on major bleeding. The study reported an increase in thrombocytopenia (RR, 4.89; 95% CI, 0.24-98.96), but this increase was very imprecise, and the panel considered thrombocytopenia an important, but not critical, outcome for decision making.

Certainty in the evidence of effects. Overall, the certainty in these estimated effects is very low owing to very serious imprecision and serious indirectness of the estimates (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of death, PE, DVT, and major bleeding was critical to patients. The panel judged that the cost of pharmacological prophylaxis for this patient group would be moderate, and it could lead to inequity, because not all patient groups would be likely to receive pharmacological prophylaxis as the result of challenges with widespread implementation in nursing homes. Pharmacological prophylaxis was otherwise judged as probably not acceptable to all patients and stakeholders but probably feasible (see equity considerations above).

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the evidence that the undesirable consequences of pharmacological thromboprophylaxis in chronically ill medical patients outweigh the desirable consequences. The evidence suggested no important reduction in VTE but increased bleeding with use of LMWH in 1 study. Pharmacological thromboprophylaxis was deemed to be of high cost and probably not acceptable to stakeholders. The panel suggested future research:

- Studies on identification of high-risk subgroups of chronically ill medical patients who could benefit from VTE prophylaxis, with consideration given to those who are immobilized;
- Studies of low-dose anticoagulant approaches, including use of DOACs or aspirin in chronically ill medical patients; and
- Research on current clinical practices for VTE prevention and patient preferences for VTE prevention in chronically ill medical inpatients or nursing home residents.

Medical outpatients with minor provoking risk factors for VTE

Question: Should VTE prophylaxis be used in medical outpatients with minor provoking factors for VTE (eg, immobility, minor injury, illness/infection)?

Recommendation 16

In medical outpatients with minor provoking factors for VTE (eg, immobility, minor injury, illness, infection), the ASH guideline panel *suggests* not using VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Because we did not find evidence addressing this question, the panel decided to extrapolate the information found in acutely ill medical inpatients in recommendation 13. Evidence for outpatients with cancer is addressed in a separate ASH guideline. The EtD framework is shown at https://dbep.gradepro.org/profile/0F91C482-0EC7-18AC-8738-817C23635ED2.

Conclusions and research needs for this recommendation. The guideline panel used indirect evidence from acutely ill medical patients that evaluated extended outpatient prophylaxis and determined that there is low certainty in the evidence for net health harm from that evidence in medical outpatients with minor provoking factors for VTE. Through extrapolation, the other EtD criteria were generally not in favor of using prophylaxis, because the undesirable consequences were greater than the desirable consequences in these patients. Given that this recommendation was based on indirect data and extrapolation, further research is required. The recommendation against thromboprophylaxis in medical outpatients with minor provoking factors for VTE, cost of treatment in this population, probable inequity of a recommendation, and lack of general acceptability were additional undesirable consequences.

The panel felt that the following research areas would be helpful:

- Development of risk-assessment methods to determine absolute risk of VTE in outpatients with minor provoking VTE risk factors and
- Trials of interventions (pharmacological or nonpharmacological) in a high-risk population of outpatients with minor provoking VTE risk factors.

Long-distance travelers

Question: Should graduated compression stockings, LMWH, or aspirin vs no VTE prophylaxis be used by long-distance (>4 hours) travelers?

Recommendation 17

In long-distance (>4 hours) travelers without risk factors for VTE, the ASH guideline panel *suggests* not using graduated compression stockings, LMWH, or aspirin for VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** People without known risk factors who place a high value on prevention of VTE may choose to use graduated compression stockings (also reduces edema).

Recommendation 18

In people who are at substantially increased VTE risk (eg, recent surgery, history of VTE, postpartum women, active malignancy, or ≥2 risk factors, including combinations of the above with hormone replacement therapy, obesity, or pregnancy), the ASH guideline panel *suggests* using graduated compression stockings or prophylactic LMWH for long-distance (>4 hours) travel (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 19

In people who are at substantially increased VTE risk (eg, recent surgery, history of VTE, postpartum women, active malignancy, or ≥2 risk factors, including combinations of the above with hormone replacement therapy, obesity, or pregnancy) and in whom LMWH or graduated compression stockings is not feasible (eg, resource-constrained setting or aversion to other indicated anticoagulants), the ASH guideline panel *suggests* using aspirin rather than no VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Air travel and VTE

Summary of the evidence for baseline risk. Worldwide, 3.4 billion passengers traveled by air in 2015 (http://data.worldbank.org/indicator/IS.AIR.PSGR). We identified 1 systematic review evaluating the risk of a symptomatic DVT event within 4 weeks of flights longer than 4 hours. Air travel is associated with a 2.8-fold increased risk for DVT or PE (95% CI, 2.1-4.2).[149] The estimated absolute risk for symptomatic DVT with air travel is ~0.05% (95% CI, 0.01-0.19) and for asymptomatic DVT is 2.6% for a 4-hour flight and 3.6% for a ≥7-hour flight.[150] The risk was deemed to be 1 per 4600 flights taken,[151] and it suggested that the risk for a severe PE occurring immediately after air travel increases with the duration of travel, to up to 4.8 per million for flights longer than 12 hours. Our update of the review identified 11 additional relevant studies.[152-162] We did not consider studies addressing biomarkers as predictors of travel-related VTE. These associations were no longer evident by 12 weeks after travel. If symptomatic DVT develops, the potential impact is high. In ambulatory population-based cohorts, the estimated 28-day mortality for a first episode of symptomatic VTE is 11%.[163]

It is not clear that patients with prior VTE are particularly susceptible to air travel–related VTE. A case-control study did not show a higher risk for VTE with air travel or long-duration travel by car, bus, or train among patients with prior VTE compared with those without prior VTE.[160] This lack of increased risk was not explained by preventive measures taken during travel, because these were equally distributed between cases and controls. Two available studies assessed the risk of VTE in total joint arthroplasty patients, finding no association between preoperative or postoperative air travel and VTE risk.[154,156] However, findings might be biased if travelers took precautions to reduce their risk of VTE, and studies might have been underpowered to detect associations.

Several VTE risk factors (eg, cancer, plaster casts, hormone replacement therapy, oral contraceptives, and pregnancy) multiplicatively increase the risk of air travel–related VTE.[162] For example, pregnant women who traveled by air had an odds ratio (OR) for VTE of 14.3 (95% CI, 1.7-121.0) compared with an OR of 4.3 (95%, 0.9-19.8) associated with pregnancy alone.[164] Women who traveled by air while using oral contraceptives had an 8.2-fold (95% CI, 2.3-28.7) elevated risk for VTE compared with nontravelers who were not on contraceptives, whereas the risk with oral contraceptives alone was increased 2.5-fold (95% CI, 0.9-7.0).[162]

To interpret research for these questions, we used a baseline risk for symptomatic VTE of 215 per million trips for symptomatic VTE after travel longer than 4 hours (based on 1 in 4600 flights).[151] The shape of the relationship between duration of air travel and VTE risk is not well known, and these recommendations may require extrapolation to shorter or longer duration of travel.

Graduated compression stockings for long-distance travelers

Summary of the evidence for effects. We found 1 systematic review of 9 RCTs that addressed the impact of graduated compression stockings compared with not using stockings in long-distance travelers.[165] We did not find additional studies addressing this question. The EtD framework is shown at https://dbep.gradepro.org/profile/C18330E4-93EB-5807-ABAB-5F926CD54CCF.

Benefits. In absolute terms and on a population level, graduated compression stockings appeared to have very small and very uncertain effects on VTE, with an RR of 0.10 (95% CI, 0.04-0.25) extrapolated to all VTE events. For PE, the ARR was 11 fewer per 1 000 000 (95% CI, 9-12 fewer per 1 000 000), for proximal DVT, the ARR was 540 fewer per 1 000 000 (95% CI, 450-576 fewer per 1 000 000), and for distal DVT, the ARR was 2112 fewer per 1 000 000 (95% CI, 1760-2253 fewer per 1 000 000). Death did not occur in any of the studies.

Harms and burden. The panel did not consider any of the possible harms as critical. The tolerability of graduated compression stockings was described as very good, with no reported side effects in 4 RCTs. None of the 5 trials reported serious adverse effects of wearing the stockings, but in 1 trial, 4 patients developed varicose vein thrombosis, possibly as a result of the stockings.[165] The panel was concerned about potential allergy to the stocking material, but this adverse effect was not reported in the trials.

Certainty in the evidence of effects. Overall, the certainty in these estimated effects is very low owing to very serious

indirectness and serious risk of bias for the estimates (see evidence profile and online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding was critical or important for decision making to patients. Graduated compression stockings were considered to not be cost-effective, to be acceptable to some but not to other stakeholders, and probably feasible.

LMWH and aspirin for long-distance travelers

Summary of the evidence for effects. We found several narrative and systematic reviews that addressed the impact of LMWH or aspirin compared with no prophylaxis in long-distance travelers.[150,166,167] Our updated search for studies did not identify eligible RCTs. Only 1 small RCT evaluated the impact of LMWH, aspirin, or no prophylaxis on VTE.[168] The EtD frameworks are shown at https://dbep.gradepro.org/profile/916AAFBA-F72C-2CBE-BD33-8EA86A031824 and https://dbep.gradepro.org/profile/7E083128-12E4-1EB2-9567-2E37334ECB8D.

Benefits. In absolute terms and on a population level, LMWH appeared to have a very small and very uncertain effect on VTE compared with no treatment (RR, 0.10; 95% CI, 0.10-2.11 extrapolated to all VTE events; ARR, 3 fewer per 1 000 000; 95% CI, from 3 fewer to 4 more per 1 000 000 for PE; ARR, 176 fewer per 1 000 000; 95% CI, from 194 fewer to 217 more per 1 000 000 for proximal DVT; ARR, 702 fewer per 1 000 000; 95% CI, from 772 fewer to 866 more per 1 000 000 for distal DVT; death did not occur in this trial). In absolute terms and on a population level, aspirin appeared to have an even smaller and very uncertain effect on VTE compared with no treatment (RR, 0.75; 95% CI, 0.13-4.32 extrapolated to all VTE events; ARR, 1 fewer per 1 000 000; 95% CI, from 3 fewer to 12 more per 1 000 000 for PE; ARR for proximal DVT, 49 fewer per 1 000 000; 95% CI, from 170 fewer to 650 more per 1 000 000; ARR for distal DVT, 195 fewer per 1 000 000; 95% CI, from 679 fewer to 2590 more per 1 000 000; death did not occur in this trial).

Harms and burden. Bleeding did not occur with LMWH or aspirin in the 1 available RCT.

Certainty in the evidence of effects. Overall, the certainty in these estimated effects is very low owing to very serious indirectness and serious risk of bias for the estimates (see evidence profile in the online EtD framework).

Other EtD criteria and considerations. The panel assumed that avoidance of PE, DVT, and bleeding events was critical or important to patients for decision making. Given the panel's judgment that LMWH and aspirin showed no net health benefit, they were not cost-effective. Although the panel assumed no impact on health equity for aspirin, it felt that equity would be reduced if LMWH were recommended, given challenges with access. The use of LMWH was considered acceptable to some but not to other stakeholders and probably not feasible for all travelers, but use of aspirin was considered acceptable and feasible.

Conclusions and research needs for recommendations for long-distance travelers

The guideline panel determined that, although the health effects may suggest net benefit for the use of graduated compression stockings, cost would be moderate, and use of stockings would not be cost-effective. Equity would probably be reduced because graduated compression stockings would likely be an out-of-pocket cost, and acceptability would vary because insurance companies may not be willing to cover the cost. Proper use of graduated compression stockings might require support in the elderly and people with disabilities, but stockings on a population level were considered probably feasible. Overall, the panel judged that, for all interventions, the undesirable consequences were greater than the desirable consequences and made recommendations against their use, with the exception of patients with VTE risk factors. People without known VTE risk factors who place a high value on prevention of VTE may choose to use graduated compression stockings. For LMWH and aspirin, people with substantially increased risk for VTE (eg, recent surgery, history of VTE, hormone replacement therapy, pregnant or postpartum women, active malignancy, or $\geq$2 VTE risk factors) may experience more health benefits than harms.

With regard to research needs, the panel identified:

- Risk-assessment methods to define travelers at sufficiently high VTE risk to warrant VTE prophylaxis intervention; and
- Large pragmatic trials of interventions to prevent VTE in travelers, particularly those at high VTE risk; and
- Evidence on effectiveness and safety of DOACs to prevent VTE in travelers at risk of VTE.

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

There are 5 other recent guidelines available on the prevention of VTE in medical patients: the 2011 American College of Physicians guidelines,[169] the 2012 American College of Chest Physicians (ACCP) guidelines,[170] the 2013 update from the International Union of Angiology (IUA),[24] the 2017 update from the Asian Venous Thrombosis Forum,[171] and the 2018 National Institute for Health and Care Excellence guidelines.[172] The Agency for Healthcare Research and Quality in the United States also provides a guide for implementing effective quality improvement in this area.[173] Two major differences between the ASH guidelines and many of the others is the consistent use of systematic reviews and EtDs, which increases transparency, and the use of marker states to estimate the relative importance of key outcomes of treatment to patients.

All guidelines advocated assessing the risk of VTE and bleeding in admitted medical patients. The American College of Physicians issued 2 additional recommendations: for the use of heparin or a related drug, unless patients were at high bleeding risk, and against use of graduated compression stockings. The ACCP guidelines were most similar to the ASH guideline in scope and methods. The ACCP advised not to use prophylaxis in medical patients at low risk of VTE, based on the Padua Prediction Score, or at high risk of bleeding. For at-risk medical or critically ill patients, LMWH, UFH twice daily or thrice daily, and fondaparinux were all recommended, with selection among these based on patient preference, compliance, and local factors related to formularies. The ASH panel recommended LMWH or fondaparinux over UFH. For patients at risk of bleeding, the ACCP recommended mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression, with consideration of pharmacologic prophylaxis if the bleeding risk resolved. This is similar to the ASH guidelines, although the recommendations were not specifically keyed to bleeding risk but to persons at risk who are not receiving pharmacological prophylaxis. Unlike ACCP, the ASH panel

Table 4. Research priorities identified by patient population

Acutely or critically ill medical inpatients
Better information on baseline risk assessment of thrombosis and bleeding in acutely or critically ill medical inpatients is needed, in particular whether risk varies over the course of admission
More information on the optimal dosing of parenteral anticoagulation to prevent VTE in acutely or critically ill medical inpatients is needed. In particular, can lower or higher doses be used in different settings (perhaps dependent on baseline risk), and should dosing be adjusted in obese patients, underweight patients, and patients with renal disease?
Determination of the acceptable balance between bleeding and thrombosis risk in the context of selecting the optimal VTE prophylaxis in critically ill medical patients
Net health benefit of mechanical prophylaxis in a lower risk medical inpatient population
Utility of outpatient use of mechanical prophylaxis in medical outpatients at risk of VTE
Direct comparisons between graduated compression stockings and pneumatic compression devices in acutely or critically ill medical inpatients
Impact of use of pneumatic compression devices in acutely or critically ill medical inpatients at high bleeding risk or with active bleeding
Better information on bleeding risk in acutely or critically ill medical inpatients to inform decisions about use of mechanical or pharmacological VTE prophylaxis
More direct evidence on combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone via clinical trials on efficacy, harms, and adherence to the intervention, particularly in high-risk medical inpatients in whom the balance of potential benefits vs harms might be more favorable than among lower-risk patients
Obtain patient preferences for mechanical or pharmacological prophylaxis in the hospital setting by studying feasibility, equity, and acceptability
Determine current utilization rate of combined mechanical and pharmacological prophylaxis in practice among acutely or critically ill medical inpatients
Provide more direct evidence on combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone via clinical trials on efficacy, harms and adherence to the intervention, particularly in high-risk medical inpatients in whom the balance of potential benefits vs harms might be more favorable than among lower-risk patients
Comparative effectiveness research on combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone in acutely or critically ill medical inpatients
Conduct trials of combined mechanical and pharmacological prophylaxis compared with pharmacological prophylaxis alone among very high risk patient groups
A systematic review of observational studies and a large comparative RCT are needed to increase the evidence available comparing pneumatic compression devices with graduated compression stockings in acutely or critically ill medical patients
Studies of pneumatic compression devices compared with graduated compression stockings in acutely or critically ill medical patients with contraindications to pharmacological prophylaxis or those at high bleeding risk
Study DOAC use among medical inpatients or for extended prophylaxis after discharge in larger trials assessing symptomatic VTE and bleeding end points in more selected patients based on predicted risk of VTE and of bleeding
Evaluation of lower-dose DOAC regimens in acutely ill medical inpatients or for extended use after discharge, to determine whether this might mitigate bleeding risk while preventing VTE
Trials of pharmacological or nonpharmacological interventions in selected high-risk medical patients at discharge
Studies that evaluate dose adjustments or lower doses of anticoagulants that might maximize benefit while minimizing harm when used for extended treatment to prevent VTE after hospital discharge among acutely or critically ill medical inpatients
Chronically ill medical inpatients or nursing home residents
Studies on identification of high-risk subgroups of chronically ill medical patients who could benefit from VTE prophylaxis, with consideration given to those who are immobilized
Studies of low-dose anticoagulant approaches, including use of DOACs or aspirin in chronically ill medical patients
Research on current clinical practices for VTE prevention and patient preferences for VTE prevention in chronically ill medical inpatients or nursing home residents
Studies on identification of high-risk subgroups of chronically ill medical patients who could benefit from VTE prophylaxis, with consideration given to those who are immobilized
Outpatients with minor provoking VTE risk factors
Development of risk-assessment methods to determine absolute risk of VTE in outpatients with minor provoking VTE risk factors
Trials of interventions (pharmacological or nonpharmacological) in a high-risk population of outpatients with minor provoking VTE risk factors
Travelers
Risk-assessment methods to define travelers at sufficiently high VTE risk to warrant VTE prophylaxis intervention
Large pragmatic trials of interventions to prevent VTE in travelers, particularly those at high VTE risk
Evidence on effectiveness and safety of DOACs to prevent VTE in travelers at risk of VTE

addressed combination mechanical and pharmacological prophylaxis over either alone and suggested against the combination.

The ASH panel and ACCP recommended against prophylaxis in chronically immobilized outpatients or nursing home residents. The ASH panel also specifically recommended against prophylaxis in outpatients with minor provoking factors for VTE. The ACCP and the ASH panel considered long-distance travelers and advised against prophylaxis for persons without risk factors. For long-distance travelers at increased risk for VTE, the ACCP recommended 15- to 30-mm Hg below-knee graduated compression stockings, frequent ambulation, calf muscle exercise, or sitting in an aisle seat. They recommended against the use of aspirin or anticoagulants. The ASH panel recommended LMWH or graduated compression stockings and the use of aspirin if these were not feasible or available.

In the 2013 IUA updated guidelines, risk assessment of medically ill patients and treatment with LMWH or fondaparinux was recommended, as was consideration of postdischarge treatment of women, patients older than 75 years, or those with severe immobility. They also recommended, with moderate certainty, the use of graduated compression stockings plus intermittent pneumatic compression in ischemic or hemorrhagic stroke patients in whom risks of anticoagulant prophylaxis were deemed unacceptable.

The 2017 Asian Venous Thrombosis Forum updated guidelines for medically ill patients concluded that, if prophylaxis was used, pharmacological prophylaxis was preferred in the absence of bleeding risk; otherwise, intermittent pneumatic compression, but not graduated compression stockings, were recommended.[171]

The National Institute for Health and Care Excellence guidelines released in 2018 addressed VTE prevention in all hospitalized patients.[172] For medical patients, they addressed specific subgroups separately: acute coronary syndrome, stroke, medical, renal impairment, cancer, palliative care, critically ill, and psychiatry patients. Differences from the ASH guidelines include:

- No prophylaxis generally for patients with acute coronary syndrome;
- Consider prophylaxis in those on long-term anticoagulation if this is interrupted;
- Use intermittent pneumatic compression in acute stroke patients for 30 days or until the patient is mobile or discharged;
- Use pharmacological prophylaxis in acutely ill medical patients for 7 days minimally, with LMWH preferentially;
- Use LMWH or UFH, with lower doses of each if desired, for medical patients with renal impairment;
- Use prophylaxis with LMWH in those receiving palliative care if desired, but not in the last days of life;
- Use mechanical prophylaxis in critically ill patients if pharmacological prophylaxis is contraindicated;
- Use daily, or more frequent, VTE and bleeding risk assessments in critically ill patients;
- For acute psychiatric patients, perform VTE risk assessment, and if prophylaxis is used, use fondaparinux or LMWH; and
- Recommendation for education of patients/caregivers on VTE and VTE prevention at admission and discharge.

The ASH panel addressed use of DOACs for inpatient and postdischarge prophylaxis in medical patients using data not available to other guideline groups and recommended against the use of DOACs over other treatments in the hospital. Like the ACCP and unlike the IUA, the ASH panel recommended against extending prophylaxis after discharge with a DOAC or other agent (with only enoxaparin being evaluated by the ACCP and the IUA). The other guidelines that we describe here did not address extended postdischarge prophylaxis.

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. The necessary inclusion of results from older trials might pose difficulty in interpretation of findings given secular trends in characteristics of acutely or critically ill medical inpatients over the past 2 decades (eg, length of stay, illness severity, duration of administered VTE prophylaxis). We did not address whether twice or thrice daily unfractionated heparin should be used when unfractionated heparin is chosen, because we did not develop a guideline question for this, there are little data, and there are no recent data.

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.[174] The Agency for Healthcare Research and Quality in the United States provides a guide for implementing effective quality improvement in this patient population.[175]

Priorities for research

On the basis of gaps in evidence identified during the guideline-development process, the panel identified 29 areas for further research, which are summarized in Table 4.

Acknowledgments

The authors thank Itziar Etxeandia, Arnav Agarwal, Samantha Craigie, Rana Qadeer, Farid Foroutan, Housne Ara, Federico Popoff, Maram Hakoum, Tejan Baldeh, Stephanie Ross, Luis Colunga, John Riva, and Rohan Kehar for supporting the systematic reviews. A template of the guidelines for all panels (prepared by H.J.S.) was critically reviewed by Adam Cuker, Rob Kunkle, the ASH Guideline Oversight Subcommittee, the Methods Group supporting the guidelines, and *Blood Advances* editors.

Authorship

Contribution: H.J.S. wrote the first draft of the manuscript and revised the manuscript based on authors' suggestions; M.C. contributed to drafting and critical revisions of the manuscript and contributed to further drafts; guideline panel members (H.J.S., M. C., J.B.-W., A.E.B., F.A.S., F.D., S.R.K., J.L., S.M.R., N.A.Z., K.A.B.) critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (H.J.S., S.B., A.D., G.P.M., I.N., R.N., W.W., J.J.Y.-N., Y.Z.) contributed evidence summaries to the guidelines; and W.W. checked the

manuscript accuracy and coordinated the systematic review team with R.N. and H.J.S. All authors approved the content. M.C. and H.J.S. were the chair and vice-chair of the panel and led the panel meetings.

Conflict-of-interest disclosure: All authors were members of the guideline panel, members of the systematic review team, or both. As such, they completed a disclosure of interest form, which was reviewed by ASH and is available as Supplements 2 and 3.

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