CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy

Daniel M. Witt,[1] Robby Nieuwlaat,[2] Nathan P. Clark,[3] Jack Ansell,[4] Anne Holbrook,[5] Jane Skov,[6] Nadine Shehab,[7] Juliet Mock,[8] Tarra Myers,[9] Francesco Dentali,[10] Mark A. Crowther,[11] Arnav Agarwal,[2,12] Meha Bhatt,[2] Rasha Khatib,[13] John J. Riva,[2,14] Yuan Zhang,[2] and Gordon Guyatt[2]

[1]Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT; [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [3]Clinical Pharmacy Anticoagulation and Anemia Service, Kaiser Permanente Colorado, Aurora, CO; [4]School of Medicine, Hofstra Northwell, Hempstead, NY; [5]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, ON, Canada; [6]Unit for Health Promotion Research, Department of Public Health, University of Southern Denmark, Esbjerg, Denmark; [7]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA; [8]Aurora Medical Center Summit, Summit, WI; [9]Cambridge, ON, Canada; [10]Department of Medicine and Surgery, Insubria University, Varese, Italy; [11]Department of Medicine, McMaster University, Hamilton, ON, Canada; [12]Department of Medicine, University of Toronto, Toronto, ON, Canada; [13]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL; and [14]Department of Family Medicine, McMaster University, Hamilton, ON, Canada

Background: Clinicians confront numerous practical issues in optimizing the use of anticoagulants to treat venous thromboembolism (VTE).

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians and other health care professionals in their decisions about the use of anticoagulants in the management of VTE. These guidelines assume the choice of anticoagulant has already been made.

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

Results: The panel agreed on 25 recommendations and 2 good practice statements to optimize management of patients receiving anticoagulants.

Conclusions: Strong recommendations included using patient self-management of international normalized ratio (INR) with home point-of-care INR monitoring for vitamin K antagonist therapy and against using periprocedural low-molecular-weight heparin (LMWH) bridging therapy. Conditional recommendations included basing treatment dosing of LMWH on actual body weight, not using anti–factor Xa monitoring to guide LMWH dosing, using specialized anticoagulation management services, and resuming anticoagulation after episodes of life-threatening bleeding.

Summary of recommendations

Anticoagulant therapy is complex and associated with both substantial benefits (reduced risk for thrombus extension and fatal pulmonary embolism [PE] in the setting of acute illness and recurrent venous thromboembolism [VTE] thereafter) and risks (life-threatening bleeding complications).[1] Recognizing and mitigating risk for harm from anticoagulants requires an evidence-based approach to anticoagulant management and patient education. These guidelines focus on the optimal management of anticoagulant drugs for the prevention and treatment of VTE following the choice of an anticoagulant. Key management strategies for optimal use of anticoagulants include initial anticoagulant dose selection

Submitted 16 August 2018; accepted 24 September 2018. DOI 10.1182/bloodadvances.2018024893.

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.

(recommendation 1), drug-interaction management (recommendation 2), point-of-care international normalized ratio (INR) testing (recommendations 3 and 4), INR recall interval selection (recommendations 5 and 6), laboratory monitoring of the anticoagulant response (recommendations 7-9), transitions between anticoagulants (recommendation 10), the use of specialized anticoagulation-management services (AMSs) (recommendation 11), structured patient education (recommendation 12), efforts to improve adherence to anticoagulant-medication regimens (recommendations 13a-d), invasive procedure management (recommendations 14 and 15), excessive anticoagulation and bleeding management (recommendations 16, 17, 18a and b, 19, and 20), anticoagulant resumption following bleeding (recommendation 21), and renal function monitoring (good practice statements).

These guidelines are based on updated and original systematic reviews of evidence developed under the direction of the McMaster University GRADE Centre. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[2-5] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[6-12] to assess certainty in evidence and formulate recommendations.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel *recommends*..."), or conditional ("the guideline panel *suggests*…") and has the following interpretations.

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 should assess whether decision-making is duly documented.
- For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Recommendations

Initial anticoagulant dose selection

Recommendation 1. In obese patients receiving low-molecular-weight heparin (LMWH) therapy for treatment of acute VTE, the American Society of Hematology (ASH) guideline panel *suggests* initial LMWH dose selection according to actual body weight rather than dose selection based on a fixed maximum daily dose (ie, capped dose) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Drug-interaction management

Recommendation 2. For patients requiring administration of inhibitors or inducers of P-glycoprotein (P-gp) or strong inhibitors or inducers of cytochrome P450 (CYP) enzymes, the ASH guideline panel *suggests* using an alternative anticoagulant (such as vitamin K antagonist [VKA] or LMWH) rather than a direct oral anticoagulant (DOAC) for the treatment of VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Point-of-care INR testing

Recommendation 3. For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using home point-of-care INR testing (patient self-testing [PST]) over any other INR testing approach except patient self-management (PSM) (see recommendation 4) in suitable patients (those who have demonstrated competency to perform PST and who can afford this option) (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 4. For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel *recommends* using point-of-care INR testing by the patient at home and self-adjustment of VKA dose (PSM) over any other management approach, including PST in suitable patients (those who have demonstrated competency to perform PSM and who can afford this option) (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Selecting the timing between INR measurements (INR recall interval)

Recommendation 5. For patients receiving VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using an INR recall interval of 4 weeks or fewer rather than intervals longer than

4 weeks following VKA dose adjustment *due to an out-of-target-range INR* (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 6. For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using a longer (6-12 weeks) INR recall interval rather than a shorter (4 weeks) INR recall interval *during periods of stable INR control* (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Laboratory monitoring of the anticoagulant response

Recommendation 7. For patients with renal dysfunction (creatinine clearance, <30 mL/min) receiving LMWH therapy for treatment of VTE, the ASH guideline panel *suggests against* using anti–factor Xa concentration monitoring to guide LMWH dose adjustment (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Instead of monitoring anti–factor Xa concentrations, providers should consider using doses adjusted for renal function as recommended in product labeling (eg, enoxaparin) or switching to an alternative anticoagulant with lower renal clearance, such as unfractionated heparin (UFH) or a different LMWH.

Recommendation 8. For patients with obesity receiving LMWH therapy for treatment of VTE, the ASH guideline panel *suggests against* using anti–factor Xa concentration monitoring to guide LMWH dose adjustment (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Providers should consider LMWH using doses based on actual body weight (see recommendation 1) and not monitoring anti–factor Xa concentrations, similar to the approach used in nonobese patients.

Recommendation 9. For patients receiving DOAC therapy for the treatment of VTE, the ASH guideline panel *suggests against* measuring the DOAC anticoagulant effect during management of bleeding (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Transitions between anticoagulants

Recommendation 10. For patients transitioning from DOAC to VKA, the ASH guideline panel *suggests* overlapping DOAC and VKA therapy until the INR is within the therapeutic range *over* using LMWH or UFH "bridging therapy" (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Use of specialized AMSs

Recommendation 11. For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests* using specialized AMS care rather than care provided by the patient's usual health care provider (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Structured patient education

Recommendation 12. For patients receiving oral anticoagulation therapy for VTE treatment, the ASH guideline panel *suggests* using supplementary patient education in addition to basic education (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Efforts to improve anticoagulant-medication adherence

Recommendation 13a. For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using a daily lottery (between a 1-in-5 and 1-in-100 chance of a monetary reward each day if a pill compartment on a sophisticated electronic-medication-monitoring system is accessed) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 13b. For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using electronic reminders (daily alarm via an electronic-medication-monitoring system) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation applies specifically to a sophisticated alert system used in the study evaluated by the panel.

Recommendation 13c. For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *recommends against* using a daily lottery (see recommendation 13a) plus electronic reminders (see recommendation 13b) to improve medication adherence (strong recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation applies specifically to a sophisticated alert system used in the study evaluated by the panel.

Recommendation 13d. For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using visual medication schedules (provided to patients at each visit, along with brief counseling) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Invasive procedure management

Recommendation 14. For patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures, the ASH guideline panel *recommends against* periprocedural bridging with LMWH or UHF in favor of interruption of VKA alone (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 15. For patients interrupting DOAC therapy for scheduled invasive procedures, the ASH guideline panel *suggests against* performing laboratory testing for DOAC anticoagulant effect prior to procedures (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Excessive anticoagulation and bleeding management

Recommendation 16. For patients receiving VKA for treatment of VTE with INRs of >4.5 but <10 and without clinically relevant bleeding, the ASH guideline panel *suggests* using temporary cessation of VKA alone *without* the addition of vitamin K (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 17. For patients with life-threatening bleeding during VKA treatment of VTE who have an elevated INR, the ASH guideline panel *suggests* using 4-factor prothrombin complex concentrates (PCCs) rather than fresh-frozen plasma (FFP) as an addition to cessation of VKA and IV vitamin K (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 18a. For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using *either* 4-factor PCC administration as an addition to cessation of oral direct Xa inhibitor *or* cessation of oral direct Xa inhibitor alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Recommendation 18b. For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using coagulation factor Xa (recombinant), inactivated-zhzo in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Recommendation 19. For patients with life-threatening bleeding during dabigatran treatment of VTE, the ASH guideline panel *suggests* using idarucizumab in addition to cessation of dabigatran rather than no idarucizumab (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding.

Recommendation 20. For patients with life-threatening bleeding during LMWH or UFH treatment of VTE, the ASH guideline panel *suggests* using protamine in addition to cessation of LMWH or UFH rather than no protamine (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding.

Anticoagulant resumption following bleeding

Recommendation 21. For patients receiving anticoagulation therapy for VTE who survive an episode of major bleeding, the ASH guideline panel *suggests* resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation specifically applies to patients who require long-term or indefinite anticoagulation (ie, are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and are willing to continue anticoagulation therapy).

Values and preferences

In general, these recommendations place greater value on outcomes related to prevention of mortality, PE, deep vein thrombosis (DVT), major bleeding, quality of life, and emergency department and/or hospital visits. The impact of recommendations on measures of anticoagulation control, medication adherence, and inconvenience of therapy was also considered in relation to their importance for patients.

Explanations and other considerations

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

Good practice statements: renal function monitoring

For patients with creatinine clearance of ≥50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel agrees that good practice includes renal function monitoring every 6 to 12 months (ungraded good practice statement).

For patients with creatinine clearance of <50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel agrees that good practice includes renal function monitoring approximately every 3 months (ungraded good practice statement).

Introduction

Aim(s) of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations addressing the optimal use of anticoagulant therapy in the management of VTE assuming the choice of which anticoagulant to use has already been made. Other aspects of VTE treatment (such as choice and duration of anticoagulant treatment, inpatient or outpatient management, treatment of cancer-associated VTE, indications for advanced therapies, and treatment of superficial vein thrombosis, calf vein thrombosis, and subsegmental PE) are addressed in other guidelines. Recommendations focus on commonly used anticoagulant medications, including UFH, LMWH, fondaparinux, VKA, and the DOACs apixaban, dabigatran, edoxaban, and rivaroxaban (betrixaban was not available during panel deliberations and is not currently approved for treatment of VTE; thus, it was not considered in any of the evidence). The specific objectives of the recommendations are to improve patient-important outcomes, including overall mortality, recurrent VTE, major bleeding, and quality of life. For specific recommendations, the panel considered time in the therapeutic INR range (TTR) as a surrogate for bleeding and thrombosis. For all recommendations, the panel considered resource use, cost-effectiveness, potential impact on health care equity, acceptability, and feasibility when such information was available.

The target audience for these recommendations includes patients, physicians, other clinicians, and decision-makers. Policy makers

interested in these guidelines include those involved in developing local, national, or international plans aimed at reducing the incidence and improving the management of VTE and evaluating direct and indirect harms and costs related to VTE and associated treatments. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem(s)

Optimal use of anticoagulant drugs for treatment of VTE requires a comprehensive approach to patient management.[13] Bleeding and therapeutic failure are common and serious complications of administering anticoagulant drugs.[14-16]

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[6-12] 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 Guidelines International Network–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[2-5] An article detailing the methods used to develop these guidelines is forthcoming.

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with that of 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (Adam Cuker) and vice chair (Holger J. Schünemann). 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 center team is described in supplement 1.

The panel included hematologists, internists, a clinical pharmacologist, other physicians, and pharmacists with clinical and research expertise in the use of anticoagulants; physicians and other scientists from other disciplines with similar expertise; methodologists with expertise in evidence appraisal and guideline development; and 2 patient representatives. The panel chair was a practicing anticoagulation pharmacist and content expert. The vice chair was a practicing internist and methodologist with experience in guideline development processes.

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 (www.surveymonkey.com and www.gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

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

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representatives were offered an honorarium of US $200 each (1 individual accepted the honorarium, and 1 declined it). The panelists received no other payments. Through the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine[17] and the Guidelines International Network.[5] 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, that is, no current material interest in any commercial entity with a product that could be affected by the guidelines. Some panelists disclosed new interests or relationships during the development process, but the balance of the majority was maintained.

Before appointment to the panel, individuals disclosed both financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of 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.[5,18-20] The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

None of the McMaster-affiliated researchers who supported the guideline development process had any current, material interest in a commercial entity with any product that could be affected by the guidelines. On a recommendation-by-recommendation basis, none of the researchers who contributed to the systematic evidence reviews informing a recommendation had any current, material interest in a commercial entity with any product that could be affected by the recommendation. Supplement 3 provides the

Table 1. Prioritized questions for optimal management of anticoagulation therapy

Prioritized questions
1. In obese patients receiving LMWH therapy for treatment of acute VTE, should initial LMWH dose selection according to actual body weight vs dose selection based on a fixed maximum daily dose (i.e., capped dose) be used?
2. For patients requiring administration of inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP enzymes, should a DOAC or an alternative anticoagulant be used for treatment of VTE?
3. For patients receiving maintenance VKA therapy for treatment of VTE, should point-of-care INR testing by the patient at home (PST) vs any other INR testing approach be used?
4. For patients receiving maintenance VKA therapy for treatment of VTE, should point-of-care INR testing by the patient at home and self-adjustment of VKA dose (PSM) vs any other management approach be used?
5. For patients receiving VKA therapy for treatment of VTE, should a shorter INR recall interval vs a longer INR recall interval be used following VKA dose adjustment due to an out-of-target-range INR?
6. For patients receiving maintenance VKA therapy for treatment of VTE, should a longer (eg, 6-12 wk) INR recall interval vs a shorter (eg, 4 wk) INR recall interval be used during periods of stable INR control?
7. For patients with renal dysfunction (creatinine clearance of <30 mL/min) receiving LMWH therapy for treatment of VTE, should clinicians monitor anti–factor Xa concentration to guide LMWH dose adjustment vs no such monitoring?
8. For patients with obesity receiving LMWH therapy for treatment of VTE, should clinicians monitor anti–factor Xa concentration to guide LMWH dose adjustment vs no such monitoring?
9. For patients receiving DOAC therapy for the treatment of VTE, should measurement of the DOAC anticoagulant effect vs no measurement of DOAC anticoagulant effect be used during management of bleeding?
10. For patients transitioning from DOAC to VKA, should LMWH or UFH "bridging therapy" vs overlapping DOAC therapy be used until the INR is within the therapeutic range?
11. For patients receiving anticoagulation therapy for treatment of VTE, should specialized AMS care vs care provided by the patient's regular health care provider be used for anticoagulation management?
12. For patients receiving oral anticoagulation therapy for VTE treatment, should supplementary patient education be offered vs no supplementary patient education?
13. For patients receiving anticoagulation therapy for VTE, should interventions to improve adherence (eg, refill reminders, INR reminders) vs usual care be used?
14. For patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures, should periprocedural bridging with LMWH or UHF vs interruption of VKA therapy alone be used?
15. For patients interrupting DOAC therapy for scheduled invasive procedures, should performing laboratory testing for DOAC anticoagulant effect be used vs interrupting DOAC therapy alone?
16. For patients receiving VKA for treatment of VTE with INR of >4.5 but <10 and without clinically relevant bleeding, should temporary cessation of VKA plus administration of vitamin K vs temporary cessation of VKA alone be used?
17. For patients with life-threatening bleeding during VKA treatment of VTE, should 4-factor PCC vs FFP be used, in addition to cessation of VKA and IV vitamin K?
18. For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, should cessation of direct Xa inhibitor plus reversal of the direct Xa inhibitor anticoagulant effect vs cessation of direct Xa inhibitor alone be used?
19. For patients with life-threatening bleeding during dabigatran treatment of VTE, should cessation of dabigatran plus idarucizumab administration vs cessation of dabigatran alone be used?
20. For patients with life-threatening bleeding during LMWH or UFH treatment of VTE, should cessation of LMWH or UFH plus protamine vs cessation of LMWH or UFH alone be used?
21. For patients receiving treatment of VTE who survive an episode of anticoagulation therapy-related major bleeding, should resumption of oral anticoagulation therapy vs discontinuation of oral anticoagulation therapy be used?
22. For patients with creatinine clearance of ≥50 mL/min receiving DOAC therapy for treatment of VTE, should renal function be monitored every 6 to 12 mo vs no such monitoring?
23. For patients with creatinine clearance of <50 mL/min receiving DOAC therapy for treatment of VTE, should renal function be monitored more frequently (every 3 mo) vs no such monitoring?

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 (www.gradepro.org)[21] and SurveyMonkey (www.surveymonkey.com) to brainstorm and then prioritize the questions described in Table 1.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[22] In brief, the panel brainstormed all possible outcomes and then rated their relative importance for decision-making following the GRADE approach.[22] During this rating process, the panel used definitions of the outcomes ("marker states") developed for these guidelines. Rating outcomes by their relative importance helps focus attention on those outcomes that are most important and helps resolve or clarify potential disagreements. The panel rated the following outcomes as critical for decision-making across questions: mortality, PE, DVT in the upper leg, DVT in the upper arm, and major bleeding. For specific questions, other outcomes were included to inform decision-making, including TTR as a surrogate for bleeding and thrombosis, impairment of quality of life, critical INR as a surrogate for bleeding and thrombosis, increased duration of hospitalization, medication adherence as a surrogate for bleeding and thrombosis, and delay of intervention. Some studies reported outcomes differently from what the panel determined to be critical or important for decision-making. Typically, outcomes are reported as "any VTE," "any PE," "any DVT," "any proximal DVT," or "any distal DVT," sometimes preceded by "asymptomatic" or "symptomatic."

Reporting of outcomes was inconsistent across studies. Some studies assessed thromboembolic and bleeding outcomes for indications other than VTE; in these cases, those results were extrapolated to PE and DVT outcomes and used to estimate the relative effects on prioritized outcomes. In such instances, the panel rated down certainty for indirectness.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE EtD table, using the GRADEpro Guideline Development Tool (www.gradepro.org).[6,7,12] The EtD table summarized the results of systematic reviews of the literature that were updated or performed specifically for these guidelines. The EtD table addressed desirable and undesirable effects of interventions, certainty in the evidence, values and preferences (relative importance of outcomes), resource use, health equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for improvement. To ensure that recent studies were not missed, searches (presented in supplement 4) were updated during February and March 2017, and panel members remained alert for new eligible studies and could bring these to the panel for potential inclusion.

Under the direction of the McMaster GRADE Centre, researchers followed the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors regarding risk of bias were accepted and checked for accuracy or conducted de novo. For new reviews, risk of bias was assessed at the outcome level using the Cochrane Collaboration's risk-of-bias tools for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values and preferences, and costs and summarized findings within the EtD frameworks.[6,7,12] 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 of the effects estimate of the outcomes of interest, test accuracy, and the importance of outcomes following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of a dose-effect relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels from very low to high.[8-10]

During a 2-day in-person meeting preceded and followed by online discussion, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and agreed on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and inferences regarding the values and preferences associated with the decision. The guideline panel explicitly considered the extent of resource use associated with alternative management options. The guideline panel agreed on the recommendations (including direction and strength), remarks, and qualifications on the basis of consensus or, in rare instances, by voting, based on the balance of all desirable and undesirable consequences. All panel members reviewed and approved the final recommendations.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "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 2 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and health care policy makers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 5 December 2017 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Ten individuals or organizations submitted comments. The document was revised to address pertinent comments. On 30 June 2018, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed, and on 3 August 2018, the officers of the ASH Executive Committee approved submission of the guidelines for 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

Initial anticoagulant dose selection

Question: In obese patients receiving LMWH therapy for treatment of acute VTE, should initial LMWH dose selection according to

Table 2. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; 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 identify possible research gaps.

actual body weight vs dose selection based on a fixed maximum daily dose (ie, capped dose) be used?

Recommendation 1

In obese patients receiving LMWH therapy for treatment of acute VTE, the ASH guideline panel *suggests* initial LMWH dose selection according to actual body weight rather than dose selection based on a fixed maximum daily dose (ie, capped dose) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no systematic reviews but did identify 5 relevant individual studies.[23-27] No study evaluated a direct comparison between LMWH doses based on actual body weight and capped doses for patients with obesity; thus, intervention and control studies represent different populations. Two studies included mortality as an outcome,[23,24] 5 studies reported development of VTE,[23-27] and 5 studies reported major bleeding outcomes.[23-27] The EtD framework is shown online at https://dbep.gradepro.org/profile/18c9f7b9-df8a-45ec-a63a-4f517a3a23d6.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. After indirectly comparing the available evidence from separate studies, we found no difference in VTE between those receiving LMWH dosed according to actual body weight and capped LMWH doses, but confidence intervals (CIs) included the possibility of appreciable benefit and harm (relative risk [RR], 0.76 [95% CI, 0.11-5.45]; absolute RR [ARR], 5 fewer events per 1000 [95% CI, 19 fewer to 95 more per 1000]; very low certainty). There was no effect of the intervention on mortality, as no deaths were reported in the included studies.

Harms and burden. Indirect comparison of the available evidence from separate studies showed that there were no major bleeding episodes reported for patients in the capped-LMWH-dose group compared with 0.5% of those in the actual-body-weight-dose group. There is very low certainty in the available evidence.

Other EtD criteria and considerations. LMWH dosing based on actual body weight is somewhat more expensive than using capped dosing and may lead to extra injections, but it is clearly feasible to implement.

Conclusions and research needs for this recommendation. Because of the very low quality evidence, the net health benefit/harm associated with using initial LMWH doses based on actual body weight compared with capped dosing is very uncertain, though it is acceptable and feasible. Because of concerns for potentially underdosing very large patients, the potentially serious consequences of therapeutic failure, and the lack of correlation between supratherapeutic anti–factor Xa concentrations and bleeding, the panel chose to make a conditional recommendation in favor of LMWH doses based on actual body weight over capped dosing.

The panel identified the following additional research priority: comparative evidence for different LMWH initiation dosing strategies in obese VTE patients.

Drug-interaction management

Question: For patients requiring administration of inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP enzymes, should a DOAC or an alternative anticoagulant be used for treatment of VTE?

Recommendation 2

For patients requiring administration of inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP enzymes, the ASH guideline panel *suggests* using an alternative anticoagulant (such as VKA or LMWH) rather than a DOAC for the treatment of VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. DOAC absorption is mediated by P-gp proteins, and, therefore, P-gp inhibitors potentially increase DOAC absorption and effect, whereas P-gp inducers potentially decrease DOAC absorption and effect. Furthermore, CYP3A4

enzymes are involved in the metabolism of oral direct Xa inhibitors, but not dabigatran, and strong inhibitors of CYP3A4 enzymes potentially decrease the metabolism and increase direct Xa inhibitor effect, whereas inducers of CYP3A4 enzymes potentially increase the metabolism and decrease direct Xa inhibitor effect. It is uncertain whether patients who require coadministration of potentially interacting drugs (see Table 3) and DOACs would have better outcomes if instead of a DOAC they received another anticoagulant. We found no systematic reviews that addressed this question. There were no randomized trials that addressed the outcomes prioritized for this question. Available evidence was very limited and consisted of pharmacokinetic studies with small sample sizes, subgroup analysis of clinical trials,[28] information from product labeling, and drug-interaction reference texts. The EtD framework is shown online at https://dbep.gradepro.org/profile/2664de1d-4462-4fe9-b675-03ff16ff4bbb.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Theoretically, the concurrent use of P-gp or CYP3A4 inducers could decrease DOAC benefits, but the panel was unable to estimate the magnitude of decrease, if any.

Harms and burden. Theoretically, the concurrent use of P-gp or CYP3A4 inhibitors could increase risk for bleeding for patients being treated with DOACs, but the panel was unable to estimate the magnitude of increase, if any. Use of P-gp/CYP inhibitors was associated with an increased risk of major bleeding and intracranial hemorrhage but not a significant change in the safety or efficacy of rivaroxaban compared with warfarin.[28]

Other EtD criteria and considerations. The panel determined that the acceptability of using DOACs for patients requiring P-gp or CYP3A4 inhibitors or inducers varies depending on factors such as the specific DOAC, whether the interacting medication was a strong inhibitor or inducer, the underlying bleeding or thromboembolic risk of the patient, comorbid disease states such as renal dysfunction, and patient preferences. The panel was unable to identify any evidence regarding other considerations.

Conclusions and research needs for this recommendation. The guideline panel was unable to determine whether using DOACs concomitantly with P-gp or CYP3A4 inhibitors or inducers would result in a net health benefit or harm. Given the lack of evidence, we suggest that clinicians consider using an alternative anticoagulant (such as VKA or LMWH) rather than DOACs for patients requiring administration of P-gp inhibitors or inducers or strong inhibitors or inducers of CYP enzymes (conditional recommendation based on very low certainty in the evidence about effects). The recommendation places a high value on avoiding the uncertainty in DOAC anticoagulant response associated with coadministration of the interacting drug and a low value on avoiding the burden of warfarin or LMWH therapy. Patients strongly adverse to INR monitoring or daily injections are likely to remain on DOACs, whereas avoiding DOACs in favor of VKA may be favored in the very elderly, those with compromised renal function, and situations where multiple drugs affecting P-gp and/or CYP enzymes are coprescribed.

The panel identified the following additional research question. What are the patient-important outcomes associated with concomitant administration of DOACs with P-gp/CYP3A4 inhibitors/inducers compared with DOACs alone or compared with other anticoagulants coadministered with strong P-gp or CYP3A4 inhibitors/inducers?

Point-of-care INR testing

Question: For patients receiving maintenance VKA therapy for treatment of VTE, should point-of-care INR testing by the patient at home (PST) vs any other INR testing approach be used?

Recommendation 3

For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using home point-of-care INR testing (PST) over any other INR testing approach except for PSM (see recommendation 4) in suitable patients (those who have demonstrated competency to perform PST and who can afford this option) (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Summary of the evidence. We found 1 systematic review that addressed this question,[29] but this review included studies using both PST and PSM. For this specific question, we were interested only in PST and performed meta-analysis on this subset of studies. We included 11 studies measuring outcomes relevant to this question for patients performing PST.[30-40] Studies included patients requiring VKA therapy for various indications, mainly for indications other than VTE treatment.

Three studies reported the effect of PST on mortality.[31,33,36,41,42] Recurrent PE and DVT rates were estimated by extrapolating pooled thromboembolic event rates from 9 studies (8 published and 1 unpublished [Scott Kaatz, data presented at the 6th National Conference of the Anticoagulation Forum, May 2001])[30,31,33,34,36,38-42] to baseline recurrent VTE rates from the LMWH/VKA arms of recent randomized, controlled trials (RCTs). Nine studies (8 published and 1 unpublished [Scott Kaatz, data presented at the 6th National Conference of the Anticoagulation Forum, May 2001])[30,31,33,34,36,38-42] assessed major bleeding risk; 6 studies[30,32,33,35,36,39,41,42] reported information on TTR; and 1 study reported quality of life.[36] The EtD framework is shown online at https://dbep.gradepro.org/profile/7eec57a8-86bb-4459-aa3e-0cc000c55993.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Studies assessing mortality found no difference between those receiving PST and control groups (RR, 0.94 [95% CI, 0.77-1.14]; ARR, 2 fewer deaths per 1000 [95% CI, 9 fewer to 5 more deaths per 1000]; high certainty). The effect of PST on recurrent PE and DVT was estimated by applying the RR estimate for thromboembolic events to baseline recurrence rates of PE and DVT. PST possibly reduces the risk for recurrent PE (RR, 0.73 [95% CI, 0.52-1.03]; ARR, 5 fewer per 1000 [95% CI, 10 fewer to 1 more per 1000]; low certainty) and DVT (RR, 0.73 [95% CI, 0.52-1.03]; ARR, 7 fewer per 1000 [95% CI, 12 fewer to 1 more per 1000]; low certainty), but the estimate is imprecise and the CI includes no effect. At 2 years (the minimum duration of follow-up), patient satisfaction with anticoagulation, as measured by the Duke Anticoagulation Satisfaction Scale (in which scores range from 25 to 225, with lower scores indicating better satisfaction), was greater in

Table 3. Examples of drugs known to inhibit or induce P-gp and/or CYP3A4 enzymes

P-gp	CYP3A4
Inhibitors	**Strong inhibitors**
Antihypertensive/heart rate control	Anti-infectives
Verapamil	Clarithromycin
Dronedarone	Telithromycin
Anti-infectives	Itraconazole
Itraconazole	Ketoconazole
Ketoconazole	Antidepressants
Voriconazole	Nefazodone
Posaconazole	Protease inhibitors
Clarithromycin	Atazanavir
	Darunavir
	Indinavir
	Lopinavir
	Nelfinavir
	Ritonavir
	Saquinavir
	Tipranavir
Inducers	**Strong inducers**
Anti-infectives	Anti-infectives
Rifampin	Rifampin
Anticonvulsants	Anticonvulsants
Carbamazepine	Carbamazepine
Phenytoin	Phenytoin
Barbiturates	Barbiturates
Natural products	Natural products
St. John's wort	St. John's wort

Not an inclusive list. Available evidence reported the effects of various drugs that inhibit or induce P-gp or CYP3A4 on DOAC pharmacokinetic parameters, such as area under the plasma concentration time curve, maximal plasma DOAC concentration, and DOAC half-life. In general, these parameters are increased by P-gp or CYP3A4 inhibitors and decreased by inducers. No studies have reported different rates of bleeding, thromboembolism, or mortality between DOACs and a comparator (eg, VKA). Reference texts on tertiary drug interaction generally suggested observing patients for symptoms of bleeding or thromboembolism and to consider adjusting DOAC doses. Depending on the specific DOAC, product labeling in some cases suggested modification of DOAC dosing (eg, apixaban) or recommended avoiding the use of DOACs when interacting drugs were coprescribed (eg, rivaroxaban).

the PST group than in the control group (difference, −2.4 points [95% CI, −3.9 to −1.0]; low certainty), and a cumulative gain in health utilities according to the Health Utilities Index Mark 319 was noted in the self-testing group compared with the control group (difference, 0.155 points [95% CI, 0.111-0.198]; low certainty). In studies assessing INR control, TTR was modestly higher in the PST group (mean difference [MD], 5.37% [95% CI, 3.17%-7.56% higher]; low certainty).

Harms and burden. The risk of major bleeding was possibly lower for patients when PST was used than when other INR monitoring methods were used, but the estimate is imprecise and the CI includes no effect (RR, 0.73 [95% CI, 0.46-1.15]; ARR, 5 fewer per 1000 [95% CI, 9 fewer to 3 more per 1000] for a population at average bleeding risk.

Other EtD criteria and considerations. The guideline panel considered that moderate costs were associated with PST resource requirements, owing mainly to the costs of the point-of-care monitors and testing supplies and more frequent INR testing generally used with PST. The likelihood of PST being cost-effective varied, with 1 review, 1 RCT, and 1 modeling study indicating that PST is likely to be cost-effective compared with usual care,[43-45] whereas 2 other reviews concluded that PST is unlikely to be cost-effective within accepted standards[46,47] and that PST implementation would probably result in reduced health equity for patients in lower socioeconomic classes and those with cognitive problems and poor manual dexterity. Because some patients are unwilling to perform PST, the panel determined that the acceptability of PST to major stakeholders varies, but the intervention is probably feasible to implement, though a substantial investment in patient training and testing equipment is necessary.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty evidence for a net health benefit from using point-of-care INR monitoring at home by the patient over other INR testing approaches (except for PSM, see recommendation 4) for patients receiving VKA maintenance therapy for treatment of VTE. This benefit is conditional upon patients and health care systems being able to afford and manage the self-testing equipment. In settings in which resources are limited or when patients are not willing or able to perform PST, deviation from this suggestion is appropriate. Furthermore, systems using PST should be able to perform regular external quality assessment of the testing equipment and patient's ability to obtain accurate INR results. The panel calls upon payers, including the Centers for Medicare and Medicaid Services, to carefully evaluate current reimbursement regulations and make changes as necessary to ensure that unnecessary testing is not incentivized, that providers and patients are aware of this testing option, and that funding is available for those who would like to use PST.

The panel identified the following additional research questions. (1) What is the effectiveness of PST compared with DOAC therapy? (2) What is the effectiveness of PST compared with other INR-testing strategies specifically for patients with VTE?

Question: For patients receiving maintenance VKA therapy for treatment of VTE, should point-of-care INR testing by the patient at home and self-adjustment of VKA dose (PSM) vs any other management approach be used?

Recommendation 4

For patients receiving maintenance VKA therapy for treatment of VTE we *recommend* using point-of-care INR testing by the patient at home and self-adjustment of VKA dose (PSM) over any other management approach, including PST, in suitable patients (those with demonstrated competency to perform PSM and who can afford this option) (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Summary of the evidence. Building on the systematic review that addressed PST and PSM,[29] we performed a meta-analysis on 16 studies measuring outcomes for patients performing

PSM.[33,48-62] Studies included patients requiring VKA therapy for various indications, mainly for indications other than VTE treatment.

Eleven studies reported the effect of PSM on mortality[33,41,48-53,56,58,59,61,63-72] recurrent PE and DVT rates were estimated by extrapolating pooled relative thromboembolic effects from 14 studies[33,41,48-51,53,54,56-59,61-73] to baseline recurrent VTE rates from the LMWH/VKA arms of recent RCTs. Fifteen studies[33,41,48-59,61-73] assessed major bleeding risk, and 9 studies[33,41,48-50,52,53,56,57,60,69-71] reported information on TTR. Two studies evaluated the effect of PSM on quality of life.[52,59] The EtD framework is shown online at https://dbep.gradepro.org/profile/323c2cad-e2ab-4fd6-b35f-be34eee8219a.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Studies assessing mortality found a benefit favoring those performing PSM (RR, 0.58 [95% CI, 0.38-0.89]; ARR, 16 fewer deaths per 1000 [95% CI, 4 fewer to 24 fewer deaths per 1000]; high certainty). PSM reduced the risk for recurrent PE (RR, 0.48 [95% CI, 0.32-0.71]; ARR, 10 fewer per 1000 [95% CI, 6 fewer to 14 fewer per 1000]; moderate certainty) and DVT (RR, 0.48 [95% CI, 0.32-0.71]; ARR, 14 fewer per 1000 [95% CI, 8 fewer to 18 fewer per 1000]; moderate certainty). In studies assessing INR control, TTR was modestly higher in the PSM group, but the estimate is imprecise and the CI includes no effect (MD, 4.41% [95% CI, 0.09% lower to 8.92% higher]; very low certainty). General treatment satisfaction and daily hassles scores improved with PSM and remained unchanged in the control group.[59] Self-efficacy and distress scores improved in both groups but improved significantly more with PSM. PSM had no significant effect on the strained social network scores.[59] After 4 months, treatment satisfaction significantly improved and daily hassles, psychological distress, and a strained social network all significantly decreased with PSM compared with the control group.[52]

Harms and burden. PSM vs other INR monitoring methods probably has no influence on the risk of major bleeding (RR, 1.09 [95% CI, 0.80-1.50]; ARR, 2 more per 1000 [95% CI, 3 fewer to 9 more per 1000] for an average bleeding risk population.

Other EtD criteria and considerations. The guideline panel considered that moderate costs were associated with PSM resource requirements, owing mainly to the costs of the point-of-care monitors and testing supplies and the more frequent INR testing that is generally used with PSM. The likelihood of PSM being cost-effective varied, with 1 modeling study indicating that PSM is likely to be cost-effective compared with usual care,[74] whereas 1 RCT concluded that PSM is unlikely to be cost-effective.[75] Most panel members also believed that PSM implementation would result in reduced health equity for patients in lower socioeconomic classes and those with cognitive problems and poor manual dexterity. The acceptability of PSM to major stakeholders varies but is probably feasible to implement. However, a substantial investment in patient training (even more so than with PST) and testing equipment is necessary.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty evidence for a net health benefit from using point-of-care INR monitoring and VKA dose adjustment by patients at home over other INR testing approaches (including PST) for patients receiving VKA maintenance therapy for treatment of VTE. This benefit is conditional upon patients and health care systems being able to afford and manage the self-testing equipment and patients being able to make independent decisions about VKA dosing based on INR results. The panel determined that PSM was superior to PST, as it has shown reduction in mortality. Although the panel agreed that a strong recommendation in favor of PSM was warranted based on the available evidence, in settings where resources are limited or when patients are not willing or able to perform PSM, system decision-makers or individual patients may choose against PSM. Furthermore, systems using PSM should be able to perform regular external quality assessment of the testing equipment and patients' ability to obtain accurate INR results and make rational VKA dosing decisions using instructions from their health care providers. The panel calls upon payers, including the Centers for Medicare and Medicaid Services, to carefully evaluate current reimbursement regulations and make changes as necessary to ensure that unnecessary testing is not incentivized, that providers and patients are aware of this testing option, and that funding is available for those who wish to use PSM.

The panel identified the following additional research questions. (1) What is the effectiveness of PSM of VKA compared with DOAC therapy? (2) What is the effectiveness of PSM compared with other INR management strategies, specifically for patients with VTE? (3) What minimum competencies are required to engage in PSM and what is the most effective way to train patients to perform PSM?

Selecting the timing between INR measurements (INR recall interval)

Question: For patients receiving VKA therapy for treatment of VTE, should a shorter INR recall interval vs a longer INR recall interval be used following VKA dose adjustment due to an out-of-target-range INR?

Recommendation 5

For patients receiving VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using an INR recall interval of 4 weeks or fewer rather than intervals longer than 4 weeks following VKA dose adjustment *due to an out-of-target-range INR* (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no systematic reviews or randomized trials that addressed this question. Three observational studies have evaluated the impact of INR recall interval on surrogate outcomes such as site-level TTR performance and TTR below 75%.[76-78] No studies reported the risks of mortality, recurrent VTE, or bleeding. The EtD framework is shown online at https://dbep.gradepro.org/profile/768b8b3c-7ac2-48ff-a5d6-e13b7b0044cf.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. The panel was unable to estimate the magnitude of benefit for clinically important outcomes such as mortality, recurrent VTE, and bleeding. One study reported a decrease in site-level TTR of 1.12% (95% CI, 0.8%-1.43%) following each additional INR recall interval day.[76] Another study reported that for patients measuring their own INRs at home and self-adjusting VKA doses, long intervals between INR measurements (>14 days) were associated with poor anticoagulation control (defined as percentage of in-range INRs

below 75%).[77] In this study, the temporal relationship between INR test interval and the outcome was unclear, and the outcome itself (poor anticoagulation control) would have an impact on the determination of the test interval. The study population was different from patients receiving INR monitoring and VKA dose adjustments from their anticoagulation providers. Another study evaluated the association between center next-visit INR interval ratio (the mean number of days after a visit with an INR outside the therapeutic range, divided by the number of days after a visit with an INR within the therapeutic range) and site-level TTR.[78] The results suggested that site-level TTR increased with shorter INR recall intervals.

Harms and burden. No studies reported adverse effects, and the panel assumed no harms but greater burden associated with more frequent INR testing after an out-of-range INR.

Other EtD criteria and considerations. There was little evidence bearing on other criteria, which, as a result, had little impact on the recommendation.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty evidence for net health benefit/harm associated with the INR recall interval following an out-of-range INR. Based on the limited body of available evidence, the panel was able only to suggest INR recall intervals of 4 weeks or less vs longer intervals. Most patients are adverse to frequent INR monitoring yet will return for INRs as directed by their anticoagulation provider. How much the INR is out of range should guide the choice for the INR recall interval, as well as the etiology of the out-of-range INR. For example, a recall interval between 2 and 4 weeks might be reasonable following a VKA dose adjustment for an INR of 3.3 in a patient with generally stable INR control, whereas a recall interval not exceeding a few days might be needed after temporary interruption of VKA following an INR of 8.2 in a patient who recently started taking antibiotics.

The panel identified the following additional research questions. (1) Does a strategy of using 1-week recall intervals for INRs that are farther out of range (eg, >4.0 or <1.5) and 2- to 3-week recall intervals following INRs that are only slightly out of range (eg, 3.1-4.0 or 1.5-1.9) reduce the risk of mortality, recurrent VTE, and bleeding? (2) Could pharmacogenomic testing inform INR recall intervals by helping to predict the time required for a given patient to reach a new steady state following VKA dose adjustments?

Question: For patients receiving maintenance VKA therapy for treatment of VTE should a longer (eg, 6-12 weeks) INR recall interval vs a shorter (eg, 4 weeks) INR recall interval be used during periods of stable INR control?

Recommendation 6

For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel *suggests* using a longer (6-12 weeks) INR recall interval rather than a shorter (4 weeks) INR recall interval *during periods of stable INR control* (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no systematic reviews but identified 2 RCTs[79,80] and 3 observational studies[81-83] that addressed this question. All studies included patients receiving VKA anticoagulation therapy but were not limited to patients being treated for VTE.

The 2 RCTs directly compared outcomes between 4-week INR recall intervals and 6-week[79] or 12-week[80] recall intervals for patients meeting predefined criteria for stable VKA anticoagulation. No studies reported the impact of INR recall interval on quality of life. The EtD framework is shown online at https://dbep.gradepro.org/profile/87B38659-8876-FBC5-97CC-195E03A1F1FE.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Mortality was lower in the groups randomized to 6- to 12-week INR recall intervals, but the estimate is very imprecise, and CIs include both large increases and decreases in mortality (RR, 0.73 [95% CI, 0.12-4.60]; ARR, 11 fewer deaths per 1000 [95% CI, 34 fewer to 140 more per 1000]; very low certainty). The 12-week INR recall interval was associated with a reduced risk for PE and DVT, but the estimates were based on only 1 event, and the CIs therefore include both important benefit and harm. The thromboembolic event rate from the other study was not used as it only included patients receiving anticoagulants for mechanical heart valves. There were also no differences between those using 6- to 12-week INR recall intervals and 4-week recall intervals for surrogate outcomes, including TTR and the number of extreme low/high INRs. Fewer patients using 6- to 12-week INR recall intervals had at least 1 dosing change during follow-up than those using 4-week recall intervals (RR, 0.67 [95% CI, 0.51-0.88]; ARR, 183 fewer per 1000 [95% CI, 272 fewer to 67 fewer per 1000]; very low certainty).

Harms and burden. Studies assessing major bleeding found no difference between those using 6- to 12-week INR recall intervals and those using 4-week recall intervals (RR, 1.05 [95% CI, 0.30-3.65]; ARR, 1 more per 1000 [95% CI, 12 fewer to 45 more per 1000] for average-bleeding-risk patients; low certainty).

Other EtD criteria and considerations. The guideline panel agreed that 6- to 12-week INR recall intervals would probably result in moderate resources savings. The panel determined that longer INR recall intervals would increase health equity, would be acceptable to key stakeholders, and are feasible.

Conclusions and research needs for this recommendation. Given that less frequent INR monitoring reduces the burden on patients, lessens workload on anticoagulation providers, is acceptable to key stakeholders, and is feasible to implement and likely reduces cost without incurring convincing adverse consequences, the panel made a conditional recommendation in favor of longer INR recall intervals. The panel did not specify a definition of stable INR control and agreed that this should be defined according to local standards. The panel also determined that this recommendation should not be used for patients engaging in PST or PSM, as these patients were not included in the RCTs for longer INR recall intervals and are usually monitored more frequently than the 4-week INR recall interval comparator used for this recommendation. Patients with psychiatric disorders and/or history of poor adherence were also excluded from these studies and are poor candidates for extended INR recall intervals. Patients should be instructed to have their INR tested any time their health status changes, their current medications change, or

there is a significant change in their dietary intake of vitamin K–containing foods.

The panel identified the following additional research questions. (1) What is the comparative effectiveness of 6- to 12-week INR recall intervals compared with a 4-week recall interval in real-world patients during periods of stable INR control? Given the low risk of adverse events in stable patients, a very large patient sample will likely be required to answer this question. (2) What is the cost-effectiveness of 6- to 12-week INR recall intervals compared with a 4-week recall interval from the societal perspective?

Laboratory monitoring of the anticoagulant response

Question: For patients with renal dysfunction (creatinine clearance of <30 mL/min) receiving LMWH therapy for treatment of VTE, should clinicians monitor anti–factor Xa concentration to guide LMWH dose adjustment vs no such monitoring?

Recommendation 7

For patients with renal dysfunction (creatinine clearance of <30 mL/min) receiving LMWH therapy for treatment of VTE, the ASH guideline panel *suggests against* using anti–factor Xa concentration monitoring to guide LMWH dose adjustment (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Instead of monitoring anti–factor Xa concentrations, providers should consider using doses adjusted for renal function as recommended in product labeling (eg, enoxaparin) or switching to an alternative anticoagulant with lower renal clearance, such as UFH or a different LMWH.

Summary of the evidence. We included eligible studies from the most recent systematic review of LMWH for patients with renal dysfunction.[84] The search was updated from 2006 onward, yielding a total of 11 studies.[85-95] No studies directly compared anti-Xa monitoring to no such monitoring. Most included studies were single-arm cohort studies in which patients receiving LMWH with renal dysfunction had anti-Xa concentrations monitored. For the no-monitoring comparator group, we used a study that reported no anti-Xa monitoring or dose adjustments (enoxaparin, 1 mg/kg body weight, was administered subcutaneously twice a day) to determine the risk of major bleeding.[96] We found no studies that reported the risk of VTE or mortality associated with no anti-Xa monitoring. Included studies grouped patients with varying indications for LMWH, most commonly patients with acute VTE, atrial fibrillation, and acute coronary syndrome. The panel agreed that studies with grouped indications would be used for the outcome of major bleeding and the evidence rated down for indirectness. Studies with grouped indications were also combined for the outcome of percentage of anti-Xa concentrations in the therapeutic range. Studies with grouped indications were not used for the outcome of PE, DVT, or mortality. Combined studies administered different LMWHs (enoxaparin and tinzaparin) and used different dosing regimens (once daily and twice daily). The EtD framework is shown in online at https://dbep.gradepro.org/profile/44981d40-71aa-4205-bda3-a8471c085c8b.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. After indirect comparison of the available evidence from separate studies, it appears that adjusting the LMWH dose based on monitoring anti–factor Xa concentrations for patients with renal dysfunction was associated with reduced risk of developing major bleeding (RR, 0.12 [95% CI, 0.03-0.44]; ARR, 95 fewer episodes per 1000 [95% CI, 60 fewer to 104 fewer episodes per 1000]; very low certainty). In an analysis of observational studies not included in the evidence profile, 129 of 236 (54.7% [95% CI, 48.3%-60.9%]) measured peak enoxaparin anti–factor Xa concentrations were found to be within the defined therapeutic range.[86,88,90,93-95] In another observational study, 8 of 8 (100% [95% CI, 67.6%-100.0%]) measured tinzaparin anti–factor Xa concentrations fell within the defined therapeutic range.[91] It was difficult to put these results into perspective given the lack of a control group where LMWH doses were not adjusted based on anti–factor Xa concentrations.

Harms and burden. Given the limited information regarding potential undesirable effects associated with adjusting LMWH doses based on the results of anti–factor Xa monitoring that was available, the panel determined that the balance between desirable and undesirable effects of this intervention is very uncertain.

Other EtD criteria and considerations. The panel agreed that there would likely be moderate costs associated with measuring anti–factor Xa concentrations; cost-effectiveness remains unclear. Many payers would not consider this intervention acceptable without convincing evidence of benefit, and this evidence is lacking. The feasibility of implementing this intervention may also be affected by the following barriers reported by observational studies: (1) anti–factor Xa tests are not widely available[97]; (2) anti–factor Xa tests are poorly standardized between laboratories, making proper LMWH dose adjustments impossible in some cases[97]; and (3) anti–factor Xa test reproducibility is poor.[98-100]

Conclusions and research needs for this recommendation. The guideline panel considered the net benefit associated with adjusting LMWH doses based on the results of anti–factor Xa monitoring very uncertain. Because of concerns relating to anti–factor Xa test standardization and reproducibility and weak correlation between bleeding events and anti–factor Xa concentrations,[101] the panel suggests against adjusting LMWH doses based on anti–factor Xa concentration monitoring. Seven panel members preferred making a strong recommendation against the intervention, but this majority was not sufficiently large to satisfy the criterion for a strong recommendation (80% of the panel).

The panel identified the following additional research questions. (1) What are the anti–factor Xa concentration cutoffs (determined in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events? (2) What percentage change in LMWH dose in response to an out-of-range anti–factor Xa concentration is optimal to return the concentration to the therapeutic range? (3) What is the comparative effectiveness of adjusting LMWH doses based on the results of anti–factor Xa concentrations (performed in a manner that ensures accuracy and reproducibility) vs no such monitoring for patients with estimated creatinine clearance values of <30 mL/min requiring treatment of VTE?

Question: For patients with obesity receiving LMWH therapy for treatment of VTE, should clinicians monitor anti–factor Xa

concentration to guide LMWH dose adjustment vs no such monitoring?

Recommendation 8

For patients with obesity receiving LMWH therapy for treatment of VTE, the ASH guideline panel *suggests against* using anti–factor Xa concentration monitoring to guide LMWH dose adjustment (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Providers should consider LMWH using doses based on actual body weight (see recommendation 1) and not monitoring anti–factor Xa concentrations, similar to the approach used in nonobese patients.

Summary of the evidence. We included eligible studies from the most recent systematic review for patients with obesity receiving LMWH for VTE treatment.[101] The search was updated from 2014 onward, yielding a total of 7 studies.[27,86,93,102-105] No studies directly compared anti–factor Xa monitoring to no such monitoring. Included studies were single-arm cohort studies in which patients with obesity receiving LMWH had anti–factor Xa concentrations monitored. For the no-monitoring arm, we used a study that reported no anti–factor Xa monitoring to determine the risk of major bleeding and VTE events.[23] Included studies grouped patients with varying indications for LMWH—most commonly patients with acute VTE, atrial fibrillation, and acute coronary syndrome. We used studies with grouped indications for the outcome of major bleeding and rated down the evidence for indirectness. Studies with grouped indications were also combined for the outcome of percentage of anti–factor Xa concentrations in the therapeutic range. Studies with grouped indications were not used for PE or DVT. No studies reported the outcome of mortality. When multiple studies reported the prioritized outcomes, the number of events was added across all studies and reported over the total sample. The EtD framework is shown online at https://dbep.gradepro.org/profile/dcf00058-0d87-40b3-9ebc-4dec32706a8b.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. In an analysis of observational studies not included in the evidence profile, 102 of 227 (44.9% [95% CI, 38.6%-51.4%]) measured peak enoxaparin anti–factor Xa concentrations were found to be within the therapeutic range defined by the individual studies following a therapeutic enoxaparin dose (1.5 mg/kg once daily or 1 mg/kg twice daily).[86,93,102,103] In another observational study, 15 of 21 (71.4% [95% CI, 50.1%-86.2%]) measured dalteparin anti–factor Xa concentrations fell within the defined therapeutic range (between 0.5 and 1.0 units per milliliter for twice-daily dosing and between 1.0 and 2.0 units per milliliter for once-daily dosing) following a therapeutic dalteparin dose (200 units per kilogram per day) (assessed with peak anti–factor Xa concentration).[105] It was difficult to put these results into perspective given the lack of a control group where LMWH doses were not adjusted based on anti–factor Xa concentrations.

Harms and burden. After indirect comparison of the available evidence from separate studies, it appears that adjusting LMWH doses based on monitoring anti–factor Xa concentrations for patients with obesity may increase the risk of recurrent PE (RR, 3.06 [95% CI, 0.19-48.27]; ARR, 11 more episodes per 1000 [95% CI, 4 fewer to 245 more episodes per 1000]; very low certainty) and DVT (RR, 1.53 [95% CI, 0.14-16.61]; ARR, 5 more episodes per 1000 [95% CI, 9 fewer to 162 more episodes per 1000]; very low certainty), but the estimates are imprecise, and CIs include large reductions and very large increases in events. Results also suggested the possibility of increased risk of major bleeding, but again, the CI includes no difference and a very large increase in bleeding (RR, 3.91 [95% CI, 0.67-22.95]; ARR, 30 more episodes per 1000 [95% CI, 3 fewer to 227 more episodes per 1000]; very low confidence).

Other EtD criteria and considerations. The panel determined that there would likely be moderate costs associated with measuring anti–factor Xa concentrations, but the actual cost-effectiveness of this intervention could not be estimated due to the lack of comparative studies. Some payers would not consider this intervention acceptable without convincing evidence of benefit, and this evidence is currently lacking. The feasibility of implementing this intervention may also be affected by the following barriers reported by observational studies. (1) Anti–factor Xa tests are not widely available.[97] (2) Anti–factor Xa tests are poorly standardized between laboratories, making proper LMWH dose adjustments impossible in some cases.[97] (3) Anti–factor Xa test reproducibility is poor.[98-100] Thus, whereas it is feasible to order and obtain the results of anti–factor Xa tests for patients with obesity during LMWH therapy in some settings, the panel determined that poor anti–factor Xa test standardization and reproducibility were significant issues arguing against adjusting LMWH doses based on results of these tests.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty evidence for net harm from adjusting LMWH doses based on anti–factor Xa concentration monitoring over no such monitoring for patients with obesity on LMWH therapy for treatment of VTE. In addition, there were concerns relating to anti–factor Xa test standardization and reproducibility, weak correlation between bleeding events and anti–factor Xa concentrations,[101] and no evidence that anti–factor Xa testing is needed for patients with obesity.

The panel identified the following additional research questions. (1) What are the anti–factor Xa concentration cutoffs (determined in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events? (2) What percentage change in LMWH dose in response to an out-of-range anti–factor Xa concentration is optimal to return the concentration to the therapeutic range? (3) What is the comparative effectiveness of adjusting LMWH doses based on the results of anti–factor Xa concentrations (performed in a manner that ensures accuracy and reproducibility) vs no such monitoring for patients with obesity requiring treatment of VTE?

Question: For patients receiving DOAC therapy for the treatment of VTE, should measurement of the DOAC anticoagulant effect vs no

measurement of DOAC anticoagulant effect be used during management of bleeding?

Recommendation 9

For patients receiving DOAC therapy for the treatment of VTE, the ASH guideline panel *suggests against* measuring the DOAC anticoagulant effect during management of bleeding (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no relevant systematic reviews but did identify 8 studies[106-113] that included patients on DOACs receiving treatment of bleeding, some of whom had measurements of the DOAC anticoagulant effect using a variety of tests (eg, activated partial thromboplastin time, anti–factor Xa concentrations, and thrombin time), but none had a primary objective of evaluating the impact of measuring DOAC anticoagulant effect or reported a direct comparison of outcomes for patients who did and did not receive DOAC anticoagulant effect measurement.

Eight studies reported mortality as an outcome,[106-113] 2 studies reported development of thromboembolism,[106,111] and 1 study assessed the occurrence of major bleeding during the 30 days following the index bleeding event.[107] The EtD framework is shown online at https://dbep.gradepro.org/profile/9e7da133-8251-461a-9a11-7b08b197a77e.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. After indirectly comparing the available evidence from separate studies, we found no difference in mortality between patients in whom the DOAC anticoagulant effect was measured and those in whom it was not measured, but CIs included appreciable mortality increases and decreases (RR, 1.28 [95% CI, 0.80-2.05]; ARR, 44 more deaths per 1000 [95% CI, 32 fewer to 166 more]; very low certainty).

Harms and burden. Estimating the relative and absolute risk estimates was not possible, as there were no thromboembolic events in the intervention group and no bleeding events reported in the comparison group, leaving very low certainty evidence.

Other EtD criteria and considerations. Very little evidence was available regarding other EtD criteria.

Conclusions and research needs for this recommendation. Considering that only very low–quality evidence is available regarding the net health benefit/harm from measuring the DOAC anticoagulant effect during management of bleeding, clinical use of DOAC tests is not well established, and no evidence supports a beneficial effect, the panel judged that it is better not to delay intervention for bleeding while waiting for a DOAC test result. It is advisable not to rely on any single (either pharmacokinetic or laboratory) strategy in isolation to assess DOAC effect during bleeding management but instead to use a comprehensive approach to assessing, confirming, and communicating when the last DOAC dose was administered among the patient and all providers involved.

The panel identified the following additional research priorities: (1) developing validated specific DOAC effect tests, particularly those that can be performed rapidly and, ideally, at the point of care; (2) testing the effect on clinical outcomes of using a validated specific DOAC test for patients with bleeding; and (3) assessing the cost-effectiveness, acceptability, and feasibility of implementing a validated specific DOAC test during bleeding management.

Transitions between anticoagulants

Question: For patients transitioning from DOAC to VKA, should LMWH or UFH "bridging therapy" vs overlapping DOAC therapy be used until the INR is within the therapeutic range?

Recommendation 10

For patients transitioning from DOAC to VKA, the ASH guideline panel *suggests* overlapping DOAC and VKA therapy until the INR is within the therapeutic range *over* using LMWH- or UFH-bridging therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no systematic reviews but did identify 3 studies[114-116] that included patients with atrial fibrillation, not VTE, transitioning from DOAC therapy to VKA therapy at the conclusion of RCTs. Three studies reported mortality outcomes, but only in the group overlapping DOAC during the transition to VKA[114-116]; 1 study reported development of thromboembolic stroke[115]; and 1 study reported development of hemorrhagic stroke.[115] No studies reported outcomes related to quality-of-life impairment. The EtD framework is shown online at https://dbep.gradepro.org/profile/b1889d83-5875-453f-b047-fb742c25e43e.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. The effect of LMWH-bridging therapy on mortality risk during the transition from DOAC to VKA could not be estimated because data on deaths during the 30-day follow-up period were not available for the intervention group, leaving very low certainty regarding the impact of the alternative management strategies.

Harms and burden. LMWH-bridging therapy during the transition from DOAC to VKA may increase the risk for VTE compared with overlapping DOAC therapy (RR, 5.58 [95% CI, 1.32-23.65]; ARR, 20 more events per 1000 [95% CI, 1 more to 98 more per 1000]; very low certainty). In the eligible studies, the LMWH-bridging strategy was implemented only when the patient was at high thromboembolic risk; thus, intervention and control groups had important differences. The intervention was associated with a lower major bleeding risk (ARR, 1 fewer event per 1000), but no reliable RR and 95% CI could be estimated because very few bleeding events were observed and none occurred in the LMWH-bridging group, leaving very low certainty evidence regarding the risk of adverse effects.

Other EtD criteria and considerations. LMWH-bridging therapy is more expensive than overlapping DOAC therapy, potentially disadvantaging patients in lower socioeconomic strata. Patients may prefer DOAC overlap, as they would avoid the inconvenience and expense of LMWH injections. Careful INR monitoring during transitions to VKA is always required, regardless of bridging strategy.

Conclusions and research needs for this recommendation. The net health benefit/harm associated with using LMWH-bridging therapy during transitions from DOAC to VKA compared with

overlapping DOAC with VKA alone remains very uncertain, but use of LMWH is certain to increase burden and cost. In an anonymous vote of 9 eligible panel members, 6 voted for a conditional recommendation against LMWH-bridging therapy, and 3 voted for a conditional recommendation for either LMWH-bridging therapy or overlapping DOAC. To minimize DOAC interference with the INR, the panel suggests measuring the INR just before the next DOAC dose if overlapping DOAC therapy is used. However, providers will need to be aware of the varying potential among DOACs to influence INR results. Ultimately, the strategy for transitioning from DOAC to VKA should be based on patient preference and willingness to use and ability to afford injections.

The panel identified the following research priority: sufficiently powered pragmatic clinical trials comparing thromboembolic and bleeding outcomes for DOAC overlap vs LMWH-bridging therapy for patients transitioning from DOAC to VKA.

Use of specialized AMSs

Question: For patients receiving anticoagulation therapy for treatment of VTE, should specialized AMS care vs care provided by the patient's regular health care provider be used for anticoagulation management?

Recommendation 11

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests* using specialized AMS care rather than care provided by the patient's regular health care provider (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found evidence from both RCTs and observational studies and systematic reviews addressing this question. There was considerable discussion among panel members regarding the type of evidence that best represented the outcomes of contemporary anticoagulant therapy. Evidence summaries prepared for RCTs and observational studies revealed that evidence certainty was very low regardless of study type. After careful review of the included studies, the panel decided to use evidence summarized from observational studies, as these best reflected real-world anticoagulation therapy management practices. Although not required under ASH policy, 4 panelists, including the chair (N.P.C., Ann Wittkowski, J.S., and D.M.W.), recused themselves from making judgments about the evidence or deciding the recommendation thereafter, because they viewed their roles as directors of large anticoagulation clinics to be a professional and/or intellectual conflict of interest. R.N. led the panel discussion assessing both RCT and observational evidence instead of D.M.W.

We included eligible studies from a systematic review comparing the effectiveness of pharmacist-managed AMS with other models.[117] The search was updated from 2015 onward and also to include studies evaluating AMS models other than those staffed by pharmacists, yielding a total of 29 observational studies.[118-146] All studies included outcomes for patients on anticoagulants (mostly VKA) who received AMS care compared with those who received management coordinated by their regular health care provider. Five studies reported the effect of AMS care on mortality[122,123,134,140,145]; 18 studies reported development of thromboembolic complications, including DVT and PE[118,120,122,123,129-132,134-138,140,141,143,145,146]; 19 studies assessed the risk of major bleeding[118,120,122,123,129-132,134-138,140-143,145,146]; and 19 studies measured TTR.[118,122,124-129,132,133,135-138,140,141,145,146] One RCT reported on quality-of-life impairment during 30 days of follow-up using the EuroQoL instrument, whereas no observational studies reported on this outcome.[147] Two observational studies assessed medication adherence for patients taking DOACs.[130,139] The EtD framework is shown online at https://dbep.gradepro.org/profile/B936B888-511A-8A14-A111-9B7DAF184C41.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Studies assessing mortality found no difference between those receiving AMS care and the care provided by their regular health care provider (RR, 0.97 [95% CI, 0.51-1.85]; ARR, 1 fewer deaths per 1000 [95% CI, 19 fewer to 33 more per 1000]; very low certainty). Compared with the usual care provided to patients by their regular health care provider, enrollment in an AMS reduced the risk of developing PE (RR, 0.45 [95% CI, 0.26-0.78]; ARR, 11 fewer episodes per 1000 [95% CI, 4 fewer to 15 fewer per 1000]; very low certainty) and DVT (RR, 0.45 [95% CI, 0.26-0.78]; ARR, 14 fewer episodes per 1000 [95% CI, 6 fewer to 19 fewer per 1000]; very low certainty). Quality of life as measured by the EuroQoL change score from baseline to follow-up was the same in groups receiving care from AMSs and those receiving care from their regular health care providers.[147] Patients enrolled in AMS had higher TTR than patients cared for by their regular health care provider (MD, 3.51% higher [95% CI, 2.74% higher to 4.28% higher]; very low certainty).

Harms and burden. AMS care possibly reduced the risk for major bleeding in patients that were at average risk for bleeding, but the estimate is imprecise, and the CI includes no effect (RR, 0.66 [95% CI, 0.42-1.03]; ARR, 6 fewer episodes per 1000 [95% CI, 10 fewer to 1 more episodes per 1000]; very low certainty).

Other EtD criteria and considerations. The panel estimated moderate resource requirements associated with AMS care, mainly secondary to personnel costs. Several studies indicated that AMS care is cost-effective compared with care provided by the patient's regular health care provider; however, these studies were of very low quality and generally did not take into account startup costs associated with establishing an AMS.[122,143,148-151] The option to refer patients to an AMS might help practitioners feel more confident prescribing anticoagulation therapy. On the other hand, if the AMS is situated in a hospital, rural patients' out-of-pocket costs for visits might be higher. Given these competing impacts, the panel was not able to determine the effect of AMS care on health equity. The panel agreed that in general, AMS care seems acceptable to patients and providers, but the willingness of health system administrators to dedicate funds to setting up and running an AMS was less certain, especially considering that DOAC management based on AMS has been less well studied.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty evidence for a net health benefit from using AMS care over the care usually provided by a patient's regular health care provider for VTE treatment. Based on the body of available evidence, it is likely that AMS care reduces the risk of developing recurrent VTE and

possibly also major bleeding, as well as improving TTR. There is very low certainty that AMS care has an effect on mortality. The panel agreed that this recommendation mainly applies to patients using VKA, as all but 2 of the studies focused on VKA treatment. Furthermore, AMS is most likely to be beneficial when implemented in a population with inadequate TTR managed by nonspecialized providers. Decision-makers should consider the upfront costs of setting up the AMS as well as costs to maintain the service. The panel also noted that AMS can provide specialized consulting and education for health care providers in the region, thereby potentially enhancing anticoagulation management beyond the service's direct patient management. AMS providers should keep track of the service's TTR as well as anticoagulation-related clinical outcomes for their patients. Health care providers referring patients to an AMS should keep track of whether they attended the AMS.

With regard to research priorities, the panel determined that RCT evidence needs to be strengthened to be considered superior to the reported observational evidence. Cluster RCTs are needed that are appropriately randomized, enroll patients before unblinding of allocation, are sufficiently powered to detect a difference in clinical outcomes using blinded outcome assessment (including the follow-up time after dropping out of AMS care), use a consistent definition or elements of AMS, and address the impact of AMS for patients receiving DOAC therapy.

Structured patient education

Question: For patients receiving oral anticoagulation therapy for VTE treatment, should supplementary patient education be offered vs no supplementary patient education?

Recommendation 12

For patients receiving oral anticoagulation therapy for VTE treatment, the ASH guideline panel *suggests* using supplementary patient education in addition to basic education for patients receiving oral anticoagulation for VTE treatment (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. This question specifically evaluated whether educational interventions over and above what most patients receive from health care providers (eg, the prescriber and/or dispensing pharmacist) in the usual course of anticoagulant prescribing improves anticoagulation therapy outcomes. We found 1 systematic review evaluating the impact of supplemental patient education on outcomes that concluded that there was not sufficient evidence to support supplemental patient education to improve outcomes for patients with VTE.[152] The quality of evidence included in this review was deemed to have very low certainty; therefore, we sought additional studies that might provide more information. We included 8 RCTs evaluating patients receiving anticoagulation therapy that tested various educational interventions.[33,153-159]

One study reported the effect of supplemental education interventions on mortality[154]; 3 studies each reported thromboembolic[154,155,158] and bleeding[33,154,158] outcomes. Three studies assessed the impact of supplemental education interventions on TTR for patients receiving VKA therapy.[33,155,159] Five studies reported change in various knowledge assessment scores following the educational intervention.[153,156-159] The EtD framework is shown online at https://dbep.gradepro.org/profile/17f7766f-74b7-462f-9041-f509df9c7d6a.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Although supplemental education might reduce mortality (RR, 0.37 [95% CI, 0.2-8.83]; ARR, 25 fewer per 1000 [95% CI, 38 fewer to 305 more]; low certainty), PE (RR, 0.57 [95% CI, 0.17-1.95]; ARR, 9 fewer per 1000 [95% CI, 17 fewer to 19 more]; low certainty), and recurrent DVT (RR, 0.57 [95% CI, 0.17-1.95]; ARR, 11 fewer per 1000 [95% CI, 22 fewer to 25 more]; low certainty), the effect estimates are extremely imprecise, and CIs include both large benefits and great harm. Studies reporting TTR as an outcome for patients receiving VKA therapy found no difference between those receiving supplemental education and control groups (MD, 2.40% higher [95% CI, 2.79% lower to 7.58% higher]; low certainty). Supplemental education was effective in improving patient performance on various knowledge assessments (standardized MD, 0.77 higher [95% CI, 0.43-1.11 higher]; low certainty).

Harms and burden. Although supplemental education might reduce the risk of bleeding in patients that were at average risk for bleeding compared with control patients (RR, 0.54 [95% CI, 0.06 to 4.76]; ARR, 8 fewer per 1000 [95% CI, 16 fewer to 64 more]; very low certainty), the effect estimate is very imprecise, and CIs include large benefit and great harm.

Other EtD criteria and considerations. The guideline panel determined that the uncertainty about resources required to implement this intervention is large, depending on the nature of the intervention itself. Some interventions consisted of a 5-minute video,[157] whereas others involved 20 to 30 minutes of one-on-one teaching.[158] The cost-effectiveness of supplemental education could not be determined, as there were no available studies. The panel agreed that individual patients will have different experiences when supplemental education is delivered, in part due to differences in the manner in which health care providers deliver the intervention. There may also be differences between patients receiving DOACs and those receiving VKA, given that patients on DOACs may not receive the same level of follow-up or may be less likely to receive care in specialized AMSs. According to some panel members, supplemental education might increase health care equity if it is uniformly administered in a consistent way; others thought that equitable delivery is unlikely. The panel agreed that this intervention is probably acceptable to key stakeholders, including patients, health care providers, and payers (although payers may be less accepting due to lack of clear benefit), and is also feasible to implement for most patients, although less so for patients with low health literacy or those whose primary language differs from that of the educational material.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty in evidence for a net health benefit from using supplemental educational interventions. Not surprisingly, supplemental education increased performance on knowledge assessments; however, the panel viewed the importance of this outcome as uncertain relative to actual clinical outcomes. This recommendation places a high value on a very uncertain benefit of the education intervention and a low value on avoiding the burden and cost associated with the intervention.

The panel identified the following additional research priorities: (1) identifying a standardized definition of what constitutes a patient education intervention and (2) acquiring more information regarding DOAC educational interventions.

Efforts to improve anticoagulant-medication adherence

Question: For patients receiving anticoagulation therapy for VTE, should interventions to improve adherence (eg, refill reminders and INR reminders) vs usual care be used?

In general, adherence to prescribed medication regimens is associated with improved clinical outcomes for patients with chronic conditions, and nonadherence is associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased health care costs.[160,161] Initially, we searched for any evidence regarding specific interventions to improve anticoagulation therapy adherence (eg, refill reminders and INR reminders). We searched only for RCTs and identified 3 RCTs addressing specific interventions designed to improve adherence, and we prepared separate EtD frameworks for each adherence intervention (recommendations 13a through 13d).[162-164]

Recommendation 13a

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using a daily lottery (between a 1-in-5 and 1-in-100 chance of a monetary reward each day if a pill compartment on a sophisticated electronic medication monitoring system is accessed) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. Two RCTs reported the effect of a daily lottery-based incentive intervention for patients using VKA.[162,163] In the lottery arm, participants had between a 1-in-5 and a 1-in-100 chance of a monetary reward each day if they opened the pill compartment on a sophisticated electronic medication monitoring system and confirmed that they took their warfarin as prescribed that day. The main outcome was anticoagulation control, as measured by out-of-range INRs, and secondary outcomes included mortality, bleeding, and thromboembolic events. The EtD framework is shown online at https://dbep.gradepro.org/profile/e5b45031-b8d4-4f50-8472-6617781ff3e3.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. There was no difference in the percentage time out of INR range (adjusted odds ratios [ORs] for likelihood of being out of INR range, 0.98 [95% CI, 0.70-1.38][162] and 0.93 [95% CI, 0.55-1.28][163]; very low certainty) or days with incorrect adherence (fully adjusted OR for likelihood of nonadherence, 0.84 [95% CI, 0.55-1.28]; very low certainty)[163] between those receiving the daily lottery intervention and control groups.

Harms and burden. Mortality (ARR, 8 more per 1000; very low certainty), PE/DVT (ARR, 26 more per 1000; very low certainty), and major bleeding (RR, 1.63 [95% CI, 0.33-8.09]; ARR 22 more per 1000 [95% CI, 24 fewer to 249 more]; very low certainty) were all higher in the daily lottery intervention group than in controls, but the CIs were extremely wide, including both appreciable benefit and great harm.

Other EtD criteria and considerations. Resource requirements for the daily lottery would be large because the use of an electronic medication monitoring system would be required for each patient, and the cost for monetary prizes averaged $3 per patient per day. Furthermore, the panel determined that health equity would probably be reduced by the intervention, key stakeholders would probably not find a daily lottery acceptable, and given the requirement for specialized equipment, the intervention is probably not feasible to implement in most settings.

Conclusions and research needs for this recommendation. Given that no evidence supports the benefit of the lottery approach, the likely high costs, and the probable lack of acceptability and feasibility, the panel suggests against using the lottery. This recommendation should not be interpreted to mean that interventions aimed at improving anticoagulant adherence are not important. Successful strategies used to improve medication adherence in other chronic disease states have included (1) ensuring access to providers across the continuum of care and implementing team-based care (see recommendation 11); (2) educating and empowering patients to understand the treatment regimen and its benefits (see recommendation 12); (3) reducing barriers to obtaining medication, including cost reduction and efforts to retain or reengage patients in care; and (4) use of health information technology tools to improve decision-making and communication during and after office visits (see recommendations 3 and 4).[165]

The panel identified the following additional research priority: development and testing of adherence interventions that are acceptable, feasible, and affordable, especially for patients on DOAC or on VKA and not considered eligible for PST or PSM, and determining the impact of those interventions on clinical outcomes and cost-effectiveness.

Recommendation 13b

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using electronic reminders (daily alarm via an electronic medication monitoring system) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation applies specifically to a sophisticated alert system used in the study evaluated by the panel.

Summary of the evidence. One RCT reported the effect of an electronic medication monitoring system with a daily alarm to remind patients to take their anticoagulant medication as scheduled.[162] The main outcome was anticoagulation control, as measured by out-of-range INRs, and secondary outcomes included mortality, bleeding, and thromboembolic events. The EtD framework is shown online at https://dbep.gradepro.org/profile/92492887-D3C0-CAC2-BEEE-D88978A91C30.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available

online. The percentage time out-of-INR range was lower in the electronic reminder group than in controls (adjusted OR for likelihood of being out of INR range, 0.64 [95% CI, 0.45-0.93]; very low certainty). There was no difference in median days with incorrect adherence between the electronic reminder and control groups (difference in the fully adjusted model for percentage incorrect adherence, −2.0% [95% CI, −8.2 to 4.2]; very low certainty).

Harms and burden. There was no effect of electronic reminders on mortality and PE/DVT because these outcomes did not occur in any study patient. There was no difference in major bleeding between the electronic reminders group and controls (RR, 1.02 [95% CI, 0.27-3.89]; ARR, 1 more episode per 1000 [95% CI, 45 fewer to 178 more per 1000]; very low certainty).

Other EtD criteria and considerations. Resource requirements for the electronic reminder system would be large. Furthermore, the panel determined that given the requirement for specialized equipment, the intervention is probably not feasible to implement in most settings.

Conclusions and research needs for this recommendation. Given the large uncertainty regarding net health benefit/harm from using electronic reminders to improve adherence to anticoagulation therapy for patients receiving treatment of VTE, the high costs, and the probable lack of feasibility, the panel suggests against using electronic reminders. See recommendation 13a for additional comments regarding adherence interventions in general and research needs pertaining to this recommendation.

Recommendation 13c

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *recommends against* using a daily lottery (see recommendation 13a) plus electronic reminders (see recommendation 13b) to improve medication adherence (strong recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation applies specifically to a sophisticated alert system used in the study evaluated by the panel.

Summary of the evidence. One RCT reported the effect of a daily lottery-based incentive intervention combined with an electronic medication monitoring system with a daily alarm to remind patients to take their anticoagulant medication as scheduled.[162] The main outcome was anticoagulation control as measured by out-of-range INRs, and secondary outcomes included mortality, bleeding, and thromboembolic events. The EtD framework is shown online at https://dbep.gradepro.org/profile/06290825-AF53-134F-9191-7E26113C0FDA.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. The percentage time *outside* of the INR range was lower in the group with the daily lottery plus electronic reminder than in controls, but the CI was wide and included no effect (adjusted OR for likelihood of being out of INR range, 0.77 [95% CI, 0.54-1.09]; very low certainty). There was no difference in median days with incorrect adherence between the group with the daily lottery plus electronic reminder and the control group (difference in the fully adjusted model for percentage incorrect adherence, −4.6% [95% CI, −11.1 to 1.9]; very low certainty).

Harms and burden. There was no effect of a daily lottery plus electronic reminders on mortality and PE/DVT because these outcomes did not occur in any study patient. There was no difference in major bleeding between the daily lottery plus electronic reminder group and control (RR, 1.23 [95% CI, 0.35-4.38]; ARR, 14 more episodes per 1000 [95% CI, 40 fewer to 208 more per 1000]; very low certainty).

Other EtD criteria and considerations. Resource requirements for the daily lottery would be large because the use of an electronic medication monitoring system would be required for each patient, and cost for monetary prizes averaged $3 per patient per day. Furthermore, key stakeholders would probably not find a daily lottery acceptable, and given the requirement for specialized equipment, the intervention is probably not feasible to implement in most settings.

Conclusions and research needs for this recommendation. The panel decided on a strong recommendation against the intervention based on very low quality evidence pointing toward harm for all critical outcomes and on the intervention having high costs and probably not being acceptable or feasible. The GRADE approach includes situations in which strong recommendations are warranted despite very low certainty in evidence about the effects, including situations where the panel determined there is high certainty that cost of the intervention outweighs any potential benefits.[166] See recommendation 13a for additional comments regarding adherence interventions in general and research needs pertaining to this recommendation.

Recommendation 13d

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel *suggests against* using visual medication schedules (provided to patients at each visit, along with brief counseling) to improve medication adherence (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. One RCT reported the effect of a visual medication schedule provided to patients at each visit, along with brief counseling.[164] The main outcome was the time elapsed before achieving target anticoagulant control. Secondary outcomes included TTR during the 90-day study period, mortality, and hospitalizations. The EtD framework is shown online at https://dbep.gradepro.org/profile/0CF6E4C9-8344-A5B0-B8CA-1ECEC061E826.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Compared with controls, a visual medication schedule modestly increased TTR, but the CI included no effect (MD, 2.6% higher [95% CI, 7.6% lower to 12.9% higher]; very low certainty). There was no effect of a visual medication schedule on PE/DVT because these outcomes did not occur in any study patient.

Harms and burden. The estimate of the intervention on mortality was unreliable as only 1 death occurred in the study (ARR, 14 more per 1000; very low certainty). Hospitalization was increased in those using the visual medication schedule (RR, 4.93 [95% CI, 1.12-21.47]; ARR, 108 more hospitalizations per 1000 [95% CI, 3 more to 568 more per 1000]; very low certainty).

Other EtD criteria and considerations. The intervention was feasible to implement, as it is currently being used in some settings. Although costs have not been formally assessed, they are likely moderate.

Conclusions and research needs for this recommendation. Given that the net health benefit/harm from using a visual medication schedule to improve adherence to anticoagulation therapy for patients receiving treatment of VTE remains very uncertain and the costs are moderate, the panel suggests against using visual medication schedules as defined in the included study. See recommendation 13a for additional comments regarding adherence interventions in general and research needs pertaining to this recommendation.

Invasive procedure management

Question: For patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures, should periprocedural bridging with LMWH or UHF vs interruption of VKA therapy alone be used?

Recommendation 14

For patients at low to moderate risk of recurrent VTE (see Table 4) who require interruption of VKA therapy for invasive procedures, the ASH guideline panel *recommends against* periprocedural bridging with LMWH or UHF in favor of interruption of VKA alone (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Summary of the evidence. We found 1 systematic review that addressed this question,[167] but we did not use any studies in the evidence for this question because (1) they evaluated patients receiving anticoagulation therapy for mixed indications, and isolating the minority of patients with low to moderate risk of recurrent VTE was not possible, or (2) the studies included only patients with indications for anticoagulation therapy other than VTE. We identified 2 additional relevant studies.[168,169] Mortality, recurrent VTE, and clinically relevant bleeding outcomes were derived from an observational study that included patients receiving warfarin therapy for treatment of VTE who required anticoagulation interruption for invasive procedures.[168] The other study was an RCT evaluating uninterrupted vs interrupted anticoagulation during pacemaker or defibrillator surgery and reported patient satisfaction (a surrogate measure of quality-of-life impairment) and delay of intervention as outcomes.[169] Although only 5% of patients in this study had VTE as the indication for anticoagulation therapy, the evidence for these outcomes was considered relevant for our population of interest. The EtD framework is shown online at https://dbep.gradepro.org/profile/510d8142-f0d4-47f4-8998-e153cec6018f.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. There was no effect of bridging therapy on mortality risk because no deaths occurred during the 30-day follow-up period in either group (low certainty evidence). Bridging with LMWH may reduce the risk for any recurrent VTE, but the effect, if present, is probably very small, and the relative effect CI includes both important benefit and important harm. Because very few events occur for patients at low to moderate risk for recurrent VTE, the magnitude of the absolute effect, whatever the true relative effect, will be very small, and the certainty in evidence for recurrent VTE was upgraded (RR, 0.34 [95% CI, 0.02-6.58]; ARR, 2 fewer DVTs per 1000 [95% CI, 2 fewer to 13 more per 1000; moderate certainty).

Harms and burden. The risk of clinically relevant bleeding was increased among those receiving bridging with LMWH compared with those who interrupted warfarin therapy alone (RR, 31.73 [95% CI, 4.14-243.19]; ARR, 25 more bleeding episodes per 1000 [95% CI, 3 more to 196 more per 1000]; very low certainty). Bridging with LMWH was associated with lower patient satisfaction (MD, 0.5 lower [95% CI, 0.25 lower to 0.75 lower]; low certainty) and increased the risk of delay in intervention, as measured by a composite of prolonged hospitalization and hematoma requiring interruption of anticoagulation or evacuation (RR, 4.57 [95% CI, 2.49-8.38]; ARR, 125 more delayed interventions per 1000 [95% CI, 52 more to 258 more]; low certainty).

Other EtD criteria and considerations. The resource requirements associated with LMWH bridging are likely to be large, driven by the LMWH cost, complexity of teaching patients the intervention, and management of bleeding events.

Conclusions and research needs for this recommendation. When the evidence for this question was weighed, a much higher value was placed on the risk for bleeding, which has been consistently associated with LMWH bridging in available studies, than on the possible reduction in the risk of recurrent VTE, which in this patient population is very small. The panel was confident that that the desirable effects of LMWH bridging are outweighed by the undesirable effects and that a strong recommendation against LMWH bridging was warranted. This recommendation does not apply to patients requiring VKA therapy for indications in addition to VTE (eg, mechanical heart valves).

The panel identified the following additional research priority: sufficiently powered RCTs comparing LMWH/UFH bridging vs VKA interruption alone in VTE patients at high recurrent VTE risk undergoing an invasive procedure.

Question: For patients interrupting DOAC therapy for scheduled invasive procedures, should performing laboratory testing for DOAC anticoagulant effect be used vs interrupting DOAC therapy alone?

Recommendation 15

For patients interrupting DOAC therapy for scheduled invasive procedures, the ASH guideline panel *suggests against* performing laboratory testing for DOAC anticoagulant effect prior to procedures (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We found no systematic reviews but did identify 5 individual studies that included patients receiving DOAC therapy, mostly for atrial fibrillation, who required temporary interruption of anticoagulation for an invasive procedure.[170-174] No studies directly compared outcomes for patients interrupting DOAC therapy for invasive procedures in which laboratory testing to assess DOAC anticoagulant effect was

and was not performed prior to the procedure; thus, intervention and control studies represent different populations. Event rates for the intervention groups[171,172,174] came from different studies than the event rate for the control groups.[170,173] Three studies reported mortality outcomes,[170,171,174] and 5 studies reported development of any thromboembolism and major bleeding.[170-174] No studies reported quality of life or delays in procedure outcomes. The EtD framework is shown online at https://dbep.gradepro.org/profile/ee27563e-0db8-464d-ae48-0e72bec3da3b.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Indirect comparison of the available evidence from separate studies showed that laboratory testing to assess DOAC effect prior to invasive procedures may or may not reduce mortality (RR, 0.47 [95% CI, 0.12-1.86]; ARR, 5 fewer deaths per 1000 [95% CI, 8 fewer to 8 more]; very low certainty) and VTE (RR, 0.37 [95% CI, 0.07-1.81]; ARR, 7 fewer events per 1000 [95% CI, 10 fewer to 8 more]; very low certainty).

Harms and burden. Indirect comparison of the available evidence from separate studies showed that laboratory testing to assess DOAC effect prior to invasive procedures had no effect on the risk of major bleeding compared with interrupting DOAC alone (RR, 0.87 [95% CI, 0.40-1.90]; ARR, 2 fewer events per 1000 [95% CI, 10 fewer to 15 more per 1000]; very low certainty).

Other EtD criteria and considerations. There is very little evidence bearing on other EtD criteria.

Conclusions and research needs for this recommendation. The net health benefit/harm from laboratory testing to assess DOAC effect prior to scheduled invasive procedures compared with interrupting DOAC therapy remains very uncertain. Furthermore, the clinical use of DOAC tests is not well established, and there is no evidence to support a beneficial effect. Therefore, the panel made a conditional suggestion against confirming the absence of DOAC effect prior to proceeding with scheduled invasive procedures. Confirming the absence of DOAC affect may be advisable in scenarios where anticoagulant effect may be prolonged (eg, patients with renal dysfunction and/or on interacting drugs), when DOAC interruption cannot be reliably confirmed by the patient/caregiver (eg, urgent or emergent invasive procedures), or for patients undergoing a procedure that entails a very high risk of bleeding. It is advisable not to rely on any single (either pharmacokinetic or laboratory) strategy in isolation to assess DOAC effect prior to procedures but instead to use a comprehensive approach to assessing, confirming, and communicating DOAC cessation of therapy among the patient and all providers involved.

The panel identified the following additional research priorities: (1) developing validated specific DOAC effect tests, particularly those that can be performed rapidly and, ideally, at the point of care; (2) testing the effect on clinical outcomes of using a validated specific DOAC test with prespecified thresholds at which patients on DOACs can safely proceed to surgery or invasive diagnostic procedures; (3) assessing the cost-effectiveness, acceptability, and feasibility of implementing a validated specific DOAC test.

Excessive anticoagulation and bleeding management. *Question: For patients receiving VKA for treatment of VTE with INRs of >4.5 but <10 and without clinically relevant bleeding, should temporary cessation of VKA plus administration of vitamin K vs temporary cessation of VKA alone be used?*

Recommendation 16

For patients receiving VKA for treatment of VTE with INRs of >4.5 but <10 and without clinically relevant bleeding, the ASH guideline panel *suggests* using temporary cessation of VKA alone *without* the addition of vitamin K (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We included eligible studies from the most recent systematic review in nonbleeding patients who did and did not receive oral vitamin K for an INR of >4.5 but <10 (or the upper limit of the laboratory INR readout).[175] The search was updated from 2006 onward, yielding a total of 5 RCTs.[176-180]

Three studies reported the effect of vitamin K administration on mortality,[176,177,179] 2 studies reported on development of any thromboembolism and major bleeding,[176,179] 1 study reported the outcome of DVT,[176] and 5 studies reported the proportion of patients who reached various INR goal ranges.[176-180] No studies reported the outcomes of emergency department visits, hospitalization, or quality-of-life impairment. The EtD framework is shown online at https://dbep.gradepro.org/profile/a457eb13-cb1d-40a8-a081-5e0c535d2a49.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Administration of oral vitamin K in addition to withholding VKA did not reduce the risk of all-cause mortality compared with withholding VKA alone (RR, 1.24 [95% CI, 0.62-2.47]; ARR, 7 more deaths per 1000 [95% CI, 11 fewer to 44 more per 1000]; moderate certainty) or affect the proportion of patients who achieved the target INR (RR, 1.95 [95% CI, 0.88-4.33]; ARR, 165 more per 1000 [95% CI, 21 fewer to 579 more per 1000]; very low certainty), but the CI for both mortality and INR goal attainment includes appreciable reduction and increase in events. The risk of major bleeding was higher among those receiving oral vitamin K than those receiving placebo, but the CI includes the possibility of a very small bleeding reduction (RR, 2.43 [95% CI, 0.81-7.27]; ARR, 14 more major bleeds per 1000 [95% CI, 2 fewer to 61 more per 1000]; moderate certainty).

Harms and burden. Administration of oral vitamin K in addition to withholding VKA did not increase the risk of any thromboembolism compared with withholding VKA alone (RR, 1.29 [95% CI, 0.35-4.78]; ARR, 3 more thromboembolisms per 1000 [95% CI, 6 fewer to 37 more per 1000]; moderate certainty). The estimate of oral vitamin K administration on the risk for DVT is imprecise, and the CI includes the possibility of no effect (RR, 0.32 [95% CI, 0.01-8.04]; ARR, 15 fewer DVTs per 1000 [95% CI, 23 fewer to 160 more per 1000]; moderate certainty).

Other EtD criteria and considerations. The panel agreed that resource requirements associated with administering oral vitamin K are likely to be moderate owing to the high cost of pharmaceutical-grade phytonadione (vitamin K) in the United States. The feasibility of using over-the-counter (OTC) sources of vitamin K may be constrained by the variable quality and actual

Table 4. VTE recurrence risk stratification

High risk	Moderate risk	Low risk
VTE within past 3 mo	VTE within past 3-12 mo	VTE > 12 mo previously No other risk factors
Deficiency of protein C, protein S, or antithrombin	Heterozygous factor V Leiden	
Antiphospholipid antibody syndrome	Prothrombin 20210 mutation	
Multiple thrombophilic abnormalities	Recurrent VTE	
	Active cancer	

active-ingredient content of available OTC vitamin K formulations (available OTC tablet strengths would require the administration of many tablets to achieve recommended doses, and there have been reports that some OTC brands contain less or more actual vitamin K than advertised on the product label).[181]

Conclusions and research needs for this recommendation. Based on the low quality of the available evidence, the guideline panel remained uncertain regarding the net benefit associated with administration of oral vitamin K in addition to withholding VKA doses for patients presenting with INRs between 4.5 and 10.0 (or the upper limit of the laboratory readout). Given the high cost of prescription oral vitamin K tablets in the United States and the variable vitamin K content of available OTC products, the panel conditionally recommends against administering oral vitamin K. Administration of oral vitamin K might be considered for patients at high risk of developing bleeding complications (eg, those who have undergone recent surgical procedures) or in situations where the INR is expected to be prolonged for a longer period of time (eg, intentional overdose, presence of interacting drugs, or very low weekly VKA dose requirement). Data for VKAs other than warfarin are limited, reducing confidence in this recommendation for patients treated with phenprocoumon, which has a longer half-life than warfarin.

The panel identified the following additional research questions. (1) Is withholding VKA alone a safe and effective option for patients presenting with INRs of >10.0 in the absence of bleeding? (2) What is the minimum amount of oral vitamin K required to reverse the hypoprothrombinemic effect of VKA? (3) Can dietary sources of vitamin K (eg, broccoli, spinach, etc) be used to manage excessive VKA anticoagulation in nonbleeding patients?

Question: For patients with life-threatening bleeding during VKA treatment of VTE, should 4-factor PCC vs FFP be used, in addition to cessation of VKA and IV vitamin K?

Recommendation 17

For patients with life-threatening bleeding during VKA treatment of VTE who have an elevated INR, the ASH guideline panel *suggests* using 4-factor PCC rather than FFP, in addition to cessation of VKA and IV vitamin K (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We included eligible studies from the most recent systematic review for patients presenting with VKA-associated bleeding who received PCC vs FFP in addition to vitamin K and temporary cessation of VKA.[182] The search was updated from 2016 onward, yielding 3 eligible RCTs.[183-185] Additional studies included in the systematic review proved ineligible because patients needed VKA reversal for urgent or semiurgent surgery and not because of bleeding.

Three studies reported the effect of PCC vs FFP on mortality,[183-185] 2 studies reported on development of any thromboembolism and major bleeding,[184,185] 1 study reported the outcomes of PE and DVT,[185] 2 studies reported on volume overload (this outcome was not originally prioritized but was felt by the panel to be an important outcome for consideration),[183,184] and 2 studies reported on the proportion of patients who reached the INR goal of <1.3[185] or <1.4[184] (follow-up ranged from 0.5 to 3 hours). The EtD framework is shown online at https://dbep.gradepro.org/profile/e58f8d6b-8fd6-4164-b9da-2c62605e845c.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Studies assessing mortality reported no difference between those receiving 4-factor PCC and FFP (RR, 0.92 [95% CI, 0.37-2.28]; ARR, 10 fewer deaths per 1000 [95% CI, 78 fewer to 159 more per 1000]; very low certainty). Four-factor PCC reduced the incidence of volume overload (RR, 0.34 [95% CI, 0.13-0.85]; ARR, 107 fewer episodes per 1000 [95% CI, 24 fewer to 141 fewer per 1000]; low certainty) and increased the proportion of patients who reached an INR of ≤1.2 to 1.3 within 0.5 to 3 hours (RR, 6.66 [95% CI, 3.82-11.61]; moderate certainty).

Harms and burden. The risk of major bleeding during 45 to 90 days of follow-up, as assessed with hematoma expansion or recurrent intracranial hemorrhage (ICH), was higher following 4-factor PCC administration than following FFP administration, but the CI includes appreciable risk increases and decreases (RR, 1.34 [95% CI, 0.78-2.29]; ARR, 31 more episodes per 1000 [95% CI, 20 fewer to 117 more per 1000]; low certainty). Administration of 4-factor PCC possibly increased the risk of PE (ARR, 148 more PE per 1000 [95% CI was not estimable]; low certainty) and DVT (ARR, 37 more DVT per 1000 [95% CI was not estimable]; low certainty), but these estimates were unreliable due to few events in the intervention group and no events in the control group. Similarly, 4-factor PCC was possibly associated with increased risk of any thromboembolism (eg, myocardial infarction, stroke, PE, or DVT), but again, the CI included appreciable risk reduction and increase (RR, 1.60 [95% CI, 0.7-3.62]; ARR, 41 more episodes per 1000 [95% CI, 20 fewer to 179 more per 1000]; low certainty).

Other EtD criteria and considerations. In the United States, the upfront cost of PCC is approximately threefold higher than that of FFP; in Europe, however, FFP upfront costs are higher than those of PCC. Reduction of potentially severe transfusion-associated circulatory overload reactions reduces the cost and should be factored into the resource use equation.[186] In addition, FFP requires additional staff time to prepare and administer. A cost-effectiveness analysis based on a systematic review and UK National Health Service perspective estimated that the cost per quality-adjusted life-year gained with PCC vs FFP was £3000 or less, depending on hemorrhage type.[187]

Conclusions and research needs for this recommendation. The guideline panel's assessment was that the benefits and harms with 4-factor PCC vs FFP were balanced based on very low

certainty evidence. Nevertheless, the panel favored 4-factor PCC over FFP because of ease of administration, the increased probability of achieving a near-normalized INR, and the lower risk of volume overload. The panel determined that this recommendation most directly applies to intracranial bleeding, where speed of reversal is likely to be a particularly important consideration.

The panel identified the following additional research questions. (1) What is the cost-effectiveness of 4-factor PCC vs FFP from the payer perspective in various health care systems? (2) What is the true magnitude of increased thromboembolic risk associated with 4-factor PCC administration compared with the same risk for patients treated with FFP?

Question: For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, should cessation of direct Xa inhibitor plus reversal of the direct Xa inhibitor anticoagulant effect vs cessation of direct Xa inhibitor alone be used?

This question aimed to evaluate management options for life-threatening bleeding related to administration of an oral direct Xa inhibitor. Two approaches have emerged for this situation, administration of 4-factor PCC and administration of coagulation factor Xa (recombinant), inactivated-zhzo (formerly known as andexanet alpha). These approaches have not been directly compared, and the panel was unable to provide a judgment regarding which is preferred and therefore made independent recommendations regarding each intervention.

Recommendation 18a

For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using *either* 4-factor PCC administration as an addition to cessation of oral direct Xa inhibitor *or* cessation of oral direct Xa inhibitor alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Summary of the evidence. We found no systematic reviews that addressed this question, but we identified 8 individual studies.[106,110,113,188-192] Eligible studies included patients receiving direct Xa inhibitors who were experiencing major bleeding and reported the effect of 4-factor PCC on mortality, ineffective bleeding management, and thromboembolic complications.[106,110,113,188-192] The EtD framework is shown online at https://dbep.gradepro.org/profile/2ec6099d-9b00-4bac-bc31-34653ee10737.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Because a suitable comparator group was not available, the panel was unable to make a judgment on the benefits of 4-factor PCC on outcomes associated with life-threatening bleeding during oral direct Xa inhibitor therapy for VTE.

Harms and burden. Because a suitable comparator group was not available, the panel was unable to make a judgment on the harms and burdens of 4-factor PCC on outcomes associated with life-threatening bleeding during oral direct Xa inhibitor therapy. Studies did report that bleeding either worsened or did not improve in 32% of patients receiving 4-factor PCC.

Other EtD criteria and considerations. There was very limited evidence to inform other considerations.

Conclusions and research needs for this recommendation. Lack of evidence left the net health benefit/harm from using 4-factor PCC as an addition to cessation of direct Xa inhibitors very uncertain. The ASH guideline panel therefore suggests that either 4-factor PCC administration as an addition to temporary cessation of oral direct Xa inhibitor or cessation of oral direct Xa inhibitor alone be used for patients with life-threatening bleeding during treatment of VTE (conditional recommendation based on very low certainty in the evidence). In a life-threatening situation, the experience and judgment of the prescriber weighing individual risks and benefits would likely be the deciding factors. This recommendation does not apply to non–life-threatening bleeding because cost likely outweighs potential benefit and there is likely a small but quantifiable increased risk of thromboembolism associated with administration of PCC.[193]

The panel identified the following additional research questions. (1) What clinical parameters define the need for intervention with 4-factor PCC over withholding oral direct Xa inhibitor alone? (2) What is the comparative effectiveness of 4-factor PCC in real-world patients presenting with potentially life-threatening oral direct Xa inhibitor-associated bleeding vs withholding direct Xa inhibitor alone?.

Recommendation 18b

For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using coagulation factor Xa (recombinant), inactivated-zhzo in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Summary of the evidence. We found no systematic reviews that addressed this question but identified a single study that measured relevant outcomes for patients receiving direct Xa inhibitors who were experiencing major bleeding.[194] The eligible study reported the effect of administration of coagulation factor Xa (recombinant), inactivated-zhzo on mortality, ineffective bleeding management, and thromboembolic complications.[194] The EtD framework is shown online at https://dbep.gradepro.org/profile/8FD0D118-359D-B5A1-A933-FB225270E86A.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Because a suitable comparator group was not available, the panel was unable to judge the benefits of administration of coagulation factor Xa (recombinant), inactivated-zhzo on outcomes associated with life-threatening bleeding during direct Xa inhibitor therapy.

Harms and burden. Because a suitable comparator group was not available, the panel was unable to judge the harms and burdens of administration of coagulation factor Xa (recombinant),

inactivated-zhzo on outcomes associated with life-threatening bleeding during direct Xa inhibitor therapy.

Other EtD criteria and considerations. Costs of coagulation factor Xa (recombinant), inactivated-zhzo are extremely high (estimated at $27 500 to $50 000 for the bolus dose in the United States). Access to coagulation factor Xa (recombinant), inactivated-zhzo is also uncertain, due to issues pertaining to the manufacturing process. Administration of coagulation factor Xa (recombinant), inactivated-zhzo in the setting of life-threatening bleeding is likely to be somewhat complicated but is probably feasible in the hospital setting.

Conclusions and research needs for this recommendation. Based on the absence of data for the comparator, very low certainty evidence from 1 observational study, and the extremely high cost of the intervention, the panel could not come to a unanimous decision. Voting resulted in a conditional recommendation for administration of coagulation factor Xa (recombinant), inactivated-zhzo, primarily based on the evidence for direct Xa inhibitor reversal and biological plausibility of preventing worsening of bleeding for widely used anticoagulants, the direct Xa inhibitors, using a specific reversal agent. Whether coagulation factor Xa (recombinant), inactivated-zhzo is associated with excess thromboembolism is unknown. This recommendation does not apply to non–life-threatening bleeding, because the cost likely outweighs potential benefit.

The panel identified the following additional research questions. (1) What is the comparative effectiveness of administration of coagulation factor Xa (recombinant), inactivated-zhzo in the setting of direct Xa inhibitor-associated life-threatening bleeding compared with cessation of direct Xa inhibitor alone? (2) What is the cost-effectiveness of administration of coagulation factor Xa (recombinant), inactivated-zhzo using pharmacoeconomic modeling based on comparative data and the actual costs of the intervention? (3) What is the relative benefit of coagulation factor Xa (recombinant), inactivated-zhzo compared with alternate interventions such as nonspecific procoagulants (antifibrinolytics and/or PCCs)? (4) Would a rapidly available test for anti-Xa effect prevent administration of coagulation factor Xa (recombinant), inactivated-zhzo to patients who do not have significant Xa inhibitor concentrations?

Question: For patients with life-threatening bleeding during dabigatran treatment of VTE, should cessation of dabigatran plus idarucizumab administration vs cessation of dabigatran alone be used?

Recommendation 19

For patients with life-threatening bleeding during dabigatran treatment of VTE, the ASH guideline panel *suggests* using idarucizumab in addition to cessation of dabigatran rather than no idarucizumab (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding.

Summary of the evidence. We found no systematic reviews addressing this question but identified 3 relevant observational studies. Two studies included an intervention arm only (idarucizumab),[195-197] and 1 study included a control arm only (none of the patients received idarucizumab).[109] We combined the number of events and the total number of patients from the 3 studies to calculate a relative effect. All studies included patients receiving dabigatran presenting with life-threatening bleeding; 1 study[195] included some patients who were not bleeding but required urgent dabigatran reversal for invasive procedures. All studies reported the outcomes of life-threatening bleeding associated with dabigatran therapy, including death, worsening and/or recurrence of bleeding, and thromboembolic complications. The EtD framework is shown online at https://dbep.gradepro.org/profile/b1deb68f-2ed2-4734-bb86-0a66117969cd.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Idarucizumab administration may or may not reduce the mortality risk (RR, 0.47 [95% CI, 0.14-1.58]; ARR, 151 fewer deaths per 1000 [95% CI, 246 fewer to 166 more per 1000]; very low certainty) and worsening and/or recurrence of bleeding associated with life-threatening bleeding during dabigatran therapy (RR, 0.12 [95% CI, 0.03-0.43]; ARR, 251 fewer bleeding episodes per 1000 [95% CI, 163 fewer to 277 fewer per 1000]; very low certainty); the CIs are very wide and include large risk reductions and increases.

Harms and burden. There were 5 VTE events (3 DVTs and 2 PEs) reported following idarucizumab administration in 1 study.[195] Estimating the relative and absolute risk estimates was not possible, as there were no VTEs in the comparison group. The certainty in these estimated effects is very low.

Other EtD criteria and considerations. The acquisition cost of idarucizumab is considerable, although no formal economic analyses are available.

Conclusions and research needs for this recommendation. There is very low certainty evidence for a net health benefit from using idarucizumab to manage life-threatening bleeding for patients receiving dabigatran therapy for VTE, mandating a conditional recommendation. Some panel members were concerned about the possibility of VTE following idarucizumab administration. Furthermore, this recommendation does not apply to patients with non–life-threatening bleeding, as the cost likely outweighs the potential benefit.

The panel identified the following additional research questions. (1) What variables define the need for intervention with idarucizumab over withholding dabigatran alone? (2) What is the comparative effectiveness of idarucizumab in real-world patients presenting with potentially life-threatening dabigatran-associated bleeding compared with dabigatran cessation alone? (3) Would the use of a rapidly available test for a dabigatran effect prevent administration of idarucizumab to patients who do not have significant dabigatran concentrations?

Question: For patients with life-threatening bleeding during LMWH or UFH treatment of VTE, should cessation of LMWH or UFH plus protamine vs cessation of LMWH or UFH alone be used?

Recommendation 20

For patients with life-threatening bleeding during LMWH or UFH treatment of VTE, the ASH guideline panel *suggests* using protamine in addition to cessation of LMWH or UFH rather than no protamine (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding.

Summary of the evidence. We updated evidence from 2 systematic reviews that addressed this question,[198,199] identifying 3 RCTs[200-202] and 13 observational studies that measured relevant outcomes for patients receiving protamine for LMWH/UFH reversal when undergoing invasive procedures, not for major bleeding during VTE treatment.[203-215] Most studies did not specify whether "heparin" included UFH or LMWH; therefore, we could not analyze according to heparin subgroup. Given that only 74 patients receiving protamine were included in the RCTs, the panel elected to consider only the evidence from the observational studies.

Six studies reported the effect of protamine administration on mortality,[205,206,209,210,212,214] 10 studies reported development of major bleeding,[203,205-209,211-214] 10 studies assessed the risk of stroke,[203-207,209-211,213,214] and 6 studies reported the risk of myocardial infarction.[205-207,212-214] No studies reported the risk of PE or DVT. The EtD framework is shown online at https://dbep.gradepro.org/profile/770de24b-7077-4e3d-a7b9-cd7f401d31b4.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Studies assessing mortality reported no difference between those receiving protamine and control groups (RR, 0.98 [95% CI, 0.66-1.45]; ARR, 0 fewer deaths per 1000 [95% CI, 6 fewer to 9 more per 1000]; very low certainty). Protamine administration reduced the risk of developing major bleeding (RR, 0.61 [95% CI, 0.39-0.96]; ARR, 13 fewer bleeding episodes per 1000 [95% CI, 1 fewer to 20 fewer per 1000]; very low certainty).

Harms and burden. The risk of stroke (RR, 0.87 [95% CI, 0.65-1.18]; ARR, 2 fewer strokes per 1000 [95% CI, 7 fewer to 3 more per 1000]; very low certainty) and myocardial infarction (RR, 1.05 [95% CI, 0.72 to 1.54]; ARR, 0 fewer per 1000 [95% CI, 2 fewer to 4 more per 1000]; very low certainty) did not differ among those receiving protamine and controls.

Other EtD criteria and considerations. Compared with planned use of protamine at the conclusion of an invasive procedure, the panel considered that in a life-threatening bleeding situation, ordering protamine and having it prepared and infused may prove more difficult. Therefore, the feasibility of this intervention might vary according to whether centers perform invasive cardiac procedures where routine use of protamine is common.

Conclusions and research needs for this recommendation. The guideline panel determined that though there is very low certainty evidence for a net health benefit associated with administering protamine to patients receiving heparin (LMWH or UFH) who develop life-threatening bleeding in addition to heparin therapy cessation, the possibility of benefit warranted a conditional recommendation in favor of protamine administration. The recommendation does not, however, apply to patients with less serious bleeding when cessation of LMWH/UFH alone is likely to be sufficient. Although most studies did not specify whether "heparin" included UFH or LMWH, protamine should primarily be used for patients on UFH due to complete rather than partial reversal of the anticoagulant effect, as is seen with administration to patients who have been treated with LMWH.[13]

The panel identified the following additional research question. What is the comparative effectiveness of protamine administration for management of life-threatening bleeding in VTE or other patients on UFH/LMWH compared with UFH/LMWH cessation alone?

Anticoagulant resumption following bleeding

Question: For patients receiving anticoagulant treatment of VTE who survive an episode of major bleeding, should resumption of oral anticoagulation therapy vs discontinuation of oral anticoagulation therapy be used?

Recommendation 21

For patients receiving anticoagulation therapy for VTE who survive an episode of major bleeding, the ASH guideline panel *suggests* resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
Remark: This recommendation specifically applies to patients who require long-term or indefinite anticoagulation (ie, are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and are willing to continue anticoagulation therapy).

Summary of the evidence. We included eligible studies from the most recent systematic review for patients who did and did not resume anticoagulation therapy after surviving an episode of gastrointestinal tract bleeding (GIB).[216] The search was updated from 2014 onward and expanded to include ICH, yielding a total of 17 observational studies.[217-233] Most studies compared outcomes for patients who did and did not resume anticoagulation therapy following a GIB or ICH episode. Follow-up periods varied between studies (range, 3 months to 10 years).

Six studies reported the effect of anticoagulation therapy resumption on all-cause mortality,[218,219,222,229,230,233] 6 studies reported development of PE,[218,223,225,227,229,230] 7 studies reported development of DVT,[219,220,223,225,227,229,230] 9 studies reported the occurrence of VTE (PE, DVT, or both),[218-220,222,223,225,227,229,230] 12 studies reported development of thromboembolism (including events other than VTE),[217-220,222,223,225,227,229-231,233] and 14 studies reported worsening or new bleeding.[217-220,222,223,225,227-233] The EtD framework is shown online at https://dbep.gradepro.org/profile/098f8dae-062b-41b2-a51e-f7cc74379f3a.

Benefits. For benefits, see the evidence profile in the EtD framework referenced at the end of the previous section, available online. Resuming anticoagulation following GIB or ICH was associated with reduced risk of all-cause mortality (RR, 0.62 [95% CI, 0.43-0.89]; ARR, 165 fewer deaths per 1000 [95% CI, 247 fewer to 48 fewer per 1000]; very low certainty) and reduced risk of thromboembolism (RR, 0.45 [95% CI, 0.25-0.83]; ARR, 58 fewer per 1000 [95% CI, 80 fewer to 18 fewer per 1000]; low certainty). Resuming anticoagulation following GIB or ICH possibly reduces the risk for PE (RR, 0.35 [95% CI, 0.11-1.11]; ARR, 17 fewer episodes per 1000 [95% CI, 23 fewer to 3 more per 1000]; very low certainty) and VTE (RR, 0.58 [95% CI, 0.26-1.28]; ARR, 16 fewer episodes per 1000 [95% CI, 23 fewer to 11 more per

1000]; very low certainty), but the estimates are imprecise, and CIs include no effect. Studies assessing DVT found no difference between those resuming anticoagulation therapy and control groups who did not resume therapy (RR, 0.81 [95% CI, 0.31-2.16]; very low certainty).

Harms and burden. Resuming anticoagulation following GIB or ICH was associated with increased risk of major bleeding (RR, 1.57 [95% CI, 1.12-2.21; ARR, 43 more bleeding events per 1000 [95% CI, 9 more to 92 more per 1000]; very low certainty).

Other EtD criteria and considerations. There was very little evidence bearing on the other considerations. Whether the intervention is acceptable to key stakeholders likely varies: patient representatives on the panel were comfortable resuming anticoagulation therapy following bleeding, but providers were concerned about causing harm. The severity of the bleeding, presence of ongoing bleeding risk factors, and elapsed time since the bleeding episode were also felt to influence the acceptability of the intervention.

Conclusions and research needs for this recommendation. The guideline panel determined that there is uncertainty regarding the net health benefit from resuming anticoagulation therapy after surviving a major bleeding episode. Although only very low certainty evidence is available, some panel members felt that the potential to avoid mortality was more important than increasing the risk of recurrent bleeding. This recommendation specifically applies to patients who require long-term or indefinite anticoagulation (ie, are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and are willing to continue anticoagulation therapy). The available evidence was insufficient to allow the panel to state with certainty the optimal timing of anticoagulation therapy resumption. However, the panel determined that waiting at least 2 weeks but not more than 90 days after the bleeding event is reasonable based on the intervals for restarting anticoagulation therapy examined in clinical studies and depending on the patient-specific risk factors for thrombosis and bleeding (eg, indication for anticoagulation therapy and type of bleeding event). Earlier resumption may be appropriate if the source of bleeding is identified and corrected.

The panel identified the following additional research questions. (1) What is the optimal timing of and what patient-specific factors should influence anticoagulation therapy resumption? (2) For patients who developed major bleeding during oral anticoagulant therapy, how does transition to an alternative anticoagulant influence the risk of bleeding recurrence? (3) What is the impact on mortality, recurrent VTE risk, and recurrent bleeding risk associated with resumption of anticoagulation therapy following extracranial bleeding from sites other than the gastrointestinal tract? (4) Is resuming anticoagulation therapy following major bleeding a cost-effective strategy?

Good practice statements: renal function monitoring

For patients with creatinine clearance of ≥50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel agrees that good practice includes renal function monitoring every 6 to 12 months (ungraded good practice statement).

For patients with creatinine clearance of <50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel agrees that good practice includes renal function monitoring approximately every 3 months (ungraded good practice statement).

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

One other recent set of guidelines on the optimal management of anticoagulation therapy is available, issued by the 2012 American College of Chest Physicians (ACCP).[234] Major differences between the ASH guidelines and the ACCP guidelines include the consistent use of systematic reviews and EtD frameworks, which increase transparency, and the use of marker states to estimate the relative importance to patients of key outcomes of treatment.

Both ASH and ACCP guidelines suggest using longer INR recall intervals for patients receiving VKA therapy during periods of stable INR control. The ASH guidelines make a graded recommendation in favor of using AMS, whereas ACCP provided an ungraded best practice statement suggesting that health care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions. Both ASH and ACCP guidelines favor PSM over other methods of INR monitoring; however, the ASH guidelines makes a strong recommendation for PSM, whereas the ACCP guidelines make a weak (or conditional) recommendation favoring PSM. For patients with renal insufficiency (creatinine clearance of <30 mL/min), ACCP recommends using reduced LMWH doses over standard doses, whereas the ASH guidelines suggest against using anti–factor Xa monitoring to adjust LMWH doses in this patient population. These recommendations are complementary, suggesting that for patients with renal insufficiency, clinicians should use reduced LMWH doses without anti–factor Xa monitoring. Both ASH and ACCP guidelines suggest against administering vitamin K to patients presenting with INRs between 4.5 and 10.0 and no evidence of bleeding. Both guidelines suggest the administration of 4-factor PCC over FFP for patients with VKA-associated life-threatening bleeding.

The ASH guidelines include recommendations for optimal management of DOAC therapy, whereas the ACCP guidelines do not, as DOAC agents were introduced during the time when the ACCP guidelines were being prepared. Although both guidelines evaluated evidence pertaining to supplemental patient anticoagulant therapy education, only the ASH guidelines make a graded suggestion in favor of this intervention.

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. In addition, clinicians may encounter clinical questions that were not included among those prioritized by the panel.

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.[235]

Acknowledgments

The authors acknowledge Ann Wittkowski for her participation on the guideline panel. The authors acknowledge Miney Paquette, Gian Paolo Morgano, Sara Balduzzi, Meng Zhu, Samantha Craigie, Angela Barbara, Maja Ludwikowska, Piotr Stankowicz, Anna Starok, Siavash Piran, Reza Mirza, Itziar Etxeandia, Rachel Couban, Laura Fullerton, and Laura Charry for supporting the systematic reviews and Robby Nieuwlaat, Wojtek Wiercioch, and Holger Schünemann for cocoordination of the systematic review team. Holger Schünemann prepared a template of these guidelines for all panels that was critically reviewed by Adam Cuker, Rob Kunkle, the Guideline Oversight Subcommittee, the Methods Group supporting the guidelines, and *Blood Advances* editors.

Authorship

Contribution: D.M.W. prepared the first draft of this manuscript and revised the manuscript based on authors' suggestions; G.G. and R.N. contributed to drafting and critical revisions of the manuscript and contributed to further drafts; Guideline Panel members (J.A., N.P.C., M.A.C., F.D., A.H., J.M., T.M., N.S., J.S.) critically reviewed the manuscript and provided suggestions for improvement; members of the Knowledge Synthesis Team (A.A., M.B., R.K., J.J.R., Y.Z.) contributed evidence summaries to the guidelines; R.N. cocoordinated the systematic review team; D.M.W. and G.G. were the chair and vice chair of the panel and led the panel meeting; and all authors approved the content.

Conflict-of-interest disclosure: All authors were members of the guideline panel or 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.

ORCID profiles: A.A., 0000-0002-0931-7851; Y.Z., 0000-0002-4174-0641.

Correspondence: Daniel M. Witt, Department of Pharmacotherapy, College of Pharmacy, University of Utah, 30 South 2000 East, 4323, Salt Lake City, UT 84112; e-mail: dan.witt@pharm.utah.edu.

References

1. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism [published correction appears in *J Thromb Thrombolysis*. 2016;42(2):296-311]. *J Thromb Thrombolysis*. 2016;41(1):15-31.
2. Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ*. 2014;186(3):E123-E142.
3. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Washington, DC: National Academies Press; 2011.
4. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
5. Schünemann HJ, Al-Ansary LA, Forland F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548-553.
6. Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016;353:i2089.
7. Alonso-Coello P, Schünemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016.
8. Atkins D, Eccles M, Flottorp S, et al; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations. I: Critical appraisal of existing approaches. *BMC Health Serv Res*. 2004;4(1):38.
9. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
10. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
11. Schünemann HJ, Best D, Vist G, Oxman AD; GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *CMAJ*. 2003;169(7):677-680.
12. Schünemann HJ, Mustafa R, Brozek J, et al; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.
13. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published corrections appear in *Chest*. 2012;141(5):1369 and *Chest*. 2013;144(2):721]. *Chest*. 2012;141(suppl 2):e24S-e43S.
14. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e278S-e325S.

15. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in *Chest.* 2012;141(5):1369]. *Chest*. 2012;141(suppl 2):e227S-e277S.

16. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e195S-e226S.

17. Lo B, Fields M. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: National Academic Press, Institute of Medicine; 2009.

18. Akl EA, El-Hachem P, Abou-Haidar H, Neumann I, Schünemann HJ, Guyatt GH. Considering intellectual, in addition to financial, conflicts of interest proved important in a clinical practice guideline: a descriptive study. *J Clin Epidemiol*. 2014;67(11):1222-1228.

19. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med*. 2010;152(11): 738-741.

20. Schünemann HJ, Osborne M, Moss J, et al; ATS Ethics and Conflict of Interest Committee and the Documents Development and Implementation Committee. An official American Thoracic Society Policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med*. 2009;180(6):564-580.

21. Brożek J, Nowak A, Kunstman P, Schünemann HJ. GRADEpro Guideline Development Tool (G2DT). Available at: www.guidelinedevelopment.org. Accessed 17 July 2018.

22. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4): 395-400.

23. Al-Yaseen E, Wells PS, Anderson J, Martin J, Kovacs MJ. The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. *J Thromb Haemost*. 2005;3(1):100-102.

24. Cosmi B, Filippini M, Tonti D, et al; STEFLUX Investigators. A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum). *J Thromb Haemost*. 2012;10(6):1026-1035.

25. Di Nisio M, Vedovati MC, Riera-Mestre A, et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. *Thromb Haemost*. 2016;116(4):739-746.

26. Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. *Am Heart J*. 2003;146(1):33-41.

27. Wilson SJ, Wilbur K, Burton E, Anderson DR. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. *Haemostasis*. 2001;31(1):42-48.

28. Washam JB, Hellkamp AS, Lokhnygina Y, et al; ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban versus warfarin in patients taking nondihydropyridine calcium channel blockers for atrial fibrillation (from the ROCKET AF Trial). *Am J Cardiol*. 2017;120(4):588-594.

29. Heneghan CJ, Garcia-Alamino JM, Spencer EA, et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev*. 2016; (7):CD003839.

30. Azarnoush K, Camilleri L, Aublet-Cuvelier B, et al. Results of the first randomized French study evaluating self-testing of the international normalized ratio. *J Heart Valve Dis*. 2011;20(5):518-525.

31. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med*. 2000;133(9):687-695.

32. Christensen H, Lauterlein JJ, Sørensen PD, Petersen ER, Madsen JS, Brandslund I. Home management of oral anticoagulation via telemedicine versus conventional hospital-based treatment. *Telemed J E Health*. 2011;17(3):169-176.

33. Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in The Netherlands: a randomized clinical trial. *Arch Intern Med*. 2003;163(21):2639-2646.

34. Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. *J Thromb Thrombolysis*. 1998;5 suppl 1(3):19-24.

35. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol*. 2004;126(4):557-564.

36. Matchar DB, Jacobson A, Dolor R, et al; THINRS Executive Committee and Site Investigators. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363(17):1608-1620.

37. Rasmussen RS, Corell P, Madsen P, Overgaard K. Effects of computer-assisted oral anticoagulant therapy. *Thromb J*. 2012;10(1):17.

38. Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. *J Thromb Haemost*. 2009;7(8):1284-1290.

39. Thompson JL, Burkhart HM, Daly RC, et al. Anticoagulation early after mechanical valve replacement: improved management with patient self-testing. *J Thorac Cardiovasc Surg*. 2013;146(3):599-604.

40. White RH, McCurdy SA, von Marensdorff H, Woodruff DE Jr, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. *Ann Intern Med*. 1989;111(9):730-737.

41. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. *J Thromb Haemost*. 2004;2(4):584-591.

42. Matchar DB, Love SR, Jacobson AK, et al. The impact of frequency of patient self-testing of prothrombin time on time in target range within VA Cooperative Study #481: The Home INR Study (THINRS), a randomized, controlled trial. *J Thromb Thrombolysis*. 2015;40(1):17-25.

43. Sharma P, Scotland G, Cruickshank M, et al. The clinical effectiveness and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy, compared with standard UK practice: systematic review and economic evaluation. *Health Technol Assess*. 2015;19(48):1-172.

44. Phibbs CS, Love SR, Jacobson AK, et al; writing for the THINRS Executive Committee and Site Investigators. At-home versus in-clinic INR monitoring: a cost-utility analysis from the Home INR Study (THINRS). *J Gen Intern Med*. 2016;31(9):1061-1067.

45. Stevanović J, Postma MJ, Le HH. Budget impact of increasing market share of patient self-testing and patient self-management in anticoagulation. *Value Health*. 2016;19(4):383-390.

46. Connock M, Stevens C, Fry-Smith A, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess*. 2007;11(38):iii-iv, ix-66.

47. Guidance on the Use of Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy. CADTH Optimal Use Reports. Ottawa, ON, Canada: Canadian Agency for Drugs and Technologies in Health; 2014.

48. Dignan R, Keech AC, Gebski VJ, Mann KP, Hughes CF; Warfarin SMART Investigators. Is home warfarin self-management effective? Results of the randomised Self-Management of Anticoagulation Research Trial. *Int J Cardiol*. 2013;168(6):5378-5384.

49. Soliman Hamad MA, van Eekelen E, van Agt T, van Straten AH. Self-management program improves anticoagulation control and quality of life: a prospective randomized study. *Eur J Cardiothorac Surg*. 2009;35(2):265-269.

50. Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol*. 2002;55(11):845-849.

51. Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U. Self-management of oral anticoagulation in the elderly: rationale, design, baselines and oral anticoagulation control after one year of follow-up. A randomized controlled trial. *Thromb Haemost*. 2007;97(3):408-416.

52. Verret L, Couturier J, Rozon A, et al. Impact of a pharmacist-led warfarin self-management program on quality of life and anticoagulation control: a randomized trial. *Pharmacotherapy*. 2012;32(10):871-879.

53. Fitzmaurice DA, Murray ET, McCahon D, et al. Self management of oral anticoagulation: randomised trial. *BMJ*. 2005;331(7524):1057.

54. Sunderji R, Campbell L, Shalansky K, Fung A, Carter C, Gin K. Outpatient self-management of warfarin therapy: a pilot study. *Pharmacotherapy*. 1999;19(6):787-793.

55. Grunau BE, Wiens MO, Harder KK. Patient self-management of warfarin therapy: pragmatic feasibility study in Canadian primary care. *Can Fam Physician*. 2011;57(8):e292-e298.

56. Menéndez-Jándula B, Souto JC, Oliver A, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med*. 2005;142(1):1-10.

57. Völler H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). *Z Kardiol*. 2005;94(3):182-186.

58. Körtke H, Körfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? *Ann Thorac Surg*. 2001;72(1):44-48.

59. Sawicki PT; Working Group for the Study of Patient Self-Management of Oral Anticoagulation. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. *JAMA*. 1999;281(2):145-150.

60. Christensen TD, Maegaard M, Sørensen HT, Hjortdal VE, Hasenkam JM. Self-management versus conventional management of oral anticoagulant therapy: A randomized, controlled trial. *Eur J Intern Med*. 2006;17(4):260-266.

61. Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. *Ann Thorac Surg*. 2001;72(5):1523-1527.

62. Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet*. 2000;356(9224):97-102.

63. Koertke H, Minami K, Boethig D, et al. INR self-management permits lower anticoagulation levels after mechanical heart valve replacement. *Circulation*. 2003;108(suppl 1):II75-II78.

64. Koertke H, Zittermann A, Minami K, et al. Low-dose international normalized ratio self-management: a promising tool to achieve low complication rates after mechanical heart valve replacement. *Ann Thorac Surg*. 2005;79(6):1909-1914; discussion 14.

65. Koertke H, Zittermann A, Tenderich G, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. *Eur Heart J*. 2007;28(20):2479-2484.

66. Koertke H, Zittermann A, Wagner O, et al. Efficacy and safety of very low-dose self-management of oral anticoagulation in patients with mechanical heart valve replacement. *Ann Thorac Surg*. 2010;90(5):1487-1493.

67. Koertke H, Zittermann A, Wagner O, Koerfer R. Self-management of oral anticoagulation therapy improves long-term survival in patients with mechanical heart valve replacement. *Ann Thorac Surg*. 2007;83(1):24-29.

68. Körtke H, Minami K, Breymann T, et al. INR self-management after mechanical heart valve replacement: ESCAT (Early Self-Controlled Anticoagulation Trial) [in German]. *Z Kardiol*. 2001;90(suppl 6):118-124.

69. McCahon D, Fitzmaurice DA, Murray ET, et al. SMART: self-management of anticoagulation, a randomised trial [ISRCTN19313375]. *BMC Fam Pract*. 2003;4:11.

70. McCahon D, Murray ET, Murray K, Holder RL, Fitzmaurice DA. Does self-management of oral anticoagulation therapy improve quality of life and anxiety? *Fam Pract*. 2011;28(2):134-140.

71. Murray E, Fitzmaurice D, McCahon D, Fuller C, Sandhur H. Training for patients in a randomised controlled trial of self management of warfarin treatment. *BMJ*. 2004;328(7437):437-438.

72. Siebenhofer A, Hemkens LG, Rakovac I, Spat S, Didjurgeit U; SPOG 60+ Study Group. Self-management of oral anticoagulation in elderly patients - effects on treatment-related quality of life. *Thromb Res*. 2012;130(3):e60-e66.

73. Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U; SPOG 60+ Study Group. Self-management of oral anticoagulation reduces major outcomes in the elderly. A randomized controlled trial. *Thromb Haemost*. 2008;100(6):1089-1098.

74. Regier DA, Sunderji R, Lynd LD, Gin K, Marra CA. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *CMAJ*. 2006;174(13):1847-1852.

75. Jowett S, Bryan S, Murray E, et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. *Br J Haematol*. 2006; 134(6):632-639.

76. Rose AJ, Hylek EM, Berlowitz DR, Ash AS, Reisman JI, Ozonoff A. Prompt repeat testing after out-of-range INR values: a quality indicator for anticoagulation care. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):276-282.

77. Schaefer C, Wuillemin WA, Kessels A, Jacobson A, Nagler M. Predictors of anticoagulation quality in 15 834 patients performing patient self-management of oral anticoagulation with vitamin K antagonists in real-life practice: a survey of the International Self-Monitoring Association of Orally Anticoagulated Patients. *Br J Haematol*. 2016;175(4):677-685.

78. Tosetto A, Manotti C, Marongiu F; Italian Federation of Anticoagulation Clinics (FCSA) Clinical Quality Study Group. Center-related determinants of VKA anticoagulation quality: a prospective, multicenter evaluation. *PLoS One*. 2015;10(12):e0144314.

79. Pengo V, Barbero F, Biasiolo A, Pegoraro C, Cucchini U, Iliceto S. A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment. *Am J Clin Pathol*. 2003;120(6):944-947.

80. Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. Warfarin dose assessment every 4 weeks versus every 12 weeks in patients with stable international normalized ratios: a randomized trial. *Ann Intern Med*. 2011;155(10):653-659.

81. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. *Circulation*. 2014; 129(13):1407-1414.

82. Lidstone V, Janes S, Stross P. INR: intervals of measurement can safely extend to 14 weeks. *Clin Lab Haematol*. 2000;22(5):291-293.

83. Shalev V, Rogowski O, Shimron O, et al. The interval between prothrombin time tests and the quality of oral anticoagulants treatment in patients with chronic atrial fibrillation. *Thromb Res*. 2007;120(2):201-206.

84. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144(9):673-684.

85. Leizorovicz A, Siguret V, Mottier D, et al; Innohep® in Renal Insufficiency Study Steering Committee. Safety profile of tinzaparin versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis: the Innohep® in Renal Insufficiency Study (IRIS). *Thromb Res*. 2011;128(1):27-34.

86. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res*. 2005;116(1):41-50.

87. Chow SL, Zammit K, West K, Dannenhoffer M, Lopez-Candales A. Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. *J Clin Pharmacol*. 2003;43(6):586-590.

88. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J*. 2004;148(4): 582-589.

89. Pautas E, Gouin I, Bellot O, Andreux JP, Siguret V. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. *Drug Saf*. 2002;25(10):725-733.

90. Peng YG, Eikelboom JW, Tenni P, McQuillan A, Thorne J. Renal function, peak anti-Xa levels and enoxaparin dosing. *J Pharm Pract Res*. 2004; 34(1):14-17.

91. Siguret V, Pautas E, Février M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. *Thromb Haemost*. 2000;84(5):800-804.

92. Sule AA, Tay JC, Arul E. Effect of enoxaparin on peak and trough levels of antifactor Xa in patients with a creatinine clearance of less than 30 mL/min. *Int J Angiol*. 2009;18(4):184-186.

93. Ballew A, Lee Y, Vega J, Duong HN. Evaluating current recommended dose of enoxaparin in renally impaired and morbidly obese patients by monitoring anti-factor Xa levels [abstract]. *Pharmacotherapy*. 2014;34(10):e273-e274.

94. Lachish T, Rudensky B, Slotki I, Zevin S. Enoxaparin dosage adjustment in patients with severe renal failure: antifactor xa concentrations and safety. *Pharmacotherapy*. 2007;27(10):1347-1352.

95. Yildirim T, Kocak T, Buyukasik Y, et al. Are low-molecular-weight heparins appropriately dosed in patients with CKD stage 3 to 5? *Blood Coagul Fibrinolysis*. 2012;23(8):700-704.

96. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest*. 2004;125(3):856-863.

97. Barras M. Anti-Xa assays. *Aust Prescr*. 2013;36(3):98-101.

98. Favaloro EJ, Bonar R, Aboud M, et al; RCPA QAP in Haematology. How useful is the monitoring of (low molecular weight) heparin therapy by anti-Xa assay? A laboratory perspective. *Lab Hematol*. 2005;11(3):157-162.

99. Favaloro EJ, Bonar R, Sioufi J, et al; Royal College Pathologists of Australasia Quality Assurance Program in Haematology. An international survey of current practice in the laboratory assessment of anticoagulant therapy with heparin. *Pathology*. 2005;37(3):234-238.

100. Favaloro EJ, Lippi G, Koutts J. Laboratory testing of anticoagulants: the present and the future. *Pathology*. 2011;43(7):682-692.

101. Egan G, Ensom MH. Measuring anti-factor xa activity to monitor low-molecular-weight heparin in obesity: a critical review. *Can J Hosp Pharm*. 2015; 68(1):33-47.

102. Deal EN, Hollands JM, Riney JN, Skrupky LP, Smith JR, Reichley RM. Evaluation of therapeutic anticoagulation with enoxaparin and associated anti-Xa monitoring in patients with morbid obesity: a case series. *J Thromb Thrombolysis*. 2011;32(2):188-194.

103. Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. *J Thromb Thrombolysis*. 2015;39(4):516-521.

104. Hainer JW, Barrett JS, Assaid CA, et al. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. *Thromb Haemost*. 2002;87(5):817-823.

105. Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. *Am J Health Syst Pharm*. 2003;60(7):683-687.

106. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood*. 2014;124(6):955-962.

107. Beynon C, Sakowitz OW, Störzinger D, et al. Intracranial haemorrhage in patients treated with direct oral anticoagulants. *Thromb Res*. 2015;136(3): 560-565.

108. Eerenberg ES, Middeldorp S, Levi M, Lensing AW, Büller HR. Clinical impact and course of major bleeding with rivaroxaban and vitamin K antagonists. *J Thromb Haemost*. 2015;13(9):1590-1596.

109. Kumar R, Smith RE, Henry BL. A review of and recommendations for the management of patients with life-threatening dabigatran-associated hemorrhage: a single-center university hospital experience. *J Intensive Care Med*. 2015;30(8):462-472.

110. Pahs L, Beavers C, Schuler P. The real-world treatment of hemorrhages associated with dabigatran and rivaroxaban: a multicenter evaluation. *Crit Pathw Cardiol*. 2015;14(2):53-61.

111. Piccini JP, Garg J, Patel MR, et al; ROCKET AF Investigators. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. *Eur Heart J*. 2014;35(28):1873-1880.

112. Purrucker JC, Haas K, Rizos T, et al. Early clinical and radiological course, management, and outcome of intracerebral hemorrhage related to new oral anticoagulants. *JAMA Neurol*. 2016;73(2):169-177.

113. Senger S, Keiner D, Hendrix P, Oertel J. New target-specific oral anticoagulants and intracranial bleeding: management and outcome in a single-center case series. *World Neurosurg*. 2016;88:132-139.

114. Granger CB, Lopes RD, Hanna M, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [published correction appears in *Am Heart J*. 2015;169(4): 594]. *Am Heart J*. 2015;169(1):25-30.

115. Mahaffey KW, Hellkamp AS, Patel MR, et al. End of study transition from study drug to open-label vitamin K antagonist therapy: the ROCKET AF experience. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):470-478.

116. Ruff CT, Giugliano RP, Braunwald E, et al. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2014;64(6):576-584.

117. Zhou S, Sheng XY, Xiang Q, Wang ZN, Zhou Y, Cui YM. Comparing the effectiveness of pharmacist-managed warfarin anticoagulation with other models: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2016;41(6):602-611.

118. Airee A, Guirguis AB, Mohammad RA. Clinical outcomes and pharmacists' acceptance of a community hospital's anticoagulation management service utilizing decentralized clinical staff pharmacists. *Ann Pharmacother*. 2009;43(4):621-628.

119. Arbring K, Uppugunduri S, Lindahl TL. Comparison of prothrombin time (INR) results and main characteristics of patients on warfarin treatment in primary health care centers and anticoagulation clinics. *BMC Health Serv Res*. 2013;13(1):85.

120. Biscup-Horn PJ, Streiff MB, Ulbrich TR, Nesbit TW, Shermock KM. Impact of an inpatient anticoagulation management service on clinical outcomes. *Ann Pharmacother*. 2008;42(6):777-782.

121. Chamberlain MA, Sageser NA, Ruiz D. Comparison of anticoagulation clinic patient outcomes with outcomes from traditional care in a family medicine clinic. *J Am Board Fam Pract*. 2001;14(1):16-21.

122. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med*. 1998;158(15):1641-1647.

123. Duran-Parrondo C, Vazquez-Lago JM, Campos-Lopez AM, Figueiras A. Impact of a pharmacotherapeutic programme on control and safety of long-term anticoagulation treatment: a controlled follow-up study in Spain. *Drug Saf*. 2011;34(6):489-500.

124. Ernst ME, Brandt KB. Evaluation of 4 years of clinical pharmacist anticoagulation case management in a rural, private physician office. *J Am Pharm Assoc*. 2003;43(5):630-636.

125. Garton L, Crosby JF. A retrospective assessment comparing pharmacist-managed anticoagulation clinic with physician management using international normalized ratio stability. *J Thromb Thrombolysis*. 2011;32(4):426-430.

126. Gill JM, Landis MK. Benefits of a mobile, point-of-care anticoagulation therapy management program. *Jt Comm J Qual Improv*. 2002;28(11): 625-630.

127. Harrison J, Shaw JP, Harrison JE. Anticoagulation management by community pharmacists in New Zealand: an evaluation of a collaborative model in primary care. *Int J Pharm Pract*. 2015;23(3):173-181.

128. Holden J, Holden K. Comparative effectiveness of general practitioner versus pharmacist dosing of patients requiring anticoagulation in the community. *J Clin Pharm Ther*. 2000;25(1):49-54.

129. Holm T, Deutch S, Lassen JF, Jastrup B, Husted SE, Heickendorff L. Prospective evaluation of the quality of oral anticoagulation management in an outpatient clinic and in general practices. *Thromb Res*. 2002;105(2):103-108.

130. Lee PY, Han SY, Miyahara RK. Adherence and outcomes of patients treated with dabigatran: pharmacist-managed anticoagulation clinic versus usual care. *Am J Health Syst Pharm*. 2013;70(13):1154-1161.

131. Lee YP, Schommer JC. Effect of a pharmacist-managed anticoagulation clinic on warfarin-related hospital readmissions. *Am J Health Syst Pharm*. 1996; 53(13):1580-1583.

132. Lee TY, Po HL, Jin YJ, Tsun WJ, Wang SC. A collaborative care model of anticoagulation therapy in patients with stroke. *Neurol Asia*. 2011;16(2): 111-118.

133. Levine MA, Shao W, Klein D. Monitoring of international normalized ratios: comparison of community nurses with family physicians. *Can Fam Physician*. 2012;58(8):e465-e471.

134. Locke C, Ravnan SL, Patel R, Uchizono JA. Reduction in warfarin adverse events requiring patient hospitalization after implementation of a pharmacist-managed anticoagulation service. *Pharmacotherapy*. 2005;25(5):685-689.

135. Nichol MB, Knight TK, Dow T, et al. Quality of anticoagulation monitoring in nonvalvular atrial fibrillation patients: comparison of anticoagulation clinic versus usual care. *Ann Pharmacother*. 2008;42(1):62-70.

136. Patel-Naik B, Szeinbach SL, Seoane-Vazquez E, Snider MJ, Hevezi MS. Managing oral anticoagulation therapy by pharmacists in a specialty heart hospital. *J Eval Clin Pract*. 2010;16(1):192-195.

137. Poon IO, Lal L, Brown EN, Braun UK. The impact of pharmacist-managed oral anticoagulation therapy in older veterans. *J Clin Pharm Ther*. 2007;32(1): 21-29.

138. Saokaew S, Sapoo U, Nathisuwan S, Chaiyakunapruk N, Permsuwan U. Anticoagulation control of pharmacist-managed collaborative care versus usual care in Thailand. *Int J Clin Pharm*. 2012;34(1):105-112.

139. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. *JAMA*. 2015;313(14):1443-1450.

140. Stafford L, Peterson GM, Bereznicki LR, et al. Clinical outcomes of a collaborative, home-based postdischarge warfarin management service. *Ann Pharmacother*. 2011;45(3):325-334.

141. Thanimalai S, Shafie AA, Hassali MA, Sinnadurai J. Comparing effectiveness of two anticoagulation management models in a Malaysian tertiary hospital. *Int J Clin Pharm*. 2013;35(5):736-743.

142. Wallvik J, Själander A, Johansson L, Bjuhr O, Jansson JH. Bleeding complications during warfarin treatment in primary healthcare centres compared with anticoagulation clinics. *Scand J Prim Health Care*. 2007;25(2):123-128.

143. Wilt VM, Gums JG, Ahmed OI, Moore LM. Outcome analysis of a pharmacist-managed anticoagulation service. *Pharmacotherapy*. 1995;15(6):732-739.

144. Witt DM, Humphries TL. A retrospective evaluation of the management of excessive anticoagulation in an established clinical pharmacy anticoagulation service compared to traditional care. *J Thromb Thrombolysis*. 2003;15(2):113-118.

145. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest*. 2005;127(5):1515-1522.

146. Young S, Bishop L, Twells L, Dillon C, Hawboldt J, O'Shea P. Comparison of pharmacist managed anticoagulation with usual medical care in a family medicine clinic. *BMC Fam Pract*. 2011;12(1):88.

147. Lalonde L, Martineau J, Blais N, et al. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. *Am Heart J*. 2008;156(1):148-154.

148. Chua WB, Cheen HH, Kong MC, Chen LL, Wee HL. Modelling the cost-effectiveness of pharmacist-managed anticoagulation service for older adults with atrial fibrillation in Singapore. *Int J Clin Pharm*. 2016;38(5):1230-1240.

149. Lafata JE, Martin SA, Kaatz S, Ward RE. The cost-effectiveness of different management strategies for patients on chronic warfarin therapy. *J Gen Intern Med*. 2000;15(1):31-37.

150. Aziz F, Corder M, Wolffe J, Comerota AJ. Anticoagulation monitoring by an anticoagulation service is more cost-effective than routine physician care. *J Vasc Surg*. 2011;54(5):1404-1407.

151. Chang JY, Wang CC, Kang HC, Shen LJ, Huang CF. Cost-effectiveness of the pharmacist-assisted warfarin monitoring program at a medical center in Taiwan. *Int J Qual Health Care*. 2017;29(6):817-825.

152. Wong PY, Schulman S, Woodworth S, Holbrook A. Supplemental patient education for patients taking oral anticoagulants: systematic review and meta-analysis. *J Thromb Haemost*. 2013;11(3):491-502.

153. Clark CM, Bayley EW. Evaluation of the use of programmed instruction for patients maintained on Warfarin therapy. *Am J Public Health*. 1972;62(8): 1135-1139.

154. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. *PLoS One*. 2013;8(9):e74037.

155. Laporte S, Quenet S, Buchmüller-Cordier A, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. *Thromb Haemost*. 2003;89(3):458-467.

156. Marini BL, Funk K, Kraft MD, et al. The effects of an informational video on patient knowledge, satisfaction and compliance with venous thromboembolism prophylaxis: a pilot study. *Patient Educ Couns*. 2014;96(2):264-267.

157. Mazor KM, Baril J, Dugan E, Spencer F, Burgwinkle P, Gurwitz JH. Patient education about anticoagulant medication: is narrative evidence or statistical evidence more effective? *Patient Educ Couns*. 2007;69(1-3):145-157.

158. Pernod G, Labarère J, Yver J, et al. EDUC'AVK: reduction of oral anticoagulant-related adverse events after patient education: a prospective multicenter open randomized study. *J Gen Intern Med*. 2008;23(9):1441-1446.

159. Vormfelde SV, Abu Abed M, Hua TD, Schneider S, Friede T, Chenot JF. Educating orally anticoagulated patients in drug safety: a cluster-randomized study in general practice. *Dtsch Arztebl Int*. 2014;111(37):607-614.

160. Vrijens B, De Geest S, Hughes DA, et al; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.

161. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*. 2004;42(3): 200-209.

162. Kimmel SE, Troxel AB, French B, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. *Pharmacoepidemiol Drug Saf*. 2016;25(11):1219-1227.

163. Kimmel SE, Troxel AB, Loewenstein G, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. *Am Heart J*. 2012;164(2): 268-274.

164. Machtinger EL, Wang F, Chen LL, Rodriguez M, Wu S, Schillinger D. A visual medication schedule to improve anticoagulation control: a randomized, controlled trial. *Jt Comm J Qual Patient Saf*. 2007;33(10):625-635.

165. Neiman AB, Ruppar T, Ho M, et al. CDC grand rounds: improving medication adherence for chronic disease management - innovations and opportunities. *MMWR Morb Mortal Wkly Rep*. 2017;66(45):1248-1251.

166. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-735.

167. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126(13):1630-1639.

168. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. *JAMA Intern Med*. 2015;175(7):1163-1168.

169. Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013;368(22):2084-2093.

170. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J*. 2014;35(28):1888-1896.

171. Douketis JD, Wang G, Chan N, et al. Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure. *J Thromb Haemost*. 2016;14(1):89-97.

172. Godier A, Martin AC, Leblanc I, et al. Peri-procedural management of dabigatran and rivaroxaban: duration of anticoagulant discontinuation and drug concentrations. *Thromb Res*. 2015;136(4):763-768.

173. Kim JS, She F, Jongnarangsin K, et al. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm*. 2013;10(4):483-489.

174. Schulman S, Carrier M, Lee AY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a prospective cohort study. *Circulation*. 2015;132(3):167-173.

175. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'malley PG. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med*. 2006;166(4):391-397.

176. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. *Lancet*. 2000; 356(9241):1551-1553.

177. Ageno W, Garcia D, Silingardi M, Galli M, Crowther M. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. *J Am Coll Cardiol*. 2005;46(4):732-733.

178. Fondevila CG, Grosso SH, Santarelli MT, Pinto MD. Reversal of excessive oral anticoagulation with a low oral dose of vitamin K1 compared with acenocoumarine discontinuation. A prospective, randomized, open study. *Blood Coagul Fibrinolysis*. 2001;12(1):9-16.

179. Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med*. 2009;150(5):293-300.

180. Ageno W, Crowther M, Steidl L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. *Thromb Haemost*. 2002;88(1):48-51.

181. Bussey HI, Bussey M, Bussey-Smith KL, Frei CR. Evaluation of warfarin management with international normalized ratio self-testing and online remote monitoring and management plus low-dose vitamin k with genomic considerations: a pilot study. *Pharmacotherapy*. 2013;33(11):1136-1146.

182. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost*. 2016;116(5):879-890.

183. Boulis NM, Bobek MP, Schmaier A, Hoff JT. Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery*. 1999;45(5):1113-1118, discussion 1118-1119.

184. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013;128(11):1234-1243.

185. Steiner T, Poli S, Griebe M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol*. 2016;15(6):566-573.

186. Jones GM, Erdman MJ, Smetana KS, Mohrien KM, Vandigo JE, Elijovich L. 3-Factor versus 4-factor prothrombin complex concentrate for warfarin reversal in severe bleeding: a multicenter, retrospective, propensity-matched pilot study. *J Thromb Thrombolysis*. 2016;42(1):19-26.

187. Guest JF, Watson HG, Limaye S. Modeling the cost-effectiveness of prothrombin complex concentrate compared with fresh frozen plasma in emergency warfarin reversal in the United Kingdom. *Clin Ther*. 2010;32(14):2478-2493.

188. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130(15):1706-1712.

189. Yoshimura S, Sato S, Todo K, et al; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators. Prothrombin complex concentrate administration for bleeding associated with non-vitamin K antagonist oral anticoagulants: the SAMURAI-NVAF study. *J Neurol Sci*. 2017;375:150-157.

190. Gerner ST, Kuramatsu JB, Sembill JA, et al; RETRACE II (German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage II) Investigators. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol*. 2018;83(1):186-196.

191. Grandhi R, Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. *World Neurosurg*. 2015;84(6):1956-1961.

192. Schulman S, Gross PL, Ritchie B, et al; Study Investigators. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost*. 2018;118(5):842-851.

193. Dentali F, Marchesi C, Giorgi Pierfranceschi M, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost*. 2011;106(3):429-438.

194. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12):1131-1141.

195. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-520.

196. Held V, Eisele P, Eschenfelder CC, Szabo K. Idarucizumab as antidote to intracerebral hemorrhage under treatment with dabigatran. *Case Rep Neurol*. 2016;8(3):224-228.

197. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

198. De Luca G, Parodi G, Antoniucci D. Safety and benefits of protamine administration to revert anticoagulation soon after coronary angioplasty. A meta-analysis. *J Thromb Thrombolysis*. 2010;30(4):452-458.

199. Newhall KA, Saunders EC, Larson RJ, Stone DH, Goodney PP. Use of protamine for anticoagulation during carotid endarterectomy: a meta-analysis. *JAMA Surg*. 2016;151(3):247-255.

200. Fearn SJ, Parry AD, Picton AJ, Mortimer AJ, McCollum CN. Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. *Eur J Vasc Endovasc Surg*. 1997;13(4):394-397.

201. Pan M, Suárez de Lezo J, Medina A, et al. In-laboratory removal of femoral sheath following protamine administration in patients having intracoronary stent implantation. *Am J Cardiol*. 1997;80(10):1336-1338.

202. Kaneda H, Suzuki J, Hosokawa G, Tanaka S, Hiroe Y, Saito S. Impact of heparin neutralization by protamine on restenosis after coronary stent implantation. *Int J Cardiol*. 2005;105(1):111-112.

203. Mauney MC, Buchanan SA, Lawrence WA, et al. Stroke rate is markedly reduced after carotid endarterectomy by avoidance of protamine. *J Vasc Surg*. 1995;22(3):264-269, discussion 269-270.

204. Levison JA, Faust GR, Halpern VJ, et al. Relationship of protamine dosing with postoperative complications of carotid endarterectomy. *Ann Vasc Surg*. 1999;13(1):67-72.

205. Dellagrammaticas D, Lewis SC, Gough MJ; GALA Trial Collaborators. Is heparin reversal with protamine after carotid endarterectomy dangerous? *Eur J Vasc Endovasc Surg*. 2008;36(1):41-44.

206. Stone DH, Nolan BW, Schanzer A, et al. Protamine reduces bleeding complications associated with carotid endarterectomy without increasing the risk of stroke. *J Vasc Surg*. 2010;51(3):559-564.

207. Mazzalai F, Piatto G, Toniato A, Lorenzetti R, Baracchini C, Ballotta E. Using protamine can significantly reduce the incidence of bleeding complications after carotid endarterectomy without increasing the risk of ischemic cerebral events. *World J Surg*. 2014;38(5):1227-1232.

208. Morales Gisbert SM, Sala Almonacil VA, Zaragozá García JM, Genovés Gascó B, Gómez Palonés FJ, Ortiz Monzón E. Predictors of cervical bleeding after carotid endarterectomy. *Ann Vasc Surg*. 2014;28(2):366-374.

209. Treiman RL, Cossman DV, Foran RF, Levin PM, Cohen JL, Wagner WH. The influence of neutralizing heparin after carotid endarterectomy on postoperative stroke and wound hematoma. *J Vasc Surg*. 1990;12(4):440-445, discussion 445-446.

210. Salles LR, Puech-Leão P, Netto BM, et al. Risk factors of stroke in carotid endarterectomy [in Portuguese]. *Rev Hosp Clin Fac Med Sao Paulo*. 1997; 52(6):291-294.

211. Liu Q, Chen YX, Ni L, Chen Y, Liu CW. Clinical observation of neutralizing heparin with protamine in carotid endarterectomy [in Chinese]. *Zhonghua Yi Xue Za Zhi*. 2013;93(33):2650-2653.

212. Thuesen L, Andersen HR, Bøtker HE, Dalby Kristensen S, Krusell LR, Lassen JF. In-laboratory femoral sheath removal after heparin reversal by protamine after percutaneous coronary intervention. *EuroIntervention*. 2005;1(1):66-69.

213. Rossi ML, Zavalloni D, Scatturin M, Gasparini GL, Lisignoli V, Presbitero P. Immediate removal of femoral-sheath following protamine administration in patients undergoing intracoronary paclitaxel-eluting-stent implantation. *Expert Opin Pharmacother*. 2007;8(13):2017-2024.

214. McDonald JS, Kallmes DF, Lanzino G, Cloft HJ. Protamine does not increase risk of stroke in patients with elective carotid stenting. *Stroke*. 2013;44(7):2028-2030.

215. Welling RE, Ramadas HS, Gansmuller KJ. Cervical wound hematoma after carotid endarterectomy. *Ann Vasc Surg*. 1989;3(3):229-231.

216. Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. *Thromb Haemost*. 2015;114(4):819-825.

217. Chen WC, Chen YH, Hsu PI, et al. Gastrointestinal hemorrhage in warfarin anticoagulated patients: incidence, risk factor, management, and outcome. *BioMed Res Int*. 2014;2014:463767.

218. Claassen DO, Kazemi N, Zubkov AY, Wijdicks EF, Rabinstein AA. Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. *Arch Neurol*. 2008;65(10):1313-1318.

219. Gathier CS, Algra A, Rinkel GJ, van der Worp HB. Long-term outcome after anticoagulation-associated intracerebral haemorrhage with or without restarting antithrombotic therapy. *Cerebrovasc Dis*. 2013;36(1):33-37.

220. Guha D, Coyne S, Macdonald RL. Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study. *J Neurosurg*. 2016;124(3):750-759.

221. Hernandez I, Zhang Y, Brooks MM, Chin PK, Saba S. Anticoagulation use and clinical outcomes after major bleeding on dabigatran or warfarin in atrial fibrillation. *Stroke*. 2017;48(1):159-166.

222. Majeed A, Wallvik N, Eriksson J, et al. Optimal timing of vitamin K antagonist resumption after upper gastrointestinal bleeding. A risk modelling analysis. *Thromb Haemost*. 2017;117(3):491-499.

223. Mirzayan MJ, Calvelli K, Capelle HH, Weigand J, Krauss JK. Subdural hematoma and oral anticoagulation: a therapeutic dilemma from the neurosurgical point of view. *J Neurol Surg A Cent Eur Neurosurg*. 2016;77(1):31-35.

224. Nielsen PB, Larsen TB, Skjøth F, Lip GY. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. *JAMA Intern Med*. 2017;177(4):563-570.

225. Osaki M, Koga M, Maeda K, et al; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators. A multicenter, prospective, observational study of warfarin-associated intracerebral hemorrhage: the SAMURAI-WAICH study. *J Neurol Sci*. 2015;359(1-2):72-77.

226. Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation [published correction appears in *Am J Cardiol*. 2015;116(1):166]. *Am J Cardiol*. 2014;113(4):662-668.

227. Sengupta N, Feuerstein JD, Patwardhan VR, et al. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study [published correction appears in *Am J Gastroenterol*. 2015;110(3):480]. *Am J Gastroenterol*. 2015;110(2):328-335.

228. Teo KC, Mahboobani NR, Lee R, et al. Warfarin associated intracerebral hemorrhage in Hong Kong Chinese. *Neurol Res*. 2014;36(2):143-149.

229. Witt DM, Clark NP, Martinez K, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for intracranial hemorrhage. *Thromb Res*. 2015;136(5):1040-1044.

230. Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med*. 2012;172(19):1484-1491.

231. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015;313(8):824-836.

232. Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke*. 2010;41(12):2860-2866.

233. Yung D, Kapral MK, Asllani E, Fang J, Lee DS; Investigators of the Registry of the Canadian Stroke Network. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. *Can J Cardiol*. 2012;28(1):33-39.

234. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e152S-e184S.

235. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. 2017;81:101-110.