

American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism

Thomas L. Ortel,¹ Ignacio Neumann,² Walter Ageno,³ Rebecca Beyth,^{4,5} Nathan P. Clark,⁶ Adam Cuker,⁷ Barbara A. Hutten,⁸ Michael R. Jaff,⁹ Veena Manja,^{10,11} Sam Schulman,^{12,13} Caitlin Thurston,¹⁴ Suresh Vedantham,¹⁵ Peter Verhamme,¹⁶ Daniel M. Witt,¹⁷ Ivan D. Florez,^{18,19} Ariel Izcovich,²⁰ Robby Nieuwlaet,¹⁹ Stephanie Ross,¹⁹ Holger J. Schünemann,^{19,21} Wojtek Wiercioch,¹⁹ Yuan Zhang,¹⁹ and Yuqing Zhang¹⁹

¹Division of Hematology, Department of Medicine, Duke University, Durham NC; ²Pontificia Universidad Catolica de Chile, Santiago, Chile; ³Department of Medicine and Surgery, University of Insubria, Varese, Italy; ⁴Division of General Internal Medicine, Department of Medicine, University of Florida, Gainesville, FL; ⁵Malcolm Randall Veterans Affairs Medical Center, Gainesville, FL; ⁶Clinical Pharmacy Anticoagulation Service, Kaiser Permanente, Aurora, CO; ⁷Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; ⁸Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; ⁹Harvard Medical School, Boston, MA; ¹⁰University of California Davis, Sacramento, CA; ¹¹Veterans Affairs Northern California Health Care System, Mather, CA; ¹²Department of Medicine, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada; ¹³Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia; ¹⁴May-Thurner Syndrome Resource Network; ¹⁵Division of Diagnostic Radiology, Washington University School of Medicine in St. Louis, St. Louis, MO; ¹⁶KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; ¹⁷Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT; ¹⁸Department of Pediatrics, University of Antioquia, Medellin, Colombia; ¹⁹Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; ²⁰Internal Medicine Department, German Hospital, Buenos Aires, Argentina; and ²¹Department of Medicine, McMaster University, Hamilton, ON, Canada

Background: Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in ~1 to 2 individuals per 1000 each year, corresponding to ~300 000 to 600 000 events in the United States annually.

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

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and adult 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 28 recommendations for the initial management of VTE, primary treatment, secondary prevention, and treatment of recurrent VTE events.

Conclusions: Strong recommendations include the use of thrombolytic therapy for patients with PE and hemodynamic compromise, use of an international normalized ratio (INR) range of 2.0 to 3.0 over a lower INR range for patients with VTE who use a vitamin K antagonist (VKA) for secondary prevention, and use of indefinite anticoagulation for patients with recurrent unprovoked VTE. Conditional recommendations include the preference for home treatment over hospital-based treatment for uncomplicated DVT and PE at low risk for complications and a preference for direct oral anticoagulants over VKA for primary treatment of VTE.

Summary of recommendations

Initial management

Recommendation 1. For patients with uncomplicated deep vein thrombosis (DVT), the American Society of Hematology (ASH) guideline panel *suggests* offering home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor compliance. Patients with limb-threatening DVT or a high risk for bleeding and those requiring IV analgesics may benefit from initial treatment in the hospital.

Recommendation 2. For patients with pulmonary embolism (PE) with a low risk for complications, the ASH guideline panel *suggests* offering home treatment over hospital treatment (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Clinical prediction scores have, at best, a moderate ability to predict patient outcomes and, therefore, do not replace clinical judgment. However, they may help to select patients at low risk for complications. The Pulmonary Embolism Severity Index (PESI)¹ and simplified PESI² have been most widely validated. This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor adherence. Patients with submassive (ie, intermediate-high risk) or massive PE or at high risk for bleeding and those requiring IV analgesics may benefit from initial treatment in the hospital.

Recommendation 3. For patients with DVT and/or PE, the ASH guideline panel *suggests* using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance <30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

Recommendation 4. For patients with DVT and/or PE, the ASH guideline panel *does not suggest* 1 DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects ⊕○○○).

Remarks: Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (eg, need for a concomitant drug metabolized through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice.

Recommendation 5. In most patients with proximal DVT, the ASH guideline panel *suggests* anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic DVT involving the iliac and common femoral veins (higher risk for more severe postthrombotic syndrome [PTS]³). Patients in these categories who value rapid resolution of symptoms, are averse to the possibility of PTS, and accept the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein.

Recommendation 6. For patients with PE and hemodynamic compromise, the ASH guideline panel *recommends* using

thrombolytic therapy followed by anticoagulation over anticoagulation alone (strong recommendation despite low certainty in the evidence of effects ⊕⊕○○).

Remarks: Strong recommendations based on low certainty in the evidence are exceptional. In this case, the high mortality of patients with PE and hemodynamic compromise, as well as the potential lifesaving effect of thrombolytics, warranted a strong recommendation. This exception is in accordance with the exceptional circumstances that allow strong recommendations based on low-certainty evidence in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) ASH rules.

Recommendation 7. For patients with PE with echocardiography and/or biomarkers compatible with right ventricular dysfunction but without hemodynamic compromise (submassive PE), the ASH guideline panel *suggests* anticoagulation alone over the routine use of thrombolysis in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: Thrombolysis is reasonable to consider for submassive PE and low risk for bleeding in selected younger patients or for patients at high risk for decompensation due to concomitant cardiopulmonary disease. Patients with submassive PE should be monitored closely for the development of hemodynamic compromise.

Recommendation 8. For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel *suggests* using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Given the very-low-certainty evidence (uncertainty regarding the benefits and harms of catheter-directed thrombolysis compared with systemic thrombolysis), the panel followed the GRADE ASH rules and issued a conditional recommendation. However, 4 panel members believed the recommendation should have been graded as strong based on the lack of evidence showing meaningful clinical benefits outweighing the known bleeding risks associated with systemic thrombolysis.

Recommendation 9. For patients with PE in whom thrombolysis is considered appropriate, the ASH guideline panel *suggests* using systemic thrombolysis over catheter-directed thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: This recommendation reflects uncertainty about catheter-directed thrombolysis for PE rooted in the paucity of randomized trial data and variability in procedural experience across centers. In centers with the appropriate infrastructure, clinical staff, and procedural experience, catheter-directed thrombolysis may be an alternative to systemic thrombolysis, especially for patients with an intermediate to high risk for bleeding, because the total dose and duration of administration of thrombolytic agents are lower when delivered by catheter.

Recommendations 10 and 11. For patients with proximal DVT and significant preexisting cardiopulmonary disease, as well as for patients with PE and hemodynamic compromise, the ASH guideline panel *suggests* anticoagulation alone rather than anticoagulation plus insertion of an inferior vena cava (IVC) filter (conditional recommendations based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: These recommendations apply to patients who are eligible to receive anticoagulation. For patients with a contraindication to anticoagulation, insertion of a retrievable IVC filter may be indicated with retrieval as soon as the patient is able to receive anticoagulation.

Primary treatment

Primary treatment refers to the minimal length of time a patient must be on therapeutic anticoagulation to treat the initial venous thromboembolism (VTE) before consideration is given to discontinuing anticoagulation or switching to a long-term anticoagulation regimen aimed at preventing VTE recurrence (secondary prevention) (Figure 1). Recommendations 12 through 14 refer to the length of time for primary treatment of the initial VTE in 3 patient populations.

Recommendations 12, 13, and 14. For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor (recommendation 12) or by a chronic risk factor (recommendation 13) or unprovoked (recommendation 14), the ASH guideline panel *suggests* using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary treatment (6-12 months) (conditional recommendations based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: These recommendations are intended to address the duration of primary anticoagulant treatment for all patients with DVT and/or PE, defined as the minimal length of time for treatment of the initial VTE (Figure 1). Most patients with DVT and/or PE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. In contrast, many patients with DVT and/or PE provoked by chronic risk factors, as well as patients with unprovoked DVT and/or PE, may continue anticoagulant therapy indefinitely for secondary prevention after completion of the primary treatment (Figure 1). However, if patients and clinicians decide to stop anticoagulation, the ASH guideline panel *suggests against* using a longer course of primary anticoagulant therapy (6-12 months). For selected patients with a chronic risk factor for which some improvement is expected over time (eg, improved mobility with rehabilitation), a longer course of anticoagulation for the primary treatment phase (eg, 6-12 months) could be justified.

Secondary prevention

Following completion of primary treatment for the initial VTE, providers must decide whether to discontinue anticoagulant therapy or continue with long-term anticoagulation with the intent to prevent VTE recurrence, referred to as secondary prevention. Recommendations 15 through 19 address which patients should be considered for indefinite secondary prevention, and recommendations 20 through 22 address which antithrombotic therapies could be chosen for patients continuing indefinite secondary prevention.

Recommendations 15, 16, and 17. For patients with unprovoked DVT and/or PE, the ASH guideline panel *suggests against* routine use of prognostic scores (recommendation 15), D-dimer testing (recommendation 16), or ultrasound to detect residual vein thrombosis (recommendation 17) to guide the duration of anticoagulation (conditional recommendations based on very low certainty in the evidence of effects ⊕○○○).

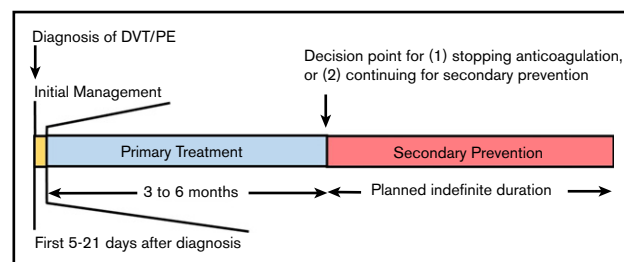


Figure 1. Time frame of the decisions. Initial management (yellow box) spans the first 5 to 21 days following diagnosis of a new VTE and includes issues concerning whether the patient can be treated at home or requires admission to the hospital, use of thrombolytic therapy, whether an IVC filter needs to be placed, and initial anticoagulant therapy. Primary treatment continues anticoagulant therapy for 3 to 6 months total and represents the minimal duration of treatment for the VTE. After completion of primary treatment, the next decision concerns whether anticoagulant therapy will be discontinued or if it will be continued for secondary prevention of recurrent VTE. Typically, secondary prevention is continued indefinitely, although patients should be reevaluated on a regular basis to review the benefits and risks of continued anticoagulant therapy. Our choice of terminology reflects the distinct clinical intentions of the different phases of VTE management, linking them to important clinical decisions addressed in the guidelines, rather than using terms reflecting the relative duration of therapy.

Remarks: Indefinite anticoagulation is probably appropriate for the majority of patients with unprovoked VTE. However, in certain circumstances, such as when patients are undecided or the balance between risks and benefits is uncertain, clinicians and patients may use prognostic scores, D-dimer testing, or ultrasound assessment for residual thrombosis from an initial DVT to aid in reaching a final decision.

Recommendation 18. After completion of primary treatment for patients with DVT and/or PE provoked by a chronic risk factor, the ASH guideline panel *suggests* indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: Patients with DVT and/or PE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment. This recommendation refers to patients with DVT and/or PE provoked by a chronic persistent risk factor. However, this recommendation does not apply to patients who have a high risk for bleeding complications. For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20. Decisions regarding anticoagulation in individuals with cancer are discussed in a separate ASH guideline.

Recommendation 19. After completion of primary treatment for patients with unprovoked DVT and/or PE, the ASH guideline panel *suggests* indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: This recommendation does *not* apply to patients who have a high risk for bleeding complications. For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20.

Recommendation 20. For patients with DVT and/or PE who have completed primary treatment and will continue to receive secondary prevention, the ASH guideline panel *suggests* using

anticoagulation over aspirin (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Recommendation 21. For patients with DVT and/or PE who have completed primary treatment and will continue VKA therapy as secondary prevention, the ASH guideline panel *recommends* using an international normalized ratio (INR) range of 2.0 to 3.0 over a lower INR range (eg, 1.5-1.9) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Recommendation 22. For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel *suggests* using a standard-dose DOAC or a lower-dose DOAC (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: Lower-dose DOAC regimens that may be considered for patients who have completed primary treatment and will continue with a DOAC include rivaroxaban, 10 mg daily, or apixaban, 2.5 mg twice daily.

Treatment of recurrent events

Recommendation 23. For patients with breakthrough DVT and/or PE during therapeutic VKA treatment, the ASH guideline panel *suggests* using low-molecular-weight heparin (LMWH) over DOAC therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Patients who present with a new VTE event during therapeutic VKA treatment should be further investigated to identify potential underlying causes. This recommendation does not apply to patients who develop breakthrough VTE in the setting of poor INR control, in whom a DOAC may be a reasonable option.

Recommendation 24a. For patients who develop DVT and/or PE provoked by a transient risk factor and have a history of previous unprovoked VTE or VTE provoked by a chronic risk factor, the ASH guideline panel *suggests* indefinite antithrombotic therapy over stopping anticoagulation after completing primary treatment (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Introduction

Aim of the guideline and specific objectives

The purpose of this guideline is to provide evidence-based recommendations about the treatment of DVT and PE for patients without cancer. The target audience includes patients, hematologists, general practitioners, internists, hospitalists, vascular interventionalists, intensivists, other clinicians, pharmacists, and decision makers. Policy makers interested in these guidelines include those involved in developing local, national, or international programs aiming to reduce the incidence of VTE or to evaluate direct and indirect harms and costs related to VTE. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

VTE, which includes DVT and PE, occurs in ~1 to 2 individuals per 1000 each year, or ~300 000 to 600 000 events in the United States annually.⁴ DVT most commonly occurs in the lower extremities but also affects the upper extremities.^{5,6} Approximately one third of all

Recommendation 24b. For patients who develop DVT and/or PE provoked by a transient risk factor and have a history of a previous VTE also provoked by a transient risk factor, the ASH guideline panel *suggests* stopping anticoagulation after completion of primary treatment over indefinite antithrombotic therapy (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Recommendation 25. For patients with a recurrent unprovoked DVT and/or PE, the ASH guideline panel *recommends* indefinite antithrombotic therapy over stopping anticoagulation after completion of primary treatment (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks (Recommendations 24a, 24b, and 25): For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20.

Additional management issues

Recommendation 26. For patients with DVT and/or PE with stable cardiovascular disease (CVD) who initiate anticoagulation and were previously taking aspirin for cardiovascular risk modification, the ASH guideline panel *suggests* suspending aspirin over continuing it for the duration of anticoagulation therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: A critical review of the indication for aspirin therapy is needed at the time anticoagulant therapy is initiated, considering the increased risk of bleeding vs the potential benefit in terms of cardiovascular prevention. This recommendation does not apply to patients with a recent acute coronary event or coronary intervention.

Recommendations 27 and 28. For patients with DVT, with (Recommendation 27) or without (Recommendation 28) an increased risk for PTS, the ASH guideline panel *suggests against* the routine use of compression stockings (conditional recommendations based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Although the majority of patients may not benefit from the use of stockings to reduce the risk of PTS, stockings may help to reduce edema and pain associated with acute DVT in selected patients.

patients with a new diagnosis of VTE have PE, with or without DVT,⁷⁻⁹ and it is estimated that up to a quarter of all patients with PE present with sudden death.⁴

The risk for recurrent VTE varies according to whether the initial event was associated with an acquired risk factor, referred to as a provoked event, or in the absence of any provoking risk factors, referred to as an unprovoked event.¹⁰ For patients with unprovoked VTE, the risks of recurrent VTE after completing a course of anticoagulant therapy have been estimated to be 10% by 2 years and >30% by 10 years.^{11,12} Long-term complications include PTS, which develops in 20% to 50% of patients after DVT and is severe in up to 5% of cases,¹³ and chronic thromboembolic pulmonary hypertension, which may develop in up to 5% of patients with PE.¹⁴

Anticoagulant therapy is very effective at preventing recurrent VTE but is associated with an increased frequency of bleeding complications. Major bleeding events may occur in ~1% to 3% of

patients on VKAs each year, compared to an ~30% lower relative risk for major bleeding with DOACs.¹⁵

Description of the target populations

The incidence of VTE increases with age, ranging from ~1 in 10 000 in individuals younger than 20 years of age to as high as ~1 in 100 in individuals who are 80 years of age and older.¹⁶ VTE affects all races and ethnicities, with black persons having a higher incidence than white persons in most studies and individuals of Asian descent having a lower incidence than other races.¹⁷⁻¹⁹ Certain acquired characteristics identify subsets of individuals at higher risk for VTE, including individuals who are currently or were recently hospitalized, residents in long-term care facilities, and patients undergoing surgical procedures.⁴

Time frame of the decisions

Conceptually, the therapeutic management of patients with a new diagnosis of VTE can be divided into 3 phases: (1) initial management, which occurs from the time of diagnosis through the first 3 weeks of therapy; (2) primary treatment, which is a time-limited phase that typically runs for a minimum of 3 months; and (3) secondary prevention, which begins after completion of the primary treatment phase and extends for a prolonged, usually indefinite, period of time (Figure 1). The specific questions addressed by the guideline committee are most relevant at specific points in time during treatment, as summarized below.

Initial management

- Home treatment vs hospital treatment (Recommendations 1 and 2)
- Choice of anticoagulant therapy (Recommendations 3 and 4)
- Use of fibrinolytic therapy (Recommendations 5-9)
- Use of IVC filters (Recommendations 10 and 11)

Primary treatment

- Duration of primary treatment (Recommendations 12-14)

Secondary prevention

- Choice between stopping anticoagulation and indefinite therapy (Recommendations 15-19)
- Choice of treatment for secondary prevention (Recommendations 20-22)

The following sections represent topics that may occur during any phase of treatment

- Management of breakthrough and recurrent DVT/PE (Recommendations 23-25)
- Decision concerning use of aspirin while on anticoagulant therapy (Recommendation 26)
- Decision concerning use of compression stockings (Recommendations 27 and 28)

Methods

The guideline panel assessed the certainty in the supporting evidence and developed and graded the recommendations following the GRADE approach.²⁰⁻²⁴ The overall guideline-development process, including funding of the work, panel formation, management

of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guideline International Network–McMaster Guideline Development Checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>). We developed our recommendations using the principles outlined by the Institute of Medicine and Guideline International Network.²⁵⁻²⁷ An article detailing the methods used to develop these guidelines has been published.³⁶⁰

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (A.C.) and vice chair (H.J.S.). ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and to coordinate the guideline-development process. The membership of the panel and the GRADE Centre team is described in Supplement 1.

The panel included hematologists, internists, specialists in vascular medicine, an interventional radiologist, a cardiologist, and pharmacists who all had clinical and research expertise in VTE treatment; methodologists with expertise in evidence appraisal and guideline development; and 2 patient representatives. The panel chair was a hematologist with content expertise, whereas the vice chair was an internist with expertise in guideline development methodology.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline-development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (<https://www.surveymonkey.com> and <https://www.gradepr.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 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 but received no other payments. The patient representative was offered, but declined, an honorarium of \$200. 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 and Guideline International Network.^{26,27} At the time of appointment, a majority of the guideline panel, including the chair and the vice chair, had no conflicts of interest, as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during

the development process, but the balance of the majority was maintained.

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

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

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

Formulating specific clinical questions and determining outcomes of interest

We initially brainstormed clinical issues relevant for VTE management. Then, using an on-line survey developed with SurveyMonkey (<https://www.surveymonkey.com>) and in an online meeting, we prioritized 32 clinical questions. We addressed 28 such questions in this guideline. Three questions related to clinical issues were seen more frequently for cancer patients and, therefore, will be addressed in the chapter about management of VTE for patients with cancer. One additional question was dropped at the in-person panel meeting because we considered that the clinical issue was sufficiently addressed by another recommendation (Table 1).

Panelists then selected outcomes of interest for each question a priori, following an approach described in detail elsewhere.²⁸ In brief, the panel first brainstormed all possible outcomes before rating the relative importance for decision making of each. During this rating process, the panel used definitions of the outcomes (“marker states”) that were developed for these guidelines. The panel rated the following outcomes as critical for clinical decision making across questions: mortality, PE, proximal DVT, and major bleeding. Additionally, for the questions related to thrombolysis in DVT and the use of compression stockings, the panel also rated the incidence of PTS as critical.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org). The EtD table summarized the results of systematic reviews of the literature that were

Table 1. Patient populations and interventions in VTE treatment

Initial management: up through the first week
Home treatment vs hospital treatment for patients with uncomplicated DVT
Home treatment vs hospital treatment for patients with PE and low risk for complication
DOAC vs VKA for patients with VTE
One DOAC vs another DOAC for patients with VTE
Thrombolytic therapy plus anticoagulation vs anticoagulation alone for patients with extensive proximal DVT
Thrombolytic therapy plus anticoagulation vs anticoagulation alone for patients with PE and hemodynamic compromise
Thrombolytic therapy plus anticoagulation vs anticoagulation alone for patients with submassive PE
Catheter-directed thrombolysis vs systemic thrombolysis for patients with DVT
Catheter-directed thrombolysis vs systemic thrombolysis for patients with PE
IVC filter plus anticoagulation vs anticoagulation alone for patients with DVT and significant cardiopulmonary disease
IVC filter plus anticoagulation vs anticoagulation alone for patients with PE and hemodynamic compromise
Primary treatment: treatment of the acute event
Longer course of anticoagulation vs shorter course for patients with VTE related to a transient risk factor
Longer course of anticoagulation vs shorter course for patients with VTE related to a chronic risk factor
Longer course of anticoagulation vs shorter course for patients with unprovoked VTE
Secondary prevention: continuation of anticoagulation after primary treatment
Prognostic scores vs no prognostic score to decide duration of treatment for patients with unprovoked VTE
D-dimer vs no D-dimer to decide duration of treatment for patients with unprovoked VTE
Ultrasound vs no ultrasound to decide duration of treatment for patients with unprovoked VTE
Indefinite anticoagulation vs discontinuation for patients with VTE related to a chronic risk factor
Indefinite anticoagulation vs discontinuation for patients with unprovoked VTE
Aspirin vs anticoagulation for patients with VTE who are going to continue antithrombotic therapy
Lower-target INR vs standard target for patients with VTE who are going to continue on anticoagulation
Lower-dose DOAC vs standard-dose DOAC for patients with VTE who are going to continue on anticoagulation
Treatment of recurrent events
DOAC vs LMWH for patients with breakthrough VTE during treatment with VKA
Indefinite anticoagulation vs discontinuation for patients with recurrent VTE related to a transient risk factor
Indefinite anticoagulation vs discontinuation for patients with recurrent unprovoked VTE
Additional management issues
Continuation of aspirin vs discontinuation for patients with VTE who initiate anticoagulation
Compression stockings plus anticoagulation vs anticoagulation alone for patients with DVT
Compression stockings plus anticoagulation vs anticoagulation alone for patients with DVT and high risk for PTS
Excluded questions and reason for exclusion
Anticoagulation vs no anticoagulation for patients with CVC-associated DVT (addressed in future guideline document from ASH)
Removal of CVC vs maintaining CVC for patients with CVC-associated DVT (addressed in future guideline document from ASH)
Anticoagulation vs no anticoagulation for patients with incidental PE (addressed in future guideline document from ASH)
One DOAC vs another DOAC for patients with VTE during treatment with VKA (already addressed by related question above, “One DOAC vs another DOAC for patients with VTE”)

CVC, central venous catheter.

conducted for these guidelines. Each EtD table addressed the effects of interventions, resource use (cost effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for correction and identified missing evidence.

To estimate the effect of the interventions covered in this guideline, we conducted a search for systematic reviews on MEDLINE, Embase, the Cochrane Library, and Epistemonikos from their respective dates of inception to January 2017. We also conducted a search of potentially missed trials in MEDLINE and Embase from January 2014 to January 2017. Before the publication of this guideline, we updated the searches to January 2019 (detailed search strategies are described in Supplement 4). Additionally, panel members were asked to suggest any studies that may have been missed and fulfilled the inclusion criteria for the individual questions. We excluded trials evaluating the effects of the direct thrombin inhibitor ximelagatran, given that this drug was withdrawn from the market because of safety concerns in those countries where it had received approval.

We used existing systematic reviews as a way to identify relevant trials, but we conducted our own meta-analyses for all of the questions following the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions (<https://training.cochrane.org/handbook>). We meta-analyzed the data using a random effects model according to the method of Mantel-Haenszel. We explored heterogeneity with the χ^2 test and with the I^2 statistic. When significant heterogeneity was detected ($I^2 \geq 50\%$), we explored differences among trials in the included population, the way that interventions were used, outcomes measurement, and risk of bias.

All of the meta-analyses were conducted using RevMan (version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Publication bias was assessed graphically by evaluating symmetry in the funnel plots. To estimate the absolute effect of the intervention, we calculated the risk difference by multiplying the pooled risk ratio and the baseline risk of each outcome. As baseline risk, we used the median of the risks observed in control groups of the included trials. Additionally, when possible, we used the baseline risk observed in large observational studies.

Certainty in the body of evidence was assessed (also known as quality of the evidence or confidence in the estimated effects) following the GRADE approach. We made judgments regarding risk of bias, precision, consistency, directness, and likelihood of publication bias and categorized the certainty in the evidence into 4 levels ranging from very low to high.^{22,23} In addition, we conducted systematic searches to identify evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD tables.

During a 2-day in-person meeting, followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took

into account the extent of resource use associated with alternative management options.

The panel agreed on recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation) based on the balance of all desirable and undesirable consequences. In such circumstances, the result of the voting was recorded on the respective EtD table. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

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

Document review

All panel members reviewed the recommendations and remarks. The full EtD tables (including recommendations) were made available from 30 November 2018 to 19 January 2019 for external review by stakeholders, including allied organizations, medical professionals, patients, and the general public. We received comments and additional references from 17 individuals and organizations. The final document and supplemental material were revised to address pertinent inputs, but no changes were made to recommendations. The guidelines were approved by the ASH Guideline Oversight Subcommittee and Committee on Quality on 18 February 2020 and by the ASH Executive Committee on 26 February 2020 and then subjected to peer review.

How to use these guidelines

These guidelines are primarily intended to help clinicians make decisions about treatment alternatives. Other purposes are to inform policy, to promote education and advocacy, and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared decision-making process that considers the patient’s values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, or availability of treatments.

These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation.

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, and clinicians must help each patient to arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

They should never be omitted when recommendations from these guidelines are quoted or translated. 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 management: up through the first week

Recommendation 1

For patients with uncomplicated DVT, the ASH guideline panel *suggests* offering home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor compliance. Patients with limb-threatening DVT or at high risk for bleeding and those requiring IV analgesics may benefit from initial treatment in the hospital.

Summary of the evidence

We identified 1 systematic review²⁹ and 7 randomized controlled trials (RCTs) (n = 1922).³⁰⁻³⁶ Trials included individuals with an objectively confirmed symptomatic DVT. Participants were randomized to home or hospital management with LMWH, warfarin (both can be used in either setting), or unfractionated heparin (UFH) (which is generally used in hospital only). Four RCTs^{30,33-35} had partial hospital treatment for some participants in the home group, ranging from a mean of 1 to 3 days, compared with 6.5 to 9.6 days in the hospital treatment arm. Trials with a hospital stay ≥3 days prior to home treatment were excluded. All seven trials reported the effect of antithrombotic therapy on mortality and PE and assessed the risk of major bleeding. Six trials reported the effect on proximal DVT. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/A269DB76-A3AE-4994-A718-6F1E493D0A75>.

Benefits

Treating patients with DVT at home, rather than in the hospital, reduced the risk of PE (relative risk [RR], 0.64; 95% confidence interval [CI], 0.44-0.93; absolute risk reduction [ARR], 25 fewer per 1000 patients; 95% CI, 38 fewer to 5 fewer; moderate-certainty evidence) and the risk of subsequent DVT (RR, 0.61; 95% CI, 0.42-0.90; ARR, 29 fewer per 1000 patients; 95% CI, 43 fewer to 7 fewer; moderate-certainty evidence). In a low-risk population,³⁷ home treatment reduces the risk of PE (2 fewer per 1000 patients with 95% CI of 4 fewer to 0 fewer; moderate-certainty evidence) and proximal DVT (4 fewer per 1000 patients with 95% CI of 6 fewer to 1 fewer; moderate-certainty evidence) as well. Home treatment was associated with a reduction in long-term mortality (RR, 0.72; 95% CI, 0.45-1.15; ARR, 13 fewer per 1000 patients; 95% CI, 25 fewer to 7 more; low-certainty evidence), although this was not statistically significant. When considering the mortality at 90 days for patients with DVT treated in the hospital as the baseline risk,³⁷ treating at home instead of treating in the hospital may lead to a reduction of 19 fewer deaths per 1000 patients (95% CI, 37 fewer to 10 more; low-certainty evidence).

Harms and burden

The risk of major bleeding may be lower when treating patients at home rather than in the hospital (RR, 0.67; 95% CI, 0.33-1.36; ARR, 6 fewer per 1000 patients; 95% CI, 13 fewer to 7 more; low-certainty evidence). In populations with a low bleeding risk,³⁷ treating at home instead of treating in the hospital may lead to a reduction of 5 fewer bleeding events per 1000 patients (95% CI, 11 fewer to 6 more; low-certainty evidence).

Different types of burdens are associated with both interventions. Hospital stay is associated with procedures, risk, and burden for patients. Home treatment is associated with increased burden on patients and family (eg, self-injection of LMWH and/or clinic visits for INR monitoring).

Certainty in the evidence of effects

The certainty in the evidence was judged low for mortality because of the serious risk of bias and imprecision and moderate for PE and proximal DVT because of the serious risk of bias. Of 7 RCTs,

allocation was clearly concealed in 3 (unclear in 3 and probably unconcealed in 1 with unspecified opaque envelope), outcome adjudicators were clearly blinded in the 2 largest RCTs (unclear in remaining 5), and missing data were significant in 1 small RCT. Considering that the CIs around the absolute estimates likely include values suggesting substantial benefit and substantial harm, we also rated down the certainty in the evidence because of imprecision for mortality. For major bleeding, the certainty in the evidence was judged low because of serious risk of bias and imprecision.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and bleeding was critical for patients. However, there are likely important variations in how individual patients may value thrombosis vs bleeding risk.

We identified 5 reports based on real-world data that compared the treatment cost of home management vs hospital management.^{30,32,38-40} All reports showed that home management is cost saving compared with inpatient management. LMWH was used in these reports for home management. We also identified 5 reports that compared the cost and effectiveness of home treatment and hospital treatment for patients with DVT or for VTE patients in general. One economic evaluation in a Canadian setting based on a decision tree suggests home treatment as cost effective compared with hospital management.⁴¹ The other 4 reports suggest that home management leads to cost savings without compromising outcome effects and safety. LMWH was used for home management in all of these studies, whereas UFH was primarily used in hospital-based management.⁴²⁻⁴⁵

Health equity may decrease in rural areas or settings with limited health care access. In health systems with good primary care, home treatment is feasible and safe. In health systems with poor primary care, home treatment may reduce equity.

The panel considered home treatment acceptable and feasible in most cases, although economic incentives might favor in-hospital treatment in fee-for-service systems.

Health equity may be reduced for selected groups of patients based on observational studies evaluating outcomes after VTE treatment, including uninsured patients,⁴⁶ African American patients,⁴⁷ female patients,⁴⁸ and older patients.⁴⁹ Reductions in health equity for ≥ 1 of these groups of patients may be present for all of the recommendations considered in this guideline document.

Conclusions and implementation considerations

Although our analysis suggests that patients with uncomplicated DVT treated at home rather than in the hospital have a lower risk for PE and DVT, as well as a lower risk for major bleeding, the evidence in support of these observations is of low quality, making the recommendation conditional. The decision to treat a patient with an isolated DVT at home needs to be individualized, and certain patients would be more appropriately treated in the hospital, including patients with massive DVT (defined as being associated with severe pain, swelling of the entire limb, phlegmasia cerulea dolens, or limb ischemia), at high risk for anticoagulant-related bleeding, or with major comorbidities.⁵⁰ Social factors, such as limited home support, history of noncompliance, and limited

financial resources, may also favor the hospital setting for the initial phase of treatment.

Recommendation 2

For patients with PE with low risk for complications, the ASH guideline panel *suggests* offering home treatment over hospital treatment (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Clinical prediction scores for PE severity have, at best, a moderate ability to predict patient outcomes and, therefore, do not replace clinical judgment. However, they may help to select patients with PE at low risk for complications. The PESI¹ and simplified PESI² have been most widely validated. This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor adherence. Patients with submassive or massive PE or a high risk for bleeding or requiring IV analgesics may benefit from initial treatment in the hospital.

Summary of the evidence

We identified 5 systematic reviews,⁵¹⁻⁵⁵ 2 RCTs^{56,57} (n = 451), and 3 observational studies (n = 451).⁵⁸⁻⁶⁰ The RCTs included participants who had an objectively confirmed low-risk acute PE. In 1 trial, participants were randomized to home or hospital management; regardless of the treatment arm, all participants received subcutaneous enoxaparin, 1 mg/kg twice daily, followed by VKA.⁵⁶ In another trial,⁵⁷ patients were randomized to early discharge on 15 mg of oral rivaroxaban twice daily, followed by 20 mg of oral rivaroxaban once daily for 90 days, whereas the inpatient group received local standard of care, which included any US Food and Drug Administration–approved anticoagulant strategy. In both trials, the outpatient treatment groups were discharged within 24 hours after randomization. These trials reported the effect of antithrombotic therapy on mortality, VTE, and major bleeding. Additionally, 3 observational studies reported mortality and major bleeding at 3 months follow-up, and 1 reported PE at 3 months. The EtD framework is shown online at: <https://guidelines.grade.pro.org/profile/BC081756-C49E-138F-A6D3-7C40D5A6EB57>.

Benefits

Analysis of RCTs showed that treating patients with PE and a low risk for complications at home, rather than in the hospital, may reduce the risk of mortality at 30 days (RR, 0.33; 95% CI, 0.01-7.98; ARR, 2 fewer per 1000 patients, 95% CI, 2 fewer to 16 more for low-risk PE patients treated in the hospital⁵¹; low-certainty evidence) and 90 days (RR, 0.98; 95% CI, 0.06-15.58; ARR, 0 fewer per 1000 patients, 95% CI, 7 fewer to 108 more for low-risk PE patients treated in the hospital⁵¹; low-certainty evidence), although CIs included significant benefit and harm. The analyses of observational studies also suggested a possible small reduction in long-term mortality at 90 days of follow-up (RR, 0.81; 95% CI, 0.42-1.58; ARR, 18 fewer per 1000 patients; 95% CI, 56 fewer to 56 more; very-low-certainty evidence) or PE (RR, 0.72; 95% CI, 0.07-7.70; ARR, 9 fewer per 1000 patients; 95% CI, 30 fewer to 216 more; very-low-certainty evidence).

Harms and burden

Evidence from the included RCTs demonstrates that treating patients with PE at low risk for complications at home, rather than in the hospital, may increase the risk of subsequent PE (RR, 2.95; 95% CI, 0.12-71.85; ARR, 23 more per 1000 patients; 95% CI, 11 fewer to 850 more; low-certainty evidence) and major bleeding (RR, 6.88; 95% CI, 0.36-132.14; ARR, 59 more per 1000 patients; 95% CI, 6 fewer to 1000 more; low-certainty evidence), although CI included significant benefit and harm. Observational studies also demonstrated a potential increase in major bleeding risk (RR, 2.68; 95% CI, 0.11-63.45; ARR could not be calculated; very-low-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence from the included RCTs was judged low for short-term and long-term mortality, PE, DVT, and major bleeding because of the small number of events and wide CI that covered appreciable benefit and harm. The certainty in the evidence from observational studies was judged very low for PE and major bleeding because of the inappropriate adjustment for additional factors, the lack of reporting for the assessment of outcomes and adequacy of follow-up in most studies, the small number of events among the included studies, and wide CIs that covered appreciable benefit and harm. The certainty in the evidence from observational studies was judged very low for long-term mortality for the same reasons as well as a high degree of inconsistency among the pooled estimates. In addition, 1 of the studies included patients who had active or palliative cancer and may have had a higher risk for dying than the other patient populations included in the systematic review.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. However, there is likely important variation in how individual patients may value the risk of thrombosis vs the risk of bleeding.

We identified 5 reports based on real-world data that compared the cost of home management vs hospital management.^{30,32,38-40} All reports showed that home management is cost saving compared with inpatient management. LMWH was used in these reports for home management. We also identified 5 reports that compared the cost and effectiveness of home treatment and hospital treatment for patients with DVT or for VTE patients, in general. One economic evaluation in a Canadian setting based on a decision tree suggests that home treatment is cost effective compared with hospital management.⁴¹ The other 4 reports suggest that home management leads to cost savings without compromising effects and safety. In all of these studies, LMWH was used for home management, whereas UFH was primarily used in hospital management.⁴²⁻⁴⁵

Health equity may decrease in rural areas or settings with limited health care access. In health systems with good primary care, home treatment is feasible and safe. In health systems with poor primary care, home treatment may reduce equity.

The panel considered home treatment acceptable and feasible in most cases, although economic incentives might favor in-hospital treatment in fee-for-service systems.

Conclusions and implementation considerations

Several studies have demonstrated that patients with PE who are at low risk for complications can be effectively and safely treated at home; however, the quality of evidence in support of this recommendation is of very low certainty, making this a conditional recommendation. Most patients with PE continue to be admitted to the hospital for treatment initiation, including a significant proportion of individuals who could be treated at home.⁶¹ Multiple factors likely contribute to the selection of the treatment setting, and implementation of an outpatient treatment program for PE requires several steps. First, there needs to be a systematic approach to determine which individuals with PE can be considered for outpatient management.⁶¹ Several assessment tools that use baseline clinical information to identify patients at low risk for adverse events during the first few months after diagnosis of PE have been developed, but these prognostic risk scores have not been evaluated prospectively for identification of patients with PE who can be safely treated at home. Clinical assessment and judgment are still required for identifying patients with PE who are appropriate for home management. Second, it is essential that risk stratification be performed quickly, shortly after the patient has been diagnosed with PE, to facilitate discharge from the emergency department and avoid hospitalization. Lastly, and most importantly, an infrastructure to provide outpatient PE treatment needs to be established to ensure that patients can be followed closely. As with outpatient DVT treatment, social factors, such as limited home support, history of nonadherence, and limited financial resources, would favor the hospital setting for the initial phase of treatment. Well-designed prospective studies that confirm the safety and efficacy of home treatment for selected patients with PE would be helpful, but the barriers listed above would need to be addressed prior to more widespread adoption of this recommendation.

Recommendation 3

For patients with DVT and/or PE, the ASH guideline panel *suggests* using DOACs over VKAs (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance <30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

Summary of the evidence

We identified 24 systematic reviews⁶²⁻⁸⁵ and 12 randomized trials⁸⁶⁻⁹⁷ (n = 28 876). Trials included individuals with an objectively confirmed symptomatic proximal DVT or PE. Participants were randomized to DOACs or to an initial treatment with LMWH (5-10 days) with dose-adjusted warfarin (INR range, 2.0-3.0). Dabigatran and edoxaban were also administered after an initial treatment of 5 to 10 days with LMWH, whereas rivaroxaban and apixaban were administered without initial parenteral anticoagulants. The length of the anticoagulation varied across trials from 3 to 12 months. Individuals with significant renal impairment, as indicated by an estimated creatinine clearance <25 mL/min (apixaban) or 30 mL/min (all other DOACs) and patients at high risk for bleeding were excluded. The EtD framework is shown online at: <https://guidelines.gradepr.org/profile/B7293C21-767F-B3F8-8BB2-A4E5173CDAC3>.

Benefits

The use of a DOAC instead of a VKA for patients with VTE does not impact mortality (RR, 0.99; 95% CI, 0.85-0.15; ARR, 0 fewer per 1000 patients; 95% CI, 6 fewer to 6 more; moderate-certainty evidence) or the risk of PE (RR, 0.97; 95% CI, 0.77-1.23; ARR, 1 fewer per 1000 patients; 95% CI, 5 fewer to 5 more; moderate-certainty evidence). However, we did observe a reduction in the risk of DVT (RR, 0.80; 95% CI, 0.59-1.09; ARR, 5 fewer per 1000 patients; 95% CI, 11 fewer to 2 more; moderate-certainty evidence), although this was not statistically significant.

Harms and burden

The use of a DOAC was associated with a reduction in the risk of major bleeding (RR, 0.63; 95% CI, 0.47-0.84; ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer; high-certainty evidence). In populations with a high risk for bleeding,⁹⁸ the use of a DOAC instead of a VKA may lead to a reduction of 8 fewer bleeding events per 1000 (95% CI, 11 fewer to 3 fewer; high-certainty evidence).

Additionally, given that the DOACs do not require frequent dose adjustment, monitoring of the INR, or dietary restrictions, they are probably associated with a lower burden for patients, particularly during anticoagulant initiation.

Certainty in the evidence of effects

The certainty in the evidence was judged moderate for mortality, PE, and DVT because of imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes. For major bleeding, the certainty in the evidence was judged high.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. However, there is likely an important variation in how individual patients value the risk of thrombosis vs the risk of bleeding.

We identified 5 cost comparisons between DOACs and VKA for patients with VTE. Four reports suggested that a DOAC is cost saving compared with warfarin,⁹⁹⁻¹⁰² and 1 study found an equivalent cost between a DOAC and a VKA.¹⁰³ Also, we identified 14 economic evaluations comparing the cost and effectiveness of DOACs vs VKA. All of them suggested that DOACs are cost-effective relative to VKA.^{100,104-116}

Finally, we considered DOACs to be acceptable and feasible to implement in most scenarios. However, given their cost, some patients might not be able to afford them.

Conclusions and implementation considerations

The ASH VTE treatment guideline panel has provided a conditional recommendation for the use of DOACs over VKAs as treatment for patients with a new diagnosis of VTE. Although the evidence supporting a reduced risk for bleeding with the use of a DOAC compared with a VKA was of high certainty, the lack of benefit for the VTE outcomes resulted in the conditional recommendation.

Several additional variables need to be taken into consideration when selecting an anticoagulant for an individual patient.

For example, patients who require medications that are inhibitors or inducers of P-glycoprotein, or strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) enzymes, should consider treatment with a VKA or LMWH rather than a DOAC, given the interactions of these medications with DOACs. Renal and/or hepatic insufficiency also needs to be taken into consideration prior to selecting an anticoagulant. Other variables that may impact the choice of anticoagulant therapy for individual patients include the cost of the DOACs and patient preference for once- or twice-daily dosing. Finally, patients with antiphospholipid antibody syndrome, bariatric surgery, short gut, or other conditions that may influence medication absorption, as well as patients at extremes of body weight, are not optimal candidates for DOACs. See the ASH guideline on optimal anticoagulant therapy for additional details.¹¹⁷

Anticoagulant therapy needs to be started during the initial management phase of VTE treatment and continued through the primary treatment phase for all patients with VTE who do not have a contraindication to anticoagulant therapy (Figure 1). For patients who will be treated with a VKA, initiation must be overlapped with UFH or LMWH for a minimum of 5 days and a therapeutic INR is achieved for 24 hours, at which time the heparin is discontinued. For patients who will be treated with dabigatran or edoxaban, pretreatment with UFH or LMWH for up to 5 to 10 days is needed before switching to the DOAC. For patients treated with rivaroxaban or apixaban, there is no need for pretreatment with UFH or LMWH. In contrast, a higher dose is administered for the 3 three weeks of therapy with rivaroxaban and for the first week of therapy with apixaban. These differences can be particularly important for those patients being considered for treatment at home rather than in the hospital.

Recommendation 4

For patients with DVT and/or PE, the ASH guideline panel does not suggest 1 DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects ⊕○○○).

Remarks: Factors such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (eg, need for a concomitant drug metabolized through CYP3A4 enzymes or P-glycoprotein), and the presence of cancer, may also impact DOAC choice.

Summary of the evidence

We did not find any systematic reviews or randomized trials comparing different DOACs head to head. We conducted a subgroup analysis of the evidence of DOACs vs VKAs⁸⁶⁻⁹⁷ and found no interaction between the specific agent used and the risk of mortality, PE, symptomatic DVT, or major bleeding. The EtD framework is shown online at: <https://guidelines.gradepr.org/profile/FFEF27C2-5C33-BB1B-B096-9624FCBB0456>.

Benefits, harms, and burden

Given the lack of evidence of the comparative effectiveness of different DOACs, we were unable to estimate the benefits and harms of specific agents.

Certainty in the evidence of effects

The certainty in the evidence was judged very low for all of the relevant outcomes, given that only indirect evidence was available.

Other EtD criteria and considerations

Given the lack of direct evidence, economic evaluation assessing the cost utility of different DOACs is based on assumptions and indirect observations.

In addition to cost, factors like coverage by health insurers, dosing (once vs twice daily), and requirement of initial use of LMWH will probably influence patient preferences.

Conclusions and implementation considerations

For patients who will be treated with a DOAC, the ASH guideline panel *does not suggest* 1 medication over another given the very low certainty in the evidence on comparative effects. However, for patients who will be taking a DOAC, there are differences that should be taken into consideration.¹¹⁸ Renal insufficiency is a variable that needs to be taken into consideration when selecting a DOAC, because the 4 agents that are currently available differ in the proportion of drug that is cleared by the kidneys, ranging from ~80% for dabigatran to 25% for apixaban.¹¹⁸ Ongoing studies evaluating apixaban use for patients with end-stage renal disease will further clarify its safety in this population. DOACs should be avoided as a class for patients with severe hepatic disease associated with coagulopathy; however, there are differences in which drugs can be used for patients with milder hepatic insufficiency, and dabigatran is least reliant on hepatic clearance. Other variables that may be important for the individual patient include whether the medication must be taken with food, preference for once-daily vs twice-daily dosing, the need to use a pill box, or the need to crush tablets prior to administration. Prospective research studies comparing different DOACs would be valuable in selected patient populations, such as individuals with renal insufficiency, liver disease, or morbid obesity.

Recommendation 5

In most patients with proximal DVT, the ASH guideline panel *suggests* anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic DVT involving the iliac and common femoral veins (higher risk of more severe PTS). Patients in these categories who value rapid resolution of symptoms, are averse to the possibility of PTS, and accept the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein.

Summary of the evidence

We identified 11 systematic reviews¹¹⁹⁻¹²⁹ and 19 randomized trials ($n = 1944$).¹³⁰⁻¹⁴⁸ Trials included individuals with objectively confirmed symptomatic proximal DVT. Participants were randomized to thrombolytic therapy in addition to anticoagulation or to anticoagulation alone. In general, thrombolytics were systemically infused, except in 4 trials, including the recently published ATTRACT trial, in which thrombolytics were catheter directed^{133,134,146,148} and 2 trials in which thrombolytics were locoregionally infused.^{141,142} The EtD framework is shown online at: <https://guidelines.gradepr.org/profile/8C3F2B15-9D6F-8618-8A41-444E83A9B780>.

Benefits

The use of thrombolytics for patients with DVT may reduce the risk of PTS (RR, 0.70; 95% CI, 0.59-0.83; ARR, 169 fewer per 1000 patients; 95% CI, 96 fewer to 231 fewer; low-certainty evidence) without significantly impacting mortality (RR, 0.77; 95% CI, 0.26-2.28; ARR, 0 fewer per 1000 patients; 95% CI, 1 fewer to 1 more; low-certainty evidence), the risk of PE (RR, 1.33; 95% CI, 0.71-2.46; ARR, 5 more per 1000 patients; 95% CI, 4 fewer to 21 more; low-certainty evidence), or the risk of DVT (RR, 0.99; 95% CI, 0.56-1.76; ARR, 1 fewer per 1000 patients; 95% CI, 57 fewer to 99 more; low-certainty evidence).

Harms and burden

The use of thrombolytics for patients with VTE (PE or DVT) was associated with an increase in the risk of major bleeding (RR, 1.89; 95% CI, 1.46-2.46; ARR, 31 more per 1000 patients; 95% CI, 16 more to 51 more; high-certainty evidence) and intracranial bleeding (RR, 3.17; 95% CI, 1.19-8.41; ARR, 7 more per 1000 patients; 95% CI, 1 more to 22 more; moderate-certainty evidence).

We tested whether the risk of major bleeding varied with the different routes of administration (ie, systemic vs locoregional vs catheter directed) and found that major bleeding was increased, regardless of the strategy used (RR for systemic infusion, 1.74; RR for catheter-directed infusion, 3.77; RR for locoregional infusion, 4.14).

Certainty in the evidence of effects

The certainty in the evidence was judged as low for mortality, PE, and DVT because of risk of bias (none of the included trials were blinded) and imprecision (CI around the absolute estimates likely crossed the thresholds that patients would consider important).

The effect on PTS was considered precise, but as before, we rated it down by risk of bias. Additionally, we also rated down the certainty in the evidence by inconsistency, given that 7 of the included studies reported significant PTS reduction, whereas 1 single trial (ATTRACT trial)¹⁴⁶ reported the absence of a significant effect ($I^2 = 57\%$).

Finally, the certainty in the evidence for major bleeding was judged as high.

Other EtD criteria and considerations

The panel considered that avoidance of PE, DVT, PTS, and major bleeding was critical for patients. However, the more relevant trade-off for patients may be between the risk of PTS and the risk of major bleeding. We judged that there is probably a large variation in what informed patients may choose.

Because only catheter-directed thrombolysis is available in the United States, implementing the procedure would probably result in

large costs, which, in turn, will probably reduce equity and limit its acceptability and feasibility.

Conclusions and implementation considerations

PTS may develop in up to 30% to 50% of patients following the development of a proximal DVT,^{149,150} and this may be severe in 5% to 10% of patients.^{3,150} Thrombolytic therapy has been shown to result in a more rapid and complete lysis of thrombus than anticoagulant therapy alone, but relatively few studies have linked radiographic improvements to clinical outcomes. Based on the low certainty in the evidence, the ASH guideline panel has suggested against the addition of thrombolytic therapy to anticoagulation for patients with proximal DVT. However, as noted above, certain patients with acute DVT might benefit from the addition of thrombolytic therapy, as determined by the severity of symptoms, location and extent of the thrombosis, and/or initial response to anticoagulant therapy. The decision to proceed with thrombolytic therapy needs to take into consideration the potential bleeding risk for the individual patient, as well as the potential benefits from early clot lysis. For patients with DVT who will be treated with thrombolytic therapy, the decision about whether to use catheter-directed thrombolysis or systemic thrombolysis is addressed in Recommendation 8. Additional research is necessary to facilitate the identification of which patients with DVT would benefit most from thrombolytic therapy.

Recommendation 6

For patients with PE and hemodynamic compromise, the ASH guideline panel recommends using thrombolytic therapy followed by anticoagulation over anticoagulation alone (strong recommendation despite low certainty in the evidence of effects ⊕⊕○○).

Remarks: Strong recommendations based on low certainty in the evidence of effects are exceptional. In this case, the high mortality of patients with PE and hemodynamic compromise, as well as the potential lifesaving effect of thrombolytics, warranted a strong recommendation. This exception is in accordance with the exceptional circumstances that allow strong recommendations based on low-certainty evidence in the GRADE ASH rules.

Summary of the evidence

We identified 29 systematic reviews¹⁵¹⁻¹⁷⁹ and 26 RCTs ($n = 2787$).^{130,180-204} Trials included individuals with an objectively confirmed symptomatic PE. Most trials included patients without hemodynamic compromise but with ultrasonography or biomarkers compatible with right ventricular dysfunction (submassive PE). Participants were randomized to thrombolytic therapy in addition to anticoagulation or to anticoagulation alone. Thrombolytics were systemically infused in all of the trials with the exception of 1,¹⁹⁰ in which it was catheter directed. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/073BA619-F572-CFBA-9A07-8DC73ADB05FD>.

Benefits

The use of thrombolytics for patients with PE and hemodynamic compromise may reduce mortality (RR, 0.61; 95% CI, 0.40-0.94;

ARR, 58 fewer per 1000 patients; 95% CI, 9 fewer to 90 fewer; low-certainty evidence).

Additionally, thrombolytic therapy might reduce the risk of subsequent PE (RR, 0.56; 95% CI, 0.35-0.91; ARR, 7 fewer per 1000 patients; 95% CI, 10 fewer to 2 fewer; very-low-certainty evidence) and DVT (RR, 0.92; 95% CI, 0.14-6.03; ARR, 1 fewer per 1000 patients; 95% CI, 8 fewer to 46 more; very-low-certainty evidence).

Harms and burden

The use of thrombolytics for patients with VTE (PE or DVT) was associated with an increase in the risk of major bleeding (RR, 1.89; 95% CI, 1.46-2.46; ARR, 31 more per 1000 patients; 95% CI, 16 more to 51 more; high-certainty evidence) and intracranial bleeding (RR, 3.17; 95% CI, 1.19-8.41; ARR, 7 more per 1000 patients; 95% CI, 1 more to 21 more; moderate-certainty evidence).

We tested whether the risk of major bleeding varied with the different routes of administration (ie, systemic vs locoregional vs catheter directed) and found that the effects were similar, regardless of the strategy used (RR for systemic infusion, 1.74; RR for catheter-directed infusion, 3.77; RR for locoregional infusion, 4.14).

Certainty in the evidence of effects

The certainty in the evidence was judged as low for mortality because of indirectness and imprecision. The trials identified primarily included patients without hemodynamic compromise, and the panel judged that thrombolytic effect may be different in such patients. Also, the number of patients studied was relatively small compared with the optimal information size, and the CIs around the absolute effect likely crossed the thresholds that patients would consider important. The same was true for the outcomes PE and DVT, but in addition to indirectness and imprecision, the panel also rated this down by risk of bias, given that none of the included trials was blinded.

Finally, the certainty in the evidence for major bleeding was judged as high.

Other EtD criteria and considerations

The panel considered that most informed patients would place more value in avoiding death than in the risk of bleeding associated with thrombolysis. Also, although no direct evidence was identified, in the context of hemodynamically unstable patients, the potential benefit of thrombolytic therapy on survival would probably result in the intervention being cost-effective. Finally, the panel considered that thrombolysis is acceptable and feasible to implement in most scenarios.

Conclusions and implementation considerations

Approximately 3% to 5% of patients with an acute PE present with hemodynamic compromise, defined as a systolic blood pressure <90 mm Hg or a decrease in systolic blood pressure ≥ 40 mm Hg from baseline.^{205,206} These patients are at a significantly greater risk for mortality, as high as 50% by 90 days,²⁰⁵ compared with patients with acute PE who do not present with hemodynamic compromise. As documented above, although thrombolytic therapy may reduce mortality for patients with PE and hemodynamic compromise, it is

also associated with an increased risk for major bleeding and intracranial bleeding. Nevertheless, because of the high risk of mortality in this small subset of patients with PE, the ASH guideline panel provided a strong recommendation in favor of the use of thrombolytic therapy (the decision as to whether this should be systemic or catheter-directed thrombolysis is addressed in Recommendation 9). Implementation of this recommendation depends on the ability to rapidly evaluate patients, confirm the diagnosis of PE and associated hemodynamic compromise, and initiate appropriate therapy. Multidisciplinary PE response teams have recently been implemented at several institutions to expedite rapid assessment and decision-making for these patients^{207,208}; however, there has not been a demonstrated improvement in mortality with this approach.^{208,209} Additional research with clinical outcomes is needed to confirm the role of thrombolytic therapy for patients with PE and hemodynamic compromise, including the optimal strategy for administration of the thrombolytic.

Recommendation 7

For patients with PE with echocardiography and/or biomarkers compatible with right ventricular dysfunction but without hemodynamic compromise (submassive PE), the ASH guideline panel *suggests* anticoagulation alone over the routine use of thrombolysis in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: Thrombolysis is reasonable to consider for younger patients with submassive PE at low risk for bleeding. Patients with submassive PE should be monitored closely for the development of hemodynamic compromise.

Summary of the evidence

We identified 29 systematic reviews¹⁵¹⁻¹⁷⁹ and 26 RCTs ($n = 2787$).^{130,180-204} Trials included individuals with an objectively confirmed symptomatic PE. Most trials included patients without hemodynamic compromise but with ultrasonography or biomarkers compatible with right ventricular dysfunction (submassive PE). Participants were randomized to thrombolytic therapy in addition to anticoagulation or to anticoagulation alone. Thrombolytics were systemically infused in all of the trials with the exception of 1,¹⁹⁰ in which it was administered through a catheter-directed approach. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/536D4434-B897-EEEE-A831-DF6C4FBE4DA3>.

Benefits

The use of thrombolytics for patients with PE and hemodynamic compromise may reduce mortality (RR, 0.61; 95% CI, 0.40-0.94; ARR, 58 fewer per 1000 patients; 95% CI, 9 fewer to 90 fewer; low-certainty evidence).

Additionally, thrombolytic therapy might reduce the risk of subsequent PE (RR, 0.56; 95% CI, 0.35-0.91; ARR, 7 fewer per 1000 patients; 95% CI, 10 fewer to 2 fewer; very-low-certainty evidence) and DVT (RR, 0.92; 95% CI, 0.14-6.03; ARR, 1 fewer per 1000 patients; 95% CI, 8 fewer to 46 more; very-low-certainty evidence).

Harms and burden

The use of thrombolytics for patients with VTE (PE or DVT) was associated with an increased risk for major bleeding (RR, 1.89; 95% CI, 1.46-2.46; ARR, 31 more per 1000 patients; 95% CI, 16 more to 51 more; high-certainty evidence) and intracranial bleeding (RR, 3.17; 95% CI, 1.19-8.41; ARR, 7 more per 1000 patients; 95% CI, 1 more to 21 more; moderate-certainty evidence).

We tested whether the risk of major bleeding varied with the different routes of administration (ie, systemic vs locoregional vs catheter directed) and found that the effects were similar, regardless of the strategy used (RR for systemic infusion, 1.74; RR for catheter-directed infusion, 3.77; RR for locoregional infusion, 4.14).

Certainty in the evidence of effects

The certainty in the evidence was judged as low for mortality because of indirectness and imprecision. The trials identified primarily included patients without hemodynamic compromise, and the panel judged that thrombolytic effect may be different in such patients. Also, the number of patients studied was relatively small compared with the optimal information size, and the CIs around the absolute effect likely crossed the thresholds that patients would consider important. The same was true for the outcomes PE and DVT, but in addition to indirectness and imprecision, the panel also rated these outcomes down by risk of bias, given that none of the included trials was blinded.

Finally, the certainty in the evidence for major bleeding was judged as high.

Other EtD criteria and considerations

We considered that most informed patients would place more value in avoiding death than in the risk of bleeding associated with the intervention. Finally, we considered that thrombolysis is acceptable and feasible to implement in most scenarios.

Conclusions and implementation considerations

Patients with acute PE who do not have evidence of hemodynamic compromise, defined as a systolic blood pressure <90 mm Hg or a decrease in systolic blood pressure ≥ 40 mm Hg from baseline, but who do have evidence of right ventricular strain by echocardiography or elevated cardiac biomarker levels (eg, elevated troponins or natriuretic peptides), have a higher mortality than do patients without these findings.^{210,211} However, the mortality risk is much less than for those patients with hemodynamic compromise. Consequently, because of this lower risk for mortality and the low certainty in the evidence of effects, the ASH guideline panel has provided a conditional recommendation against the routine use of thrombolytic therapy in these patients. This decision needs to be individualized, however, because some patients with acute PE may be assessed as being at higher risk for mortality (eg, patients with comorbid cardiopulmonary conditions) than others. Implementation of this recommendation depends on the ability to rapidly evaluate patients and initiate appropriate therapy. Additional research should target whether certain subsets of patients with acute PE and evidence of right

ventricular strain, but without hemodynamic compromise, would benefit from thrombolytic therapy.

Recommendation 8

For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel *suggests* using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Given the very-low-certainty evidence (uncertainty regarding the benefits and harms of catheter-directed thrombolysis compared with systemic thrombolysis), the panel followed the GRADE rules and issued a conditional recommendation. However, 4 panel members believed that the recommendation should have been graded as strong based on the uncertain benefit of catheter-directed thrombolysis over systemic thrombolysis and the certain and serious bleeding risks associated with systemic thrombolysis.

Summary of the evidence

We identified 3 systematic reviews^{119,212,213} and 5 controlled trials (n = 427).^{142,214-217} Trials included individuals with objectively confirmed symptomatic proximal DVT. Participants were randomized to directed therapy or systemic thrombolytic therapy. In 4 trials,²¹⁴⁻²¹⁷ thrombolysis was catheter directed, whereas in 1,¹⁴² it was locoregionally infused. The EtD framework is shown online at: <https://guidelines.gradeapro.org/profile/67E4FA59-335A-6713-860C-06FCE17BAE15>.

Benefits

For patients with DVT, catheter-directed thrombolysis might reduce the risk of PE (RR, 0.26; 95% CI, 0.05-1.43; ARR, 11 fewer per 1000 patients; 95% CI, 14 fewer to 6 more; very-low-certainty evidence) and of major bleeding (RR, 0.35; 95% CI, 0.12-1.06; ARR, 29 fewer per 1000 patients; 95% CI, 40 fewer to 3 more; very-low-certainty evidence). However, there is considerable uncertainty regarding the comparative effectiveness of catheter-directed thrombolysis vs systemic thrombolysis given that CIs include evidence for benefit and harm.

Harms and burden

Catheter-directed thrombolysis might increase the risk of PTS (RR, 2.59; 95% CI, 1.42-4.74; ARR, 223 more per 1000 patients; 95% CI, 76 more to 369 more; very-low-certainty evidence). However, there is considerable uncertainty given the wide CIs surrounding the effect.

Certainty in the evidence of effects

The certainty in the evidence was judged as very low for all of the relevant outcomes. None of the trials were blinded, increasing the possibility of bias. However, the most serious limitation of the evidence supporting this decision was the small number of patients studied. The number of events in the trials was very small, which led to wide CIs around the absolute estimates. Additionally, the certainty in the evidence was rated down because of indirectness in the outcome of PTS, because the only trial that informed this outcome used locoregional thrombolysis instead of catheter-directed thrombolysis.

Other EtD criteria and considerations

Given the small body of evidence supporting this decision, there is likely to be variability in what informed patients may choose.

Also, catheter-directed thrombolysis is an expensive procedure, and its implementation would probably result in an increment of direct costs. In the absence of certainty of its effects, it is not possible to reliably estimate its cost-effectiveness.

Finally, catheter-directed thrombolysis is not universally available, given that specialized laboratory support and trained personnel are required, and it might not be acceptable for some stakeholders.

It is important to note that systemic thrombolysis is not offered as an option for DVT management in the United States. Therefore, this recommendation does not fully apply to the US setting, but the panel considered the knowledge gap underlying this practice important to note.

Conclusions and implementation considerations

The ASH guideline panel suggested that most patients with proximal DVT do not need thrombolytic therapy in addition to anticoagulation in Recommendation 5. However, for those patients with DVT for whom thrombolytic therapy is considered appropriate, the ASH guideline panel provided a conditional recommendation in favor of catheter-directed thrombolysis over systemic thrombolysis, based on the very low certainty in the level of evidence. As noted above, 4 panel members believed that this should be a strong recommendation because systemic thrombolysis is not considered appropriate therapy in the United States. Regardless of the strength of the recommendation, implementation is contingent upon the local availability of appropriate technical expertise and infrastructure. Future research studies need to focus on the patient populations with DVT in whom thrombolytic therapy is considered most appropriate, to identify the optimal approach for administration of thrombolytic therapy.

Recommendation 9

For patients with PE in whom thrombolysis is considered appropriate, the ASH guideline panel *suggests* using systemic thrombolysis over catheter-directed thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: In centers with the appropriate infrastructure, clinical staff, and procedural experience, catheter-directed thrombolysis may be an alternative to systemic thrombolysis, especially for patients with an intermediate risk for bleeding, because the total dose of thrombolytic agents is lower when delivered by catheter. In arriving at this recommendation, the panel acknowledged that the reduced dose of thrombolytic drug used for catheter-directed thrombolysis might confer a safety advantage. However, estimates of the bleeding rate associated with catheter-directed thrombolysis are very imprecise because of the paucity of quality studies and the diversity of methods used. The single published randomized trial that evaluated efficacy was small and did not demonstrate clinical outcome improvements beyond cardiac hemodynamic parameters. Hence, there remains substantial uncertainty surrounding the actual safety and efficacy of catheter-directed thrombolysis. In contrast, estimates of the safety

and efficacy of systemic thrombolysis are more confident, having been derived from many randomized trials comprising a much larger number of patients.

Summary of the evidence

We identified 1 systematic review,²¹⁸ 1 relevant controlled trial ($n = 52$),²¹⁹ and 3 relevant observational studies (matched population = 7502).²²⁰⁻²²² All of the studies included individuals with an objectively confirmed PE and compared catheter-directed thrombolysis with systemic thrombolysis. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/A7BFDBC4-6A3F-D87D-928A-7ADA50ADED1A>.

Benefits, harms, and burden

There is considerable uncertainty regarding the comparative effect of systemic thrombolysis and catheter-directed thrombolysis. Based on 1 very small trial and 3 observational studies, the use of catheter-directed thrombolysis might reduce mortality (RCT estimate: RR, 0.06; 95% CI, 0-0.96; ARR, 157 fewer per 1000 patients; 95% CI, 7 fewer to 167 fewer; very-low-certainty evidence; observational studies estimate: odds ratio [OR], 0.59; 95% CI, 0.33-1.04; ARR during hospitalization, 48 fewer per 1000 patients; 95% CI, 81 fewer to 4 more; very low certainty). Also, catheter-directed thrombolysis might reduce major bleeding (RCT estimate: RR, 0.69; 95% CI, 0.21-2.27; ARR, 24 fewer per 1000 patients; 95% CI, 62 fewer to 99 more; very-low-certainty evidence; observational studies estimate: OR, 0.87; 95% CI, 0.7-1.09; ARR, 7 fewer per 1000 patients; 95% CI, 16 fewer to 5 more; very low certainty).

PE recurrence and DVT were not reported in any of the identified studies.

Certainty in the evidence of effects

The certainty in the evidence was judged as very low for mortality and major bleeding because of the risk of bias and imprecision. The only randomized trial was not blinded, and the randomization process was not adequately described. The observational study did adjust for baseline characteristics using propensity scores, but observational studies have a residual selection bias due to unadjusted or unmeasured differences in the groups under comparison.

The other main limitation of the evidence supporting this decision was imprecision of the estimates. In the randomized trial, only 54 patients were studied, yielding a very wide CI. Although the observational studies did include more patients and events, the CIs around the absolute estimates were also wide and probably crossed the thresholds that patients would consider important.

Other EtD criteria and considerations

Given the small body of evidence supporting this decision, there is likely to be variability in what informed patients may choose.

We did not identify relevant economic evaluations, although catheter-directed thrombolysis is an expensive procedure, and its implementation probably would result in an increment of direct costs.

Because catheter-directed thrombolysis requires a specialized laboratory and trained personnel, it is not universally available. Also,

given its costs and the uncertainty regarding its effects, it might not be acceptable for some stakeholders.

Conclusions and implementation considerations

Thrombolytic therapy can be an appropriate intervention in selected patients with PE, as described in Recommendations 6 and 7, and can be administered systemically or using a catheter-directed approach. Based on the very low level of certainty in the evidence, as outlined above, the ASH guideline panel has provided a conditional recommendation favoring systemic thrombolysis over catheter-directed thrombolysis for those patients with PE in whom thrombolysis is considered clinically appropriate. The panel did recognize the potential safety advantage of using a catheter-directed approach, but the imprecision of the data limited any conclusions that would favor this approach. Future research studies need to be conducted in the appropriate patient populations and designed to answer these questions surrounding optimal administration of thrombolytic therapy for patients with PE.

Recommendations 10 and 11

For patients with proximal DVT and significant preexisting cardiopulmonary disease, as well as for patients with PE and hemodynamic compromise, the ASH guideline panel *suggests* anticoagulation alone rather than anticoagulation plus insertion of an IVC filter (conditional recommendations based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: These recommendations apply to patients who are eligible to receive anticoagulation. For patients with a contraindication to anticoagulation, insertion of a retrievable IVC filter may be indicated, with retrieval as soon as the patient is able to receive anticoagulation.

Summary of the evidence

We identified 7 systematic reviews²²³⁻²²⁹ and 2 randomized trials^{230,231} ($n = 799$). The PREPIC²³⁰ trial included 400 patients with proximal DVT with or without concomitant PE. Participants were randomized to insertion of a nonretrievable IVC filter in addition to anticoagulation or to anticoagulation alone. Patients were followed for 2 years. The PREPIC 2 trial²³¹ included 399 patients with PE and acute deep or superficial vein thrombosis. Participants were randomized to insertion of a retrievable IVC filter in addition to anticoagulation or to anticoagulation alone. Follow-up was for 6 months. The majority of patients included in the PREPIC trials did not have significant preexisting cardiopulmonary disease, and no patient had PE with hemodynamic failure. The EtD frameworks are shown online at: <https://guidelines.gradepro.org/profile/86ED15E4-C608-F07D-9AA7-5F3B5AE994B0> and <https://guidelines.gradepro.org/profile/15281C02-EE9F-4E90-B895-5A8EEA854AB9>.

Benefits

A nonsignificant reduction in the risk of PE with IVC filter was observed (RR, 0.54; 95% CI, 0.22-1.33; ARR, 2 fewer per 1000 patients; 95% CI, 4 fewer to 2 more; low-certainty evidence). Using the baseline risk of PE observed in a cohort of 4036 patients with chronic obstructive pulmonary disease and VTE,²³² we

estimated that the use of an IVC filter may lead to 13 fewer PEs (95% CI, 23 fewer to 10 more; low-certainty evidence).

Harms and burden

We observed a nonsignificant mortality increase for patients randomized to receive IVC filters (RR, 1.12; 95% CI, 0.83-1.60; ARR, 9 more per 1000 patients; 95% CI, 10 fewer to 36 more; low-certainty evidence). Using the mortality observed in a cohort of 4036 patients with chronic obstructive pulmonary disease and VTE as baseline risk,²³² we estimated that the use of IVC filters for patients with significant preexisting cardiopulmonary disease may lead to 16 more deaths per 1000 (95% CI, 19 fewer to 66 more; low-certainty evidence). Also, using the baseline risk of mortality observed for patients with PE and systolic blood pressure <90 mmHg in the RIETE registry (n = 6599),²³³ we estimated that the use of an IVC filter for patients with PE and hemodynamic compromise may lead to 22 more deaths per 1000 (95% CI, 26 fewer to 90 more; low-certainty evidence).

Additionally, we observed a nonsignificant increase in the incidence of subsequent DVT in the group randomized to IVC filters (RR, 1.64; 95% CI, 0.93-2.90; ARR, 3 more per 1000 patients; 95% CI, 0 to 10 more; low-certainty evidence).

Finally, IVC filter insertion was associated with local and mechanical complications. In the PREPIC 2 trial,²³¹ among the 193 patients who received filters, 5 (2.6%) experienced access site hematoma, 3 (1.6%) experienced filter thrombosis, and 11 (5.7%) experienced retrieval failure for mechanical reasons.

Certainty in the evidence of effects

The certainty in the evidence was judged low for all of the relevant outcomes. One of the limitations of the available evidence was that the populations included in the PREPIC trials were different from our populations of interest. Specifically, the risk of death and PE observed in the trials probably underestimated the real risk of patients with significant preexisting cardiopulmonary disease and with PE and hemodynamic failure. The panel took this factor into consideration by using baseline risks observed in the relevant populations in observational studies and by rating down by indirectness.

Additionally, the panel rated down the certainty in the evidence by imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important.

Other EtD criteria and considerations

The panel considered that the balance between the risks of PE vs death and subsequent DVT episodes was critical for patients, although there likely is important variation in how individual patients may value the different outcomes.

The panel did not find economic evaluations assessing the cost-effectiveness of IVC filters; however, the panel considered that the costs associated with the insertion and removal of IVC filters are at least moderate.

Conclusions and implementation considerations

IVC filters were designed almost 50 years ago to trap blood clots originating from the veins in the pelvis and lower extremities,

preventing them from occluding the pulmonary vasculature while maintaining caval patency.²³⁴ Recommendations 10 and 11 consider patients who would be considered most likely to benefit from this type of device, specifically those with significant preexisting cardiopulmonary disease and those with hemodynamic compromise related to preexisting PE. If these patients can be safely treated with anticoagulant therapy, however, the ASH guideline panel conditionally recommends against the use of IVC filters, based on the low certainty in the evidence of their effects. Importantly, these recommendations are not intended to apply to patients with VTE who have a contraindication to anticoagulant therapy, in whom placement of an IVC filter may be an important alternative. If an IVC filter is going to be deployed, the panel recommends use of a retrievable filter, with removal once the patient is able to be safely treated with anticoagulant therapy.

Primary treatment

Recommendations 12, 13, and 14 address the question of the appropriate duration of time that should be used for primary treatment of the acute event, as defined in Figure 2. The individual recommendations reference 3 patient populations: those with VTE provoked by transient risk factors (Recommendation 12), those with VTE provoked by chronic (persistent) risk factors (Recommendation 13), and those with VTE not associated with any provoking risk factors (ie, unprovoked VTE; Recommendation 14). Common examples of major and minor transient risk factors and chronic risk factors for VTE are provided in Table 3. Several studies have demonstrated that primary treatment should continue for a minimum of 3 to 6 months for all patients with VTE.^{235,236} The recommendations in this section address whether the 3 patient populations described above would benefit from a longer period for primary treatment of the acute thromboembolic event. Of note, these recommendations do not address whether patients should continue antithrombotic therapy indefinitely to prevent recurrent events, referred to as secondary prevention in Figure 2, which is covered in the section on secondary prevention below.

Recommendations 12, 13, and 14

For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor (Recommendation 12) or a chronic risk factor (Recommendation 13) or unprovoked (Recommendation 14), the ASH guideline panel *suggests* using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary treatment (6-12 months) (conditional recommendations based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: These recommendations are intended to address the duration of primary anticoagulant treatment for all patients with DVT and/or PE, defined as the minimal length of time for treatment of the initial VTE (Figure 2). Most patients with DVT and/or PE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. In contrast, many patients with DVT and/or PE provoked by chronic risk factors, as well as patients with unprovoked DVT and/or PE, may continue anticoagulant therapy indefinitely for

secondary prevention after completion of the primary treatment (Figure 2). However, if patients and clinicians decide to stop anticoagulation after primary treatment, the ASH guideline panel suggests against using a longer course of primary anticoagulant therapy (6-12 months). For selected patients with a chronic risk factor for which some improvement is expected over time (eg, improved mobility with rehabilitation), a longer course of anticoagulation for the primary treatment phase (eg, 6-12 months) could be justified. Recommendations 15 through 22 address decisions concerning which patients should indefinitely continue anticoagulant therapy for secondary prevention and which therapeutic options should be considered.

Recommendation 12: primary treatment for patients with DVT and/or PE provoked by a transient risk factor

Summary of the evidence. We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 10 RCTs ($n = 2857$).²⁵⁸⁻²⁶⁷ One set of trials included adults with objectively confirmed DVT and/or PE at the time of diagnosis, who were randomized to a shorter course (3-6 months) or a longer course (6-12 months) of anticoagulant therapy for primary treatment. A second set of trials included adults with objectively confirmed DVT and/or PE who had completed treatment with anticoagulants for 3 to 6 months without recurrence and who were then randomized to receive placebo or continue for ≥ 6 months of additional treatment. The longer course of therapy varied from 6 months to 24 months.²⁶² Patients were continuously followed up until the end of the longer course of anticoagulation. The outcomes were measured in both groups at the end of the follow-up. For baseline risks of VTE, we used a meta-analysis of 10 cohort studies and 5 randomized trials²⁶⁸ that reported a VTE recurrence rate of 4.2 per 100 patient-years for patients with a transient risk factor. Assuming that 45% of the VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated annualized risks of PE recurrence of 1.89 and of DVT recurrence of 2.31 per 100 patient-years for patients with a nonsurgical transient risk factor. For the baseline risk of major bleeding, we used a meta-analysis of 13 prospective cohort studies and 56 randomized trials⁹⁸ in VTE patients showing a 2.1% risk for major bleeding during a 6-month

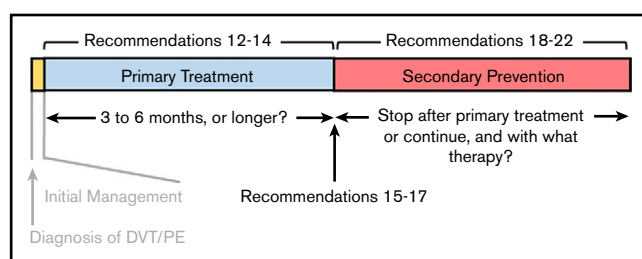


Figure 2. Relationships of Recommendations 12 to 22 with primary treatment and secondary prevention phases of VTE treatment. Recommendations 12 to 14 address the duration of the primary treatment phase of therapy. Recommendations 15 to 17 address strategies to decide whether to discontinue anticoagulant therapy or continue with secondary prevention. Recommendations 18 to 22 address which patients should receive secondary prevention and with what antithrombotic therapies.

Table 3. Risk factors and venous thromboembolism

Transient risk factors (risk factors that resolve after they have provoked VTE)*
Major transient risk factors (occur within 3 mo of VTE diagnosis); examples include:
Surgery with general anesthesia for ≥ 30 min
Confined to bed in hospital for ≥ 3 d with an acute illness ("bathroom privileges" only)
Cesarean section
Minor transient risk factors (occur within 2 mo of VTE diagnosis); examples include:
Surgery with general anesthesia for < 30 min
Admission to hospital for < 3 d with an acute illness
Estrogen therapy (eg, oral contraceptives, hormone replacement therapy)
Pregnancy and puerperium
Confined to bed out of hospital for ≥ 3 d with an acute illness
Leg injury associated with decreased mobility for ≥ 3 d
Chronic (persistent) risk factors (risk factors that persist after the development of VTE)†
Active cancer (eg, ongoing chemotherapy; recurrent or progressive disease)
Inflammatory bowel disease
Autoimmune disorders (eg, antiphospholipid syndrome, rheumatoid arthritis)
Chronic infections
Chronic immobility (eg, spinal cord injury)

Patients may present with > 1 transient risk factor or a combination of transient and chronic risk factors. Nonenvironmental risk factors for VTE include hereditary thrombophilia, older age, and male sex. These variables typically exhibit a low relative risk for VTE but may be useful in combination with acquired risk factors when considering an individual patient's risk for recurrence. Other acquired variables that confer a very weak risk for recurrence ($OR < 2$), such as obesity, varicose veins, or laparoscopic surgery, are not considered significant risk factors individually, but they may have an additive effect when combined with other risk factors listed above. Adapted from Kearon et al²³⁷ and Konstantinides et al²³⁸ with permission.

*For patients with VTE and a major transient risk factor > 3 months prior to the VTE or a single minor transient risk factor > 2 months prior to the VTE, clinical judgment is essential when considering the contribution of this variable to the initial VTE and the risk of recurrence.

†Chronic risk factors may fluctuate over time (eg, curative treatment of cancer or clinical waxing and waning of an autoimmune disorder), which may impact the relative risk of recurrent VTE. Active cancer is addressed in a future guideline document from ASH and is not considered in this article.

treatment with anticoagulants. We estimated an annualized risk for major bleeding of 2.1%, assuming a risk for major bleeding close to 0 after anticoagulant discontinuation. The EtD framework is shown online at: <https://guidelines.gradepr.org/profile/68333EE3-3DBA-5D42-A7AC-B4A3258F08E0>.

Benefits. The meta-analysis showed that, compared with a shorter course of anticoagulation, treating patients with a longer course of anticoagulation reduced the risk of DVT (RR, 0.50; 95% CI, 0.27-0.95; ARR, 59 fewer per 1000 patients; 95% CI, 86 fewer to 6 fewer; high-certainty evidence). In a low-risk population,²⁶⁸ a longer course of anticoagulation also reduced the risk of DVT (ARR, 18 fewer per 1000 patients; 95% CI, 21 fewer to 14 fewer). A longer course of anticoagulation also showed a potential reduction in the risk of PE in the study population, without statistical significance (RR, 0.66; 95% CI, 0.29-1.51; ARR, 17 fewer per 1000 patients; 95% CI, 35 fewer to 25 more; moderate-certainty evidence) and likely a small reduction in a low-risk population²⁶⁸ (ARR, 6 fewer per 1000 patients; 95% CI, 13 fewer to 10 more;

moderate-certainty evidence). Using a DOAC for the longer course of anticoagulation reduced the risk of DVT in the study population (RR, 0.21; 95% CI, 0.11-0.41; ARR, 62 fewer per 1000 patients; 95% CI, 70 fewer to 46 fewer; moderate-certainty evidence), as well as in a low-risk population²⁶⁸ (ARR, 18 fewer per 1000 patients; 95% CI, 21 fewer to 14 fewer; high-certainty evidence). A longer course of a DOAC also reduced the risk of PE for the study population (RR, 0.13; 95% CI, 0.03-0.58; ARR, 21 fewer per 1000 patients; 95% CI, 24 fewer to 10 fewer), as well as for a low-risk population (ARR, 16 fewer per 1000 patients, 95% CI, 18 fewer to 8 fewer; moderate-certainty evidence).

Using a VKA or LMWH for the longer course of anticoagulation resulted in a reduction in the risk of DVT without statistical significance for the study population (RR, 0.60; 95% CI, 0.32-1.11; ARR, 64 fewer per 1000 patients; 95% CI, 109 fewer to 18 more), as well as for a low-risk population (ARR, 9 fewer per 1000 patients; 95% CI, 16 fewer to 3 more; moderate-certainty evidence). There was no significant impact on the risk of PE in the study population (RR, 0.84; 95% CI, 0.43-1.66; ARR, 13 fewer per 1000 patients; 95% CI, 47 fewer to 55 more) or for a low-risk population²⁶⁸ (ARR, 3 fewer per 1000 patients; 95% CI, 11 fewer to 12 more; moderate-certainty evidence).

Harms and burden. Our analysis showed a potential increase in mortality when using a longer course of anticoagulation than with a shorter course of anticoagulation, without statistical significance (RR, 1.38; 95% CI, 0.85-2.23; ARR, 7 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence).

The use of a longer course of anticoagulation may increase the risk of major bleeding (RR, 1.46; 95% CI, 0.78-2.73; ARR, 6 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence). In populations with a low risk for bleeding,⁹⁸ the use of a longer course, instead of a shorter course, of anticoagulation may lead to an increase of 10 more bleeding events per 1000 patients (95% CI, 5 fewer to 36 more; moderate-certainty evidence).

Certainty in the evidence of effects. The certainty in the evidence was judged moderate for mortality, PE, and major bleeding because of imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes. For DVT, the certainty in the evidence was judged high. In the subgroup analysis performed, there are 2 cases in which the quality of the evidence differed from the original analysis. Both of these are for DVT outcome when using a VKA, LMWH, or a DOAC. The certainties of the evidence were judged moderate because of imprecision.

Other EtD criteria and considerations. We considered that avoidance of PE, DVT, and bleeding was critical for patients. However, there may be important variability in how individual patients value the risk of thrombosis vs the risk of bleeding. We did not identify direct evidence of a cost-effectiveness comparison for nonsurgical-provoked DVT/PE. Four Markov model analyses of cost-effectiveness for a longer course of antithrombotic therapy vs a shorter course of antithrombotic therapy for VTE treatment were identified. Three analyses showed that the longer course was

cost-effective compared with the shorter course of antithrombotic therapy,^{112,270, 271} whereas 1 analysis suggested that a longer course of anticoagulation with warfarin was cost-effective in younger patients and 3 months of anticoagulation was preferred in elderly patients (80-year-old subgroup).²⁷²

The panel considered that a longer course of treatment was probably acceptable and feasible. Observational studies suggested a higher level of patient satisfaction with a DOAC and a lower treatment burden compared with LMWH or a VKA.²⁷³

Conclusions and implementation considerations. The risk for recurrent VTE is low following completion of a course of anticoagulant therapy as primary treatment for patients who sustain a thromboembolism in the setting of a transient risk factor.²⁶⁸ Transient risk factors may be surgical or nonsurgical events (eg, hospitalization for an acute illness, estrogen therapy, or pregnancy), and, by definition, they resolve or can be discontinued (Table 3). The risk for a recurrent VTE is lower following a thromboembolism provoked by a surgical procedure or trauma compared with a nonsurgical risk factor, but the risk is low for both groups overall.²⁶⁸ A longer course of therapeutic anticoagulation for the primary treatment phase may decrease the risk of recurrent VTE while on treatment, but this is offset by an increased risk for bleeding complications. In addition, several of the studies identified above observed that any benefit associated with a longer finite course of therapy is lost after anticoagulation is discontinued.^{257,261} The ASH guideline panel provided a conditional recommendation supporting a shorter course (3-6 months) of therapy over a longer duration (6-12 months) for this phase of treatment as a result of the moderate certainty in the evidence of effects. After completion of the primary treatment phase, anticoagulant therapy is typically discontinued for patients with VTE provoked by transient risk factors, and secondary prevention does not need to be considered (Figure 2).

It should be noted that this recommendation is based primarily on data obtained from trials using VKA as the anticoagulant therapy. It is possible that newer studies using DOACs could alter the balance of benefits and harms associated with a longer course of therapy.

Recommendation 13: primary treatment for patients with DVT and/or PE provoked by a chronic risk factor

Summary of the evidence. We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 10 RCTs²⁵⁸⁻²⁶⁷ (n = 2857). One set of trials included adults with objectively confirmed DVT and/or PE at the time of diagnosis, who were randomized to a shorter course (3-6 months) or a longer course (6-12 months) of anticoagulant therapy. A second set of trials included adults with objectively confirmed DVT and/or PE who had been treated with anticoagulants for 3 to 6 months without recurrence; they were randomized to receive placebo or continue treatment for ≥6 more months. The longer course of therapy varied from 6 months to 24 months.²⁶² Patients were followed after the end of the extended anticoagulation treatment. The outcomes were measured in both groups at the end of the follow-up period. For baseline risks of VTE, we used a multicenter prospective cohort study²⁷⁴ that included 646 participants reporting a VTE recurrence rate of 9.7% per patient-year for patients with a chronic risk factor. Assuming that 45% of the VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated annualized

risks of recurrent PE of 4.4 and of recurrent DVT of 5.3 per 100 patient-years for patients with a chronic risk factor. For the baseline risk of major bleeding, we used a meta-analysis of 13 prospective cohort studies and 56 randomized trials⁹⁸ in VTE patients showing a 2.1% risk for major bleeding during a 6-month treatment with anticoagulants. We estimated an annualized risk for major bleeding of 2.1%, assuming a risk for major bleeding close to 0 after anticoagulant discontinuation. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/55B22415-DEB8-D1B7-9512-224BE01DCC76>.

Benefits. The meta-analysis showed that, compared with a shorter course of anticoagulation, treating patients with a longer course of anticoagulation reduced the risk of DVT (RR, 0.50; 95% CI, 0.27-0.95; ARR, 59 fewer per 1000 patients; 95% CI, 86 fewer to 6 fewer; high-certainty evidence). In a low-risk population,²⁷⁴ a longer course of anticoagulant therapy reduced the risk of DVT as well (ARR, 27 fewer per 1000 patients; 95% CI, 39 fewer to 3 fewer). A longer course of anticoagulation also showed a potential reduction in the risk of PE in the study population, without statistical significance (RR, 0.66; 95% CI, 0.29-1.51; ARR, 17 fewer per 1000 patients; 95% CI, 35 fewer to 25 more; moderate-certainty evidence), and likely a small reduction in the low-risk population²⁷⁴ (ARR, 15 fewer per 1000 patients; 95% CI, 31 fewer to 22 more; moderate-certainty evidence). When using a DOAC for a longer course of anticoagulation, the risk of DVT was reduced in the study population (RR, 0.21; 95% CI, 0.11-0.41; ARR, 62 fewer per 1000 patients; 95% CI, 70 fewer to 46 fewer; moderate-certainty evidence), as well as in the low-risk population²⁷⁴ (ARR, 42 fewer per 1000 patients; 95% CI, 47 fewer to 31 fewer; moderate-certainty evidence). A longer course of therapy with a DOAC also reduced the risk of PE (RR, 0.13; 95% CI, 0.03-0.58; ARR, 21 fewer per 1000 patients; 95% CI, 24 fewer to 10 fewer for study population; ARR, 38 fewer per 1000 patients; 95% CI, 42 fewer to 18 fewer for low-risk population; moderate-certainty evidence).

When using a VKA or LMWH for a longer course of anticoagulation, there was a reduction in the risk of DVT without statistical significance for the study population (RR, 0.60; 95% CI, 0.32 to 1.11; ARR, 64 fewer per 1000 patients; 95% CI, 109 fewer to 18 more), as well as for a low-risk population (ARR, 21 fewer per 1000 patients; 95% CI, 36 fewer to 6 more; moderate-certainty evidence). Similar outcomes were seen for the risk of PE for the study population (RR, 0.84; 95% CI, 0.43-1.66; ARR, 13 fewer per 1000 patients; 95% CI, 47 fewer to 55 more), as well as for a low-risk population²⁷⁴ (ARR, 7 fewer per 1000 patients; 95% CI, 25 fewer to 29 more; moderate-certainty evidence).

Harms and burden. Our analysis showed a potential increase in mortality when using a longer course of anticoagulation compared with a shorter course for primary treatment, without statistical significance (RR, 1.38; 95% CI, 0.85-2.23; ARR, 7 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence).

The use of a longer course of anticoagulant therapy may increase the risk of major bleeding (RR, 1.46; 95% CI, 0.78-2.73; ARR, 6 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence). In populations with a low risk for bleeding,⁹⁸ the use of a longer course of anticoagulation

instead of a shorter course may lead to an increase of 10 more bleeding events per 1000 patients (95% CI, 5 fewer to 36 more; moderate-certainty evidence).

Certainty in the evidence of effects. The certainty in the evidence was judged moderate for mortality, PE, and major bleeding because of imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes. For DVT, the certainty in the evidence was judged high. In the subgroup analysis performed, there were 2 cases in which the quality of the evidence differed from the original analysis. Both of these were on the outcome when using VKA, LMWH, or DOAC. The certainties of the evidence were judged moderate because of imprecision.

Other EtD criteria and considerations. We considered that avoidance of PE, DVT, and bleeding was critical for patients. However, there may be important variability in how individual patients value the risk of thrombosis vs the risk of bleeding.

We did not identify direct evidence on a cost-effectiveness comparison for nonsurgical provoked DVT/PE. Four Markov model analyses of cost-effectiveness for extended antithrombotic therapy vs limited antithrombotic therapy for VTE treatment were identified. Three analyses showed that a longer course of anticoagulation was cost-effective compared with a shorter course of antithrombotic therapy,^{112,270,271} whereas 1 analysis suggested that a longer course of anticoagulation with warfarin was cost-effective in younger patients, and 3 months of anticoagulation was preferred in elderly patients (age ≥ 80 years).²⁷²

The panel considered that a longer course of anticoagulation was probably acceptable and feasible. Observational studies suggested a higher level of patient satisfaction with a DOAC and a lower treatment burden than with LMWH or a VKA.²⁷³

Conclusions and implementation considerations. Acquired (environmental) risk factors for DVT and/or PE that are considered chronic include cancer (discussed in a future guideline document from ASH), certain autoimmune disorders (eg, inflammatory bowel disease or antiphospholipid syndrome), and chronic immobility (Table 3).²³⁷ Some of these risk factors may fluctuate over time (eg, the autoimmune disorders), but many of these patients are considered to be at a higher risk for recurrent thromboembolism if anticoagulant therapy is discontinued. As noted in the previous recommendation, any benefit associated with a longer finite course of therapy is lost after anticoagulation is discontinued. For primary treatment of the thromboembolic event, the ASH guideline panel has provided a conditional recommendation for a shorter course (3-6 months) of therapeutic anticoagulation over a longer course (6-12 months) of therapy, based on moderate certainty in the evidence of effects. After completion of the primary treatment phase, subsequent decisions (discussed in Recommendation 18) would determine whether to discontinue anticoagulant therapy or continue it indefinitely for secondary prevention of recurrent VTE (Figure 2).

It should be noted that patients with chronic risk factors for VTE may also have 1 (or more) transient risk factor (eg, surgery) or other

nonenvironmental risk factors, such as an inherited thrombophilia, older age, or male sex.²³⁷ These additional risk factors do not change this recommendation for duration of the primary treatment phase for the thromboembolic event.

Recommendation 14, primary treatment for patients with unprovoked DVT and/or PE

Summary of the evidence. We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 10 RCTs²⁵⁸⁻²⁶⁷ ($n = 2857$). One set of trials included adults with objectively confirmed DVT and/or PE at the time of diagnosis who were randomized to receive a shorter course (3-6 months) or a longer course (>6 months) of anticoagulation. A second set of trials included adults with objectively confirmed DVT and/or PE who had been treated with anticoagulants for 3 to 6 months without recurrence; they were randomized to receive placebo or continue with ≥ 6 months of additional treatment. The longer course of therapy varied from 6 months to 24 months.²⁶² Patients were continuously followed up after completion of the longer course of anticoagulation treatment. The outcomes were measured in both groups at the end of the follow-up. For baseline risks of VTE, we used a meta-analysis of 10 cohort studies and 5 randomized trials²⁶⁸ that reported a risk of recurrent VTE of 7.4 per 100 patient-years for patients with unprovoked VTE. Assuming that 45% of the VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated annualized risks of recurrent PE of 3.3 and of recurrent DVT of 4.1 per 100 patient-years for patients with unprovoked VTE. For the baseline risk of major bleeding, we used a meta-analysis of 13 prospective cohort studies and 56 randomized trials⁹⁸ in VTE patients showing a 2.1% risk for major bleeding during a 6-month period of treatment with anticoagulants. We estimated an annualized risk for major bleeding of 2.1% assuming a risk for major bleeding close to 0 after anticoagulant discontinuation. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/ADBCBA97-1E09-37C6-B664-D6FD9A489DC3>.

Benefits. The meta-analysis showed that, compared with a shorter course of anticoagulation, treating patients with a longer course of anticoagulation reduced the risk of DVT (RR, 0.50; 95% CI, 0.27-0.95; ARR, 59 fewer per 1000 patients; 95% CI, 86 fewer to 6 fewer; high-certainty evidence). In a low-risk population,²⁶⁸ a longer course of anticoagulant therapy reduced the risk of DVT as well (ARR, 20 fewer per 1000 patients; 95% CI, 30 fewer to 2 fewer). A longer course of anticoagulation also showed a potential reduction in the risk of PE in the study population, without statistical significance (RR, 0.66; 95% CI, 0.29-1.51; ARR, 17 fewer per 1000 patients; 95% CI, 35 fewer to 25 more; moderate-certainty evidence), and likely a small reduction in a low-risk population²⁶⁸ (ARR, 11 fewer per 1000 patients; 95% CI, 24 fewer to 17 more; moderate-certainty evidence). When using a DOAC for a longer course of anticoagulation, the risk of DVT was reduced in the study population (RR, 0.21; 95% CI, 0.11-0.41; ARR, 62 fewer per 1000 patients; 95% CI, 70 fewer to 46 fewer; high-certainty evidence), as well as in a low-risk population²⁶⁸ (ARR, 32 fewer per 1000 patients; 95% CI, 36 fewer to 24 fewer; moderate-certainty evidence). A longer course of therapy with a DOAC also reduced the risk of PE for the study population (RR, 0.13; 95% CI, 0.03-0.58; ARR, 21 fewer per 1000 patients; 95% CI, 24 fewer to 10 fewer), as well as for a low-risk population (ARR, 29 fewer per

1000 patients; 95% CI, 32 fewer to 14 fewer; moderate-certainty evidence).

When using a VKA or LMWH for a longer course of anticoagulation, there was a reduction in the risk of DVT without statistical significance for the study population (RR, 0.60; 95% CI, 0.32-1.11; ARR, 64 fewer per 1000 patients; 95% CI, 109 fewer to 18 more), as well as for a low-risk population (ARR, 16 fewer per 1000 patients; 95% CI, 28 fewer to 4 more; moderate-certainty evidence), and likely a small reduction in the risk of PE for the study population (RR, 0.84; 95% CI, 0.43-1.66; ARR, 13 fewer per 1000 patients; 95% CI, 47 fewer to 55 more), as well as for a low-risk population²⁶⁸ (ARR, 5 fewer per 1000 patients; 95% CI, 19 fewer to 22 more; moderate-certainty evidence).

Harms and burden. Our analysis showed a potential increase in mortality when using a longer course of anticoagulation compared with a shorter course of anticoagulation, without statistical significance (RR, 1.38; 95% CI, 0.85-2.23; ARR, 7 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence).

The use of a longer course of anticoagulant therapy may increase the risk of major bleeding (RR, 1.46; 95% CI, 0.78-2.73; ARR, 6 more per 1000 patients; 95% CI, 3 fewer to 22 more; moderate-certainty evidence). In populations with a low risk for bleeding,⁹⁸ the use of a longer course of anticoagulation instead of a shorter course may lead to an increase of 10 more bleeding events per 1000 patients (95% CI, 5 fewer to 36 more; moderate-certainty evidence).

Certainty in the evidence of effects. The certainty in the evidence was judged moderate for mortality, PE, and major bleeding because of imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes. For DVT, the certainty in the evidence was judged high. In the subgroup analysis performed, there were 2 cases in which the quality of the evidence differed from the original analysis. Both of these involved the DVT outcome when using VKAs/LMWH or DOACs. The certainties in the evidence were judged moderate because of imprecision.

Other EtD criteria and considerations. We considered that avoidance of PE, DVT, and bleeding was critical for patients. However, there is important variability in how individual patients may value the risk of thrombosis vs the risk of bleeding.

We did not identify direct evidence for a cost-effectiveness comparison for unprovoked VTE. Four Markov model analyses of cost-effectiveness for a longer course of anticoagulant therapy vs a shorter course of anticoagulant therapy for VTE treatment were identified. Three analyses showed that the longer course of anticoagulant therapy was cost-effective compared with the shorter course of therapy,^{112,270,271} whereas 1 analysis suggested that a longer course of anticoagulation with warfarin was cost-effective in younger patients, and 3 months of anticoagulation was preferred in elderly patients (≥ 80 years).²⁷²

The panel considered that a longer course of anticoagulant therapy was probably acceptable and feasible. An observational study suggested a higher level of patient satisfaction with a DOAC and a lower treatment burden than with LMWH or a VKA.²⁷³

Conclusions and implementation considerations. A DVT and/or PE that occurs in the absence of any transient or chronic environmental risk factors for VTE is considered unprovoked. These patients are considered to be at a higher risk for recurrent thromboembolism if anticoagulant therapy is discontinued. In addition, as noted above, any benefit associated with a longer finite course of therapy is lost after anticoagulation is discontinued. For primary treatment of the thromboembolic event, the ASH guideline panel has provided a conditional recommendation for a shorter course (3-6 months) of therapeutic anticoagulation over a longer course (6-12 months) of therapy, based on moderate certainty in the evidence of effects. These patients may have ≥ 1 nonenvironmental risk factor for recurrent VTE, such as inherited thrombophilia, older age, and/or male sex, but these variables would not affect this recommendation concerning the duration of the primary treatment phase for the thromboembolic event. After completion of the primary treatment phase, subsequent decisions (discussed in Recommendation 19) would determine whether to discontinue anticoagulant therapy or continue indefinitely for secondary prevention of recurrent VTE (Figure 2).

Secondary prevention. This section covers the phase of treatment identified as secondary prevention in Figures 1 and 2. This phase occurs after the patient has completed an initial course of anticoagulant therapy, referred to as primary treatment, at which time the patient will discontinue anticoagulation or continue without a predefined stop date. Recommendations 15 to 17 address the use of various tools to assist in the decision-making process concerning whether to discontinue anticoagulant therapy. Recommendations 18 and 19 address whether patients with VTE associated with chronic risk factors and patients with unprovoked VTE, who have completed primary treatment, should discontinue anticoagulation or consider an indefinite course of therapy. Recommendations 20 to 22 address the antithrombotic therapies that might be considered for patients who continue indefinite therapy.

Recommendations 15, 16, and 17

For patients with unprovoked DVT and/or PE, the ASH guideline panel *suggests against* routine use of prognostic scores (Recommendation 15), D-dimer testing (Recommendation 16), or ultrasound to detect residual vein thrombosis (Recommendation 17) to guide the duration of anticoagulation (conditional recommendations based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

Remarks: Indefinite anticoagulation is probably appropriate for the majority of patients with unprovoked VTE. However, in certain circumstances, such as when patients are undecided or the balance between risks and benefits is uncertain, clinicians and patients may use prognostic scores, the D-dimer test, or ultrasound assessment for residual thrombosis from an initial DVT to aid in reaching a final decision. Recommendations 15 to 17 address the routine use of these strategies.

Summary of the evidence

We identified 1 systematic review evaluating prognostic scores,²⁷⁵ which included 20 observational studies.²⁷⁶⁻²⁹³ Additionally, we

identified 4 systematic reviews²⁹⁴⁻²⁹⁷ and 1 relevant randomized trial²⁹⁸ assessing the role of D-dimer testing, as well as 5 systematic reviews²⁹⁹⁻³⁰³ and 1 relevant trial³⁰⁴ evaluating the use of ultrasound assessment for residual thrombosis from an initial DVT to guide the duration of anticoagulation.

The ideal way to measure the impact of various tools on patient-important outcomes would be to randomize patients to a decision guided by the tool or to a decision guided by specific guidelines without knowledge of the tool prediction. Unfortunately, such evidence is rare. We identified only 1 randomized trial³⁰⁴ that was designed this way; after the completion of 3 months of anticoagulation, 538 patients with DVT were randomized to anticoagulation for a fixed period of time or to ultrasonography-guided anticoagulation (no further anticoagulation for patients with recanalized veins and continued anticoagulation for patients with residual thrombosis). Another trial,²⁹⁸ close to the ideal design, included 223 individuals with an elevated D-dimer 1 month after completing 3 to 6 months of anticoagulation. In this study, participants were randomized to stop anticoagulation or to continue it for up to 18 months.

We did find studies evaluating the prognostic performance of the different tools: an individual patient meta-analysis of observational studies and 1 RCT ($n = 2527$)³⁰⁰ showed an independent association of residual vein thrombosis and recurrent VTE (HR, 1.32; 95% CI, 1.06-1.65). Another individual patient meta-analysis of 7 observational studies ($n = 1818$)²⁹⁶ showed that, after an initial period of anticoagulation, individuals with persistently elevated D-dimer levels have an increased risk for recurrent VTE (HR, 2.59; 95% CI, 1.90-3.52). Finally, the systematic review of prognostic models²⁷⁵ identified 3 scores: HERDOO2, Vienna, and DASH. The 3 models include D-dimer testing but differ with regard to the additional clinical characteristics considered. The Vienna score has been studied more and has showed moderate discrimination (c-statistic, 0.6) and a tendency to underestimate the true risk of VTE. Further details are provided in the EtD frameworks: <https://guidelines.gradepr.org/profile/CC2C2AC0-F4AC-F0A6-BC09-58996B7C1BC3>, <https://guidelines.gradepr.org/profile/859646ED-448E-8518-8B15-2CC804FBA8F3>, and <https://guidelines.gradepr.org/profile/6731C8B4-1AD1-1582-BA08-6FC54CDFC4B7>.

Benefits

In the trial assessing the role of residual vein thrombosis,³⁰⁴ participants randomized to ultrasonography received anticoagulation for an average of 4 to 5 months longer than did individuals randomized to the control group. Consequently, the investigators observed a nonsignificant reduction in the risk of PE (RR, 0.75; 95% CI, 0.21-2.60; ARR, 6 fewer per 1000 patients; 95% CI, 17 fewer to 35 more; low-certainty evidence) and DVT (RR, 0.64; 95% CI, 0.37-1.12; ARR, 16 fewer per 1000 patients; 95% CI, 28 fewer to 5 more; low-certainty evidence) in the intervention group.

In the trial that randomized individuals with high D-dimer levels²⁹⁸ to continue or to stop anticoagulation, the use of extended anticoagulation was associated with a reduction in PEs (RR, 0.16; 95% CI, 0.02-1.33; ARR, 8 fewer per 1000 patients; 95% CI, 10 fewer to 3 more; very-low-certainty evidence) and DVTs (RR, 0.07; 95% CI, 0.01-0.58; ARR, 9 fewer per 1000 patients; 95% CI, 4 to 10 fewer; very-low-certainty evidence).

Harms and burden

In the trial evaluating residual vein thrombosis by ultrasonography, participants in the intervention group received anticoagulation for an average of 4 to 5 months longer than did controls. Hence, they had a higher risk for bleeding (RR, 1.99; 95% CI, 0.37-10.7; ARR, 2 more per 1000 patients; 95% CI, 1 fewer to 20 more; low-certainty evidence).

Also, in the trial randomizing individuals with high D-dimer levels to continue or to stop anticoagulation, extended anticoagulation was associated with a higher risk for bleeding (RR, 3.49; 95% CI, 0.14-84.76; ARR, 24 more per 1000 patients; 95% CI, 8 fewer to 813 more; very-low-certainty evidence).

We did not find any randomized clinical trials investigating the prognostic scores that compared patient-important outcomes.

Certainty in the evidence of effects

We judged the certainty in the evidence as low for the use of ultrasonography and as very low for the use of D-dimer and prognostic scores. In the first case, we only found 1 trial comparing fixed periods of anticoagulation with ultrasonography-guided duration for patients without cancer. We rated down the certainty in the evidence for risk of bias, given that the trial was open label, and for imprecision, because the CIs around the absolute estimates include benefit and harm.

In the case of D-dimer, we also rated down the certainty in the evidence for risk of bias (unblinded study) and imprecision (wide CIs around absolute estimates). However, we rated down the certainty in the evidence 1 additional step because of indirectness, given that the trial identified did not really test the use of the D-dimer to make the decision whether to stop or continue anticoagulation. Rather, the study assessed the effect of anticoagulation in individuals with a high D-dimer level, which is a related question but not the specific question addressed by the panel.

As noted above, in the case of prognostic scores, at the time of our systematic review, we did not find any trial assessing their impact in patient-important outcomes, and the evidence regarding their discrimination ability and their validation was limited. Subsequently, a study investigating the HERDOO2 rule showed that women with a first unprovoked VTE and 0 or 1 of the HERDOO2 criteria could safely discontinue anticoagulant therapy after completing 5 to 12 months of therapeutic anticoagulation as primary treatment.³⁰⁵

Other EtD criteria and considerations

We did not identify any relevant economic evaluation; however, we considered the cost of using ultrasonography or D-dimer as moderate. Both tests are generally available, but ultrasonography is operator dependent and, therefore, results might vary in different settings.

Conclusions and implementation considerations

For the individual patient who has completed primary treatment of their VTE, information from 1 of the prognostic tools, a D-dimer, and/or an ultrasound assessment may be valuable for the provider and/or the patient in the decision-making process. The ASH guideline panel provides a conditional recommendation against the routine use of any of these modalities for all patients with VTE but

acknowledges the potential utility of 1 (or more) of these approaches for management of individual patients.

The panel felt that an important research question concerning the use of prognostic scores, D-dimer testing, and/or ultrasound centered around the identification of which patient populations would benefit most from the incorporation of ≥ 1 of these strategies into the decision-making process concerning whether anticoagulant therapy should be continued after completion of the primary treatment phase of therapy.

Recommendation 18

After completion of primary treatment for patients with DVT and/or PE provoked by a chronic risk factor, the ASH guideline panel *suggests* indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects $\oplus\oplus\oplus\bigcirc$).

Remarks: Patients with DVT and/or PE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment. This recommendation refers to patients with DVT and/or PE provoked by a chronic persistent risk factor (eg, inflammatory bowel disease or autoimmune disease). However, this recommendation does not apply to patients who have a high risk for bleeding complications. For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20. Decisions regarding anticoagulation in individuals with cancer are discussed in a future guideline from ASH.

Summary of the evidence

We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 13 RCTs^{88,258,259,261,262,265,267,298,306-310} (n = 8593) to inform this recommendation. Trials included adults with objectively confirmed DVT and/or PE who had been treated with anticoagulants for ≥ 3 months without recurrence. Patients were randomized to receive placebo or continue treatment for ≥ 6 months. The mean follow-up time varied from 24 to 28 months for different outcomes. The outcomes were measured in both groups immediately at the end of the extended-duration treatment. For baseline risks of VTE, we used a multicenter prospective cohort study²⁷⁴ that included 646 participants and reported a 9.7% per patient-year VTE recurrence rate for patients with a chronic risk factor. Assuming that 45% of the initial VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated annualized risks of 4.4 and 5.3 per 100 patient-years for PE and DVT recurrence, respectively, for patients with a chronic risk factor. For the baseline risk of major bleeding, we used data from 2 randomized trials on people with VTE, showing that the risk of major bleeding with placebo during 18 or 24 months of follow-up was as low as 0.5%³⁰⁶ and as high as 1.5% in 18 months.²⁵⁹ The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/86361A15-ECB8-E636-8A66-7B5713A17FEB>.

Benefits

The meta-analysis showed that, compared with discontinuation of anticoagulation, treating patients with indefinite antithrombotic therapy reduced the risk of PE in the study population (RR, 0.29;

95% CI, 0.15-0.56; ARR, 21 fewer per 1000 patients; 95% CI, 25 fewer to 13 fewer; high-certainty evidence), as well as for patients with chronic risk factors^{269,274} (ARR, 31 fewer per 1000 patients; 95% CI, 37 fewer to 19 fewer; high-certainty evidence). Indefinite antithrombotic therapy also showed a reduced risk for DVT in the study population (RR, 0.20; 95% CI, 0.12-0.34; ARR, 50 fewer per 1000 patients; 95% CI, 56 fewer to 42 fewer; high-certainty evidence), as well as for patients with chronic risk factors at 1 year^{269,274} (ARR, 45 fewer per 1000 patients; 95% CI, 48 fewer to 41 fewer).

There were significant subgroup effects with different antithrombotic interventions on DVT outcome. When using DOACs for indefinite anticoagulation, the risk of DVT in the study population was reduced (RR, 0.15; 95% CI, 0.10-0.23; ARR, 49 fewer per 1000 patients; 95% CI, 51 fewer to 44 fewer; high-certainty evidence), as well as for patients with chronic risk factors (ARR, 45 fewer per 1000 patients; 95% CI, 48 fewer to 41 fewer; high-certainty evidence).^{269,274} When using a VKA or LMWH for indefinite anticoagulation, a reduction in the risk of DVT for the study population was observed (RR, 0.17; 95% CI, 0.05-0.53; ARR, 54 fewer per 1000 patients; 95% CI, 61 fewer to 30 fewer), as well as for patients with chronic risk factors^{269,274} (ARR, 44 fewer per 1000 patients; 95% CI, 51 fewer to 25 fewer; high-certainty evidence). Aspirin reduced the risk of DVT in the study population (RR, 0.55; 95% CI, 0.31-0.98; ARR, 64 fewer per 1000 patients; 95% CI, 98 fewer to 3 fewer), as well as for patients with chronic risk factors^{269,274} (ARR, 24 fewer per 1000 patients; 95% CI, 37 fewer to 1 fewer; moderate-certainty evidence). Our analysis showed a potential decrease in mortality when using indefinite antithrombotic therapy compared to a defined duration of anticoagulation, but without statistical significance (RR, 0.75; 95% CI, 0.49-1.13; ARR, 4 fewer per 1000 patients; 95% CI, 8 fewer to 2 more; moderate-certainty evidence).

Harms and burden

The use of indefinite antithrombotic therapy increased the risk of major bleeding (RR, 2.17; 95% CI, 1.40-3.35; ARR, 6 more per 1000 patients; 95% CI, 2 more to 12 more; high-certainty evidence). In populations with a high risk for bleeding, the use of indefinite therapy instead of a defined duration of anticoagulation led to an increase of 18 more bleeding events per 1000 patients (95% CI, 6 more to 35 more; high-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged high for PE, DVT, and major bleeding but moderate for mortality because of imprecision, given that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on mortality. In the subgroup analysis performed for DVT when using aspirin, the certainty in the evidence was judged moderate because of imprecision.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value on the benefits of risk reduction in VTE recurrence and PTS.³¹¹ However, there is important variability in how individual patients may value the risk of recurrent VTE vs the risk of bleeding.

We did not identify direct evidence on a cost-effectiveness comparison for VTE provoked by a chronic risk factor. Four Markov model analyses of cost-effectiveness for extended antithrombotic therapy vs limited antithrombotic therapy for VTE treatment were identified. Three analyses showed cost-effectiveness for the extended strategy compared with the limited antithrombotic strategy,^{112,270,271} whereas 1 analysis suggested that longer initial conventional-intensity anticoagulation with warfarin was cost-effective in younger patients and 3 months of anticoagulation was preferred in elderly patients (≥ 80 years old).²⁷² The panel considered that cost-effectiveness varies with patients, the chronic risk factor(s) contributing to the increased risk of recurrent VTE, and the antithrombotic used.

The panel considered that indefinite treatment was probably feasible, but that acceptability varies.

Conclusions and implementation considerations

Patients with a chronic ("persistent") risk factor, such as inflammatory bowel disease or an autoimmune disorder, who sustain a VTE are considered to be at higher risk for recurrence if anticoagulation is discontinued after completion of the primary treatment phase compared with patients who have a transient risk factor. For patients with a chronic risk factor, the ASH guideline panel has provided a conditional recommendation for continuing antithrombotic therapy indefinitely after completion of primary treatment. Additional factors that may be useful for evaluation of the individual patient would include whether a transient risk factor was also present prior to the event and whether the patient has comorbid conditions that may predispose toward an increased risk for bleeding complications. Risk factors for bleeding with anticoagulant therapy include, but are not limited to, older age, history of prior bleeding, cancer, hepatic and/or renal insufficiency, hypertension, thrombocytopenia, prior stroke, need for antiplatelet therapy, anemia, alcohol abuse, and frequent falls.³¹² An individual patient's risk for bleeding will be affected by the severity of the risk factor (eg, degree of thrombocytopenia, location and extent of metastatic cancer), the number of risk factors present, and the presence of additional comorbid conditions. All patients who choose indefinite antithrombotic therapy for secondary prevention of recurrent VTE should be reevaluated at least annually to review their clinical course and reassess the clinical indication for continued indefinite therapy and bleeding risk factors.

The panel felt that additional research was needed to better define the impact of different chronic risk factors on the rate of recurrent VTE, particularly if the risk might vary over time.

Recommendation 19

After completion of primary treatment for patients with unprovoked DVT or PE, the ASH guideline panel *suggests* indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: This recommendation does not apply to patients who have a high risk for bleeding complications. For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20.

Summary of the evidence

We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 13 RCTs^{88,258,259,261,262,265,267,298,306-310} ($n = 8593$) to inform this recommendation. Trials included adults with objectively confirmed DVT or PE who had been treated with anticoagulants for ≥ 3 months without recurrence. Patients were randomized to receive placebo or continue with extended treatment for ≥ 6 months. The mean follow-up varied from 24 months to 28 months for different outcomes. The outcomes were measured in both groups immediately at the end of the extended-duration treatment. For baseline risks of VTE, we used a meta-analysis of 10 cohort studies and 5 randomized trials²⁶⁸ that reported a risk for recurrent VTE of 7.4% per patient-year for patients with unprovoked VTE. Assuming that 45% of the initial VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated annualized risks of 3.3 and 4.1 per 100 patient-years for PE and DVT recurrence, respectively, for patients with an unprovoked VTE. For the baseline risk of major bleeding, we used data from 2 randomized trials on people with VTE, which showed that the risk of major bleeding with placebo during 18 months or 24 months of follow-up was as low as 0.5%³⁰⁶ and as high as 1.5% in 18 months.²⁵⁹ The EtD framework is shown online at: <https://guidelines.grade-pro.org/profile/B4FEBC9-DEB2-C7FE-9420-79D262F2AB0F>.

Benefits

The meta-analysis showed that, compared with discontinuation of anticoagulation, treating patients with indefinite antithrombotic therapy reduced the risk of PE in the study population (RR, 0.29; 95% CI, 0.15-0.56; ARR, 21 fewer per 1000 patients; 95% CI, 25 fewer to 13 fewer; high-certainty evidence), as well as for patients with unprovoked VTE^{269,274} (ARR, 24 fewer per 1000 patients; 95% CI, 28 fewer to 15 fewer; high-certainty evidence). Indefinite antithrombotic therapy also showed a risk for reduction of DVT in the study population (RR, 0.20; 95% CI, 0.12-0.34; ARR, 50 fewer per 1000 patients; 95% CI, 56 fewer to 42 fewer; high-certainty evidence), as well as for patients with unprovoked VTE at 1 year^{269,274} (ARR, 33 fewer per 1000 patients; 95% CI, 36 fewer to 27 fewer).

There were significant subgroup effects of different antithrombotic interventions on DVT outcome. When using a DOAC for indefinite anticoagulation, the risk of DVT was reduced in the study population (RR, 0.15; 95% CI, 0.10-0.23; ARR, 49 fewer per 1000 patients; 95% CI, 51 fewer to 44 fewer; high-certainty evidence), as well as for patients with unprovoked VTE^{269,274} (ARR, 35 fewer per 1000 patients; 95% CI, 37 fewer to 31 fewer; high-certainty evidence). When using a VKA or LMWH for indefinite anticoagulation, the risk of DVT was likely reduced in the study population (RR, 0.17; 95% CI, 0.05-0.53; ARR, 54 fewer per 1000 patients; 95% CI, 61 fewer to 30 fewer; moderate-certainty evidence), as well as for patients with unprovoked VTE (ARR, 34 fewer per 1000 patients; 95% CI, 39 fewer to 19 fewer; high-certainty evidence).^{269,274} Aspirin also likely reduced the risk of DVT for the study population (RR, 0.55; 95% CI, 0.31-0.98; ARR, 64 fewer per 1000 patients; 95% CI, 98 fewer to 3 fewer; moderate-certainty evidence), as well as for patients with unprovoked VTE (ARR, 18 fewer per 1000 patients; 95% CI, 28 fewer to 1 fewer; moderate-certainty evidence).^{269,274} Our analysis showed a nonsignificant decrease in mortality when using indefinite antithrombotic therapy compared with a defined duration of anticoagulation (RR, 0.75; 95% CI, 0.49-1.13; ARR, 5

fewer per 1000 patients; 95% CI, 9 fewer to 2 more; moderate-certainty evidence).

Harms and burden

Indefinite antithrombotic therapy increased the risk of major bleeding (RR, 2.17; 95% CI, 1.40-3.35; ARR, 6 more per 1000 patients; 95% CI, 2 more to 12 more; high-certainty evidence). In populations with a high risk for bleeding, the use of indefinite antithrombotic therapy instead of a defined duration of anticoagulation led to an increase of 18 more bleeding events per 1000 patients (95% CI, 6 more to 35 more; high-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged high for PE, DVT, and major bleeding but moderate for mortality because of imprecision, given the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on mortality. In the subgroup analysis performed for recurrent DVT when using aspirin, the certainty in the evidence was judged moderate because of imprecision.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value on the benefits of risk reduction in VTE recurrence and PTS.³¹¹ However, there is important variability in how individual patients may value the risk of recurrent VTE vs the risk of bleeding.

We did not identify direct evidence on a cost-effectiveness comparison for unprovoked VTE. Four Markov model analyses of cost-effectiveness for extended antithrombotic therapy vs limited antithrombotic therapy for VTE treatment were identified. Three analyses showed that the extended strategy was cost-effective compared with limited antithrombotic therapy,^{112,270,271} whereas 1 analysis suggested that longer initial conventional-intensity anticoagulation with warfarin was cost-effective in younger patients and 3 months of anticoagulation was preferred in elderly patients (80-year-old subgroup).²⁷² The panel considered that cost-effectiveness varies with patients, any risk factor(s) contributing to the increased risk of recurrent VTE, and the specific anticoagulant used.

The panel considered that indefinite treatment was probably feasible but that the acceptability varies.

Conclusions and implementation considerations

Patients with unprovoked VTE, defined as occurring in the absence of any identifiable transient or chronic acquired risk factors, have the highest risk for recurrent VTE if anticoagulation is discontinued after the primary treatment phase. This risk has been estimated to be as high as 10% by 1 year and up to 30% by 5 to 10 years.^{10,11,313} The ASH guideline panel has provided a conditional recommendation for continuing antithrombotic therapy indefinitely after completion of primary treatment for patients with unprovoked VTE, based on moderate certainty in the evidence of effects. All patients who are recommended to take indefinite antithrombotic therapy for secondary prevention of recurrent VTE should be reevaluated at least annually to review the clinical indication for indefinite therapy and any bleeding complications that the patient may have sustained or new bleeding risk factors that the patient may have acquired.

As noted above in Recommendation 18, risk factors for bleeding with anticoagulant therapy include, but are not limited to, older age, history of prior bleeding, cancer, hepatic and/or renal insufficiency, hypertension, thrombocytopenia, prior stroke, need for antiplatelet therapy, anemia, alcohol abuse, and frequent falls.³¹² An individual patient's risk for bleeding will be affected by the severity of the risk factor (eg, degree of thrombocytopenia, location and extent of metastatic cancer), the number of risk factors present, and the presence of additional comorbid conditions.

Recommendation 20

For patients with DVT and/or PE who have completed primary treatment and will continue to receive secondary prevention, the ASH guideline panel *suggests* using anticoagulation over aspirin (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Summary of the evidence

We identified 1 RCT³¹⁷ to inform this recommendation. This trial included adults with objectively confirmed DVT and/or PE who had been treated with a DOAC or VKA for 6 to 12 months and had not interrupted therapy for more than 7 days prior to randomization. Patients were randomized to receive 20 mg of rivaroxaban or 100 mg of aspirin for 12 months. For the purpose of this question, aspirin was considered the intervention, and rivaroxaban was the comparator. The mean follow-up time was 351 days. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/355350CB-41FE-119C-8907-3B646789C1A5>.

Benefits

The analysis showed that, compared with a standard dose of anticoagulation, treating patients with aspirin may reduce the risk of major bleeding, but these results are not statistically significant (RR, 0.49; 95% CI, 0.12-1.95; ARR, 3 fewer per 1000 patients; 95% CI, 5 fewer to 5 more; moderate-certainty evidence).

Harms and burden

The use of aspirin compared with a standard dose of anticoagulation increased the risk of nonfatal PE (RR, 3.10; 95% CI, 1.24-7.73; ARR, 11 more per 1000 patients; 95% CI, 1 more to 36 more; moderate-certainty evidence) or DVT (RR, 3.15; 95% CI, 1.50-6.63; ARR, 17 more per 1000 patients; 95% CI, 4 more to 46 more; moderate-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged moderate for mortality, major bleeding, PE, and DVT because of imprecision, given a small number of events in both treatment arms that did not meet the optimal information size and the fact that the CIs around the absolute estimates likely crossed the thresholds that patients would consider important.

Other EtD criteria and considerations

We considered that the avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value

on the benefits of risk reduction in VTE recurrence and PTS.³¹¹ However, there is important variability in how individual patients may value the risk of recurrent VTE vs the risk of bleeding. The panel considered the variability of the cost of drugs across different countries and felt that the cost of anticoagulants, specifically DOACs, compared with aspirin would place at least a moderate burden on patients.

The panel considered that switching patients to aspirin at the completion of primary therapy was probably feasible and probably acceptable to relevant stakeholders.

Conclusions and implementation considerations

Extending anticoagulant therapy beyond the primary treatment phase reduces the risk of recurrent VTE but is associated with an increased risk for bleeding complications. Consequently, several studies have investigated the role of aspirin for the secondary prevention of VTE.^{309,314,315} The WARFASA³⁰⁹ and ASPIRE³¹⁸ trials compared aspirin, 100 mg daily, with placebo for secondary prevention of recurrent VTE for patients with an initial unprovoked event, and the pooled results of the 2 trials showed a decrease in recurrent VTE, as well as major vascular events, without an increased risk for clinically relevant bleeding.^{309,315} However, a systematic review and meta-analysis comparing extended anticoagulant therapy and aspirin found that anticoagulant therapy was more effective than aspirin in preventing recurrent VTE,²⁴⁶ and a single study comparing 2 doses of the direct oral anticoagulant rivaroxaban and aspirin found that anticoagulation was more effective than aspirin without an increase in bleeding rates.³¹⁴ Consequently, the ASH guideline panel has provided a conditional recommendation supporting the use of anticoagulation over aspirin for secondary prevention of VTE. For patients who are going to discontinue anticoagulant therapy after completion of the primary treatment phase, the role of aspirin can be considered but needs to be individualized. The panel did not address other nonanticoagulant options for secondary prevention of recurrent VTE.

Recommendation 21

For patients with DVT and/or PE who have completed primary treatment and will continue VKA therapy as secondary prevention, the ASH guideline panel *recommends* using an INR range of 2.0 to 3.0 over a lower INR range (eg, 1.5-1.9) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Summary of the evidence

We identified 1 RCT³¹⁶ to inform this recommendation. This trial included adults with objectively confirmed unprovoked DVT and/or PE who had been treated with oral anticoagulants for ≥at least 3 months. Patients were randomized to receive low-intensity warfarin therapy (target INR, 1.5-1.9) or conventional-intensity warfarin therapy (target INR, 2.0-3.0) after completion of the primary treatment phase of therapy. Patients were followed for an average of 2.4 years. The EtD framework is shown online at:

Benefits

We did not identify any benefits associated with use of a lower INR range.

Harms and burden

The use of warfarin with an INR range lower than 2.0 to 3.0 may increase the risk of DVT (RR, 3.25; 95% CI, 1.07-9.87; ARR, 24 more per 1000 patients; 95% CI, 1 more to 96 more; moderate-certainty evidence) and may increase the risk of nonfatal PE (RR, 5.0; 95% CI, 0.24-103.79; ARR could not be estimated; moderate-certainty evidence), although without statistical significance. Use of a lower INR range may also result in a nonsignificant increase in the risk of mortality (RR, 2.00; 95% CI, 0.86-4.47; ARR, 22 more per 1000 patients; 95% CI, 3 fewer to 75 more; moderate-certainty evidence) and major bleeding (RR, 1.13; 95% CI, 0.44-2.88; ARR, 3 more per 1000 patients; 95% CI, 12 fewer to 41 more; moderate-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged moderate for mortality, major bleeding, PE, and DVT due to imprecision, given the small number of events in both arms not meeting optimal information size and the fact that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value on the benefits of risk reduction in VTE recurrence and PTS.³¹¹ However, the panel considered the existence of an important variability in how individual patients may value the risk of recurrent VTE vs the risk of bleeding. The panel considered a negligible cost and savings between the interventions. One Markov model²⁷² compared an unlimited duration of conventional-intensity anticoagulation (INR range, 2.0-3.0) vs low-intensity anticoagulation (INR range, 1.5-2.0) with warfarin. The analysis suggested that an unlimited duration of standard-intensity anticoagulation was always more cost-effective.

The panel thought that there was no impact on health equity when choosing either intervention. The panel considered that a low target INR with warfarin was probably feasible but not acceptable to key stakeholders.

Conclusions and implementation considerations

This recommendation specifically applies to patients who are going to be treated with VKAs for secondary prevention of VTE. The ASH guideline panel provided a strong recommendation for VKAs with an INR range of 2.0 to 3.0 over an INR range of 1.5 to 1.9. However, it should be noted that patients considered to have a "high risk of bleeding" were excluded from the randomized trial described in the analysis above.³¹⁶ Decisions concerning anticoagulant therapy with warfarin for patients with a significant bleeding risk need to be

individualized, and a VKA may not be the optimal anticoagulant in this setting.

Recommendation 22

For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel *suggests* using standard-dose DOAC or lower-dose DOAC (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: Lower-dose DOAC regimens that may be considered for patients who have completed primary treatment and will continue with a DOAC include rivaroxaban at 10 mg daily and apixaban at 2.5 mg twice daily.

Summary of the evidence

We identified 2 RCTs^{306,314} to inform this recommendation. Trials included adults with objectively confirmed DVT and/or PE who had been treated with anticoagulants for 6 to 12 months. Subsequently, patients were randomized to receive 20 mg or 10 mg of rivaroxaban daily in 1 trial³¹⁴ or 5 mg or 2.5 mg of apixaban twice daily in another trial³⁰⁶ for 12 months. The follow-up time ranged from 351 to 365 days. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/011FBE1F-7460-20AC-A8BB-E3E0B4647907>.

Benefits

The analysis showed that, compared with a standard dose of rivaroxaban or apixaban, treating patients with a lower DOAC dose was associated with a nonsignificant reduction in the risk of mortality (RR, 0.68; 95% CI, 0.10-4.57; ARR, 2 fewer per 1000 patients; 95% CI, 6 fewer to 22 more; low-certainty evidence). The lower DOAC dose had little impact on the risk of DVT (RR, 0.75; 95% CI, 0.36-1.53; ARR, 2 fewer per 1000 patients; 95% CI, 6 fewer to 5 more; moderate-certainty evidence) or the risk of major bleeding (RR, 0.97; 95% CI, 0.12-1.95; ARR, 0 fewer per 1000 patients; 95% CI, 2 fewer to 7 more; moderate-certainty evidence).

Harms and burden

The use of a lower-dose DOAC compared with a standard-dose DOAC was associated with a nonsignificant increase in the risk of nonfatal PE (RR, 1.25; 95% CI, 0.54-2.91; ARR, 1 more per 1000 patients; 95% CI, 2 fewer to 10 more; moderate-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged moderate for major bleeding, nonfatal PE, and DVT because of imprecision, given the small number of events in both arms not meeting optimal information size and the fact that the CI around the absolute estimates likely crossed the thresholds that patients would consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on such outcomes. The certainty in the evidence was judged low for mortality because of the reasons mentioned above, as well as the large unexplained heterogeneity.

Other EtD criteria and considerations

The panel considered that there was important variability in how individual patients might value the risk of thrombosis vs the risk of bleeding. The panel estimated that the cost of a DOAC does not vary significantly with the dose.

The panel considered that both interventions were probably acceptable to relevant stakeholders and feasible to implement.

Conclusions and implementation considerations

Three DOACs have been studied for secondary prevention of recurrent VTE after completion of the primary treatment phase.^{306,310,314} Two of these agents, rivaroxaban and apixaban, have been studied at a reduced dose: from 20 mg daily to 10 mg daily for rivaroxaban and 5 mg to 2.5 mg twice daily for apixaban.^{306,314} The investigation into the use of the lower doses of these 2 anticoagulants for secondary prevention was prompted by the desire to reduce the risk of bleeding, as well as the documented efficacy of the lower doses to prevent VTE after elective hip or knee arthroplasty.³¹⁷⁻³²¹ However, neither study was powered for the comparisons between the standard and low doses. In addition, patients with a higher risk of recurrence were excluded from the studies (eg, multiple prior unprovoked VTE, indication for therapeutic dose anticoagulation, or antiphospholipid syndrome). Given the moderate certainty in the evidence of effects, the ASH guideline panel has provided a conditional recommendation that the standard dose or the lower dose of rivaroxaban or apixaban may be used for the secondary prevention of VTE. For patients who are treated with dabigatran for secondary prevention, only the standard regimen of 150 mg twice daily has been studied.³¹⁰

Additional research is necessary to identify which subsets of patients who are going to continue anticoagulant therapy indefinitely for secondary prevention can safely use a lower-dose DOAC and which patients should be maintained on a standard dose (eg, obese individuals and patients at higher risk for recurrence).

Treatment of recurrent events

Recommendation 23

For patients with breakthrough DVT and/or PE during therapeutic VKA treatment, the ASH guideline panel *suggests* using LMWH over DOAC therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Patients who present with a new VTE during therapeutic treatment with a VKA should be further investigated to identify potential underlying causes. This recommendation does not include patients who develop breakthrough VTE in the setting of poor INR control, in whom a DOAC may be a reasonable option.

Summary of the evidence

We did not find any systematic review or randomized trial comparing DOACs vs LMWH for patients with recurrent DVT and/or PE during treatment with VKA. DOACs vs LMWH have been compared only in the setting of VTE prophylaxis, which we

considered too indirect to make judgments about VTE treatment. The online EtD framework is available here: <https://guidelines.gradeapro.org/profile/4D133D47-A600-EC68-85E9-5221E45B47F9>.

Benefits, harms, and burden

Given the lack of evidence, we were unable to estimate the benefits and harms.

Certainty in the evidence of effects

The certainty in the evidence was judged very low for all of the relevant outcomes.

Other EtD criteria and considerations

We did not find any economic evaluation assessing the cost utility of a DOAC vs LMWH for patients with DVT and/or PE during treatment with VKA. Both interventions are widely available, and factors such as the route of administration (subcutaneous vs oral), cost, and coverage by health insurance will probably influence patients' preferences.

Conclusions and implementation considerations

The risk of recurrent VTE while on anticoagulant therapy with a VKA was 1.6% in a Cochrane meta-analysis.²⁴⁵ Frequent reasons associated with breakthrough thromboembolic events include the underlying condition or disease (eg, cancer, antiphospholipid syndrome, or vasculitis) or inappropriate selection and/or dosing of the anticoagulant (eg, noncompliance, drug-drug interactions, and drug-food interactions).³²² An initial assessment of any patient with an apparent breakthrough VTE while on therapeutic anticoagulation includes confirmation of compliance with the therapy being administered and confirmation that the medication and dosing regimen are appropriate for the individual patient. Initial laboratory testing includes an INR to confirm the patient is therapeutically anticoagulated with a VKA.

A recurrent or breakthrough event for patients receiving a VKA who were recently being treated with UFH or, less commonly, a LMWH may be suggestive of heparin-induced thrombocytopenia (HIT). In this setting, the VKA should be discontinued, the anticoagulant effect should be reversed with vitamin K, and the patient should be started on a nonheparin anticoagulant. The diagnosis and treatment of patients with suspected HIT are discussed in a separate ASH guideline document.³²³

For patients who sustain a breakthrough thrombotic event while taking a VKA who do not have HIT, there are minimal data available concerning which anticoagulant to select. The ASH guideline panel has provided a conditional recommendation favoring anticoagulation with LMWH over a DOAC, but this recommendation is based on very low certainty in the evidence of effects. These patients need to be carefully evaluated for underlying conditions and potential contraindications to individual anticoagulant agents, such as antiphospholipid syndrome, in which LMWH may be preferred over a DOAC. In addition, these patients need to be reevaluated when clinically stable to determine whether they need to continue LMWH or switch to an oral agent.

The evaluation and management of patients who sustain recurrent thromboembolic events while taking therapeutic anticoagulation

constitute an area needing well-designed prospective studies to provide guidance.

Recommendation 24a

For patients who develop DVT and/or PE provoked by a transient risk factor and have a history of previous unprovoked VTE or VTE provoked by a chronic risk factor, the ASH guideline panel *suggests* continuing antithrombotic therapy over stopping anticoagulation after completing primary treatment (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Recommendation 24b

For patients who develop a DVT and/or PE provoked by a transient risk factor and have a history of a previous thrombotic event also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of the primary treatment phase of therapy over indefinite duration therapy (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Remarks: For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20.

Summary of the evidence

We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 13 RCTs^{88,258,259,261,262,265,267,298,306-310} ($n = 8593$) to inform this recommendation. Trials included adults with objectively confirmed DVT and/or PE who had been treated with anticoagulants for ≥ 3 months without recurrence, referred to as the “study population” below. Patients were subsequently randomized to placebo or extended anticoagulation for ≥ 6 months of additional treatment. The mean follow-up time varied from 24 to 28 months for different outcomes. The outcomes were measured in both groups immediately at the end of the extended-duration treatment. For baseline risks of VTE, we used a prospective cohort study³²⁴ that reported an incidence rate for recurrent VTE of 5.6 per 100 patient-years for patients with a provoked VTE who had discontinued anticoagulation after completion of primary treatment. For patients with recurrent provoked VTE, assuming that 45% of the VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated the risks of PE recurrence to be 2.5 per 100 patient-years and the risks of DVT recurrence to be 3.1 per 100 patient-years. These estimates, however, do not differentiate the risk of recurrence according to the nature of the first thrombotic episode (ie, provoked or unprovoked). For the baseline risk of major bleeding, we used data from 2 randomized trials on people with VTE; the risk of major bleeding with placebo during an 18- or 24-month treatment with anticoagulants was as low as 0.5%³⁰⁶ and as high as 1.5% in 18 months.²⁵⁹ The EtD framework is shown online at: <https://guidelines.gradepr.org/profile/D9F5564D-D7EE-97A3-8AAB-24FF9D0C32F4>.

Benefits

The meta-analysis showed that, compared with discontinuation of anticoagulation, treating patients with indefinite antithrombotic therapy reduced the risk of PE in the study population (RR, 0.29; 95% CI, 0.15-0.56; ARR, 21 fewer per 1000 patients;

95% CI, 25 fewer to 13 fewer; high-certainty evidence), as well as for patients with recurrent provoked VTE^{269,324} (ARR, 18 fewer per 1000 patients; 95% CI, 21 fewer to 11 fewer; high-certainty evidence). Indefinite antithrombotic therapy also showed a risk reduction in DVT (RR, 0.20; 95% CI, 0.12-0.34; ARR, 50 fewer per 1000 patients; 95% CI, 56 fewer to 42 fewer; high-certainty evidence). Indefinite antithrombotic therapy also reduced the risk of DVT for patients with recurrent provoked VTE at 1 year^{269,324} (ARR, 25 fewer per 1000 patients; 95% CI, 27 fewer to 20 fewer).

There were significant subgroup effects with the different antithrombotic interventions on DVT outcome. When using a DOAC for indefinite anticoagulation, the risk of DVT was reduced in the study population (RR, 0.15; 95% CI, 0.10-0.23; ARR, 49 fewer per 1000 patients; 95% CI 51 fewer to 44 fewer; high-certainty evidence), as well as for patients with recurrent provoked VTE^{269,324} (ARR, 26 fewer per 1000 patients; 95% CI, 28 fewer to 24 fewer; high-certainty evidence). When using a VKA or LMWH for indefinite anticoagulation, we observed a reduction in the risk of recurrent DVT in the study population (RR, 0.17; 95% CI, 0.05-0.53; ARR, 54 fewer per 1000 patients; 95% CI, 61 fewer to 30 fewer), as well as for patients with recurrent provoked VTE (ARR, 26 fewer per 1000 patients; 95% CI, 29 fewer to 14 fewer; high-certainty evidence).^{269,324} Aspirin reduced the risk of DVT in the study population (RR, 0.55; 95% CI, 0.31-0.98; ARR, 64 fewer per 1000 patients; 95% CI, 98 fewer to 3 fewer), as well as for patients with recurrent provoked VTE (ARR, 14 fewer per 1000 patients; 95% CI, 21 fewer to 1 fewer; moderate-certainty evidence).^{269,324} Our analysis showed a potential decrease in mortality when using indefinite antithrombotic therapy compared with a defined duration of anticoagulation, without statistical significance (RR, 0.75; 95% CI, 0.49-1.13; ARR, 5 fewer per 1000 patients; 95% CI, 9 fewer to 2 more; moderate-certainty evidence).

Harms and burden

The use of indefinite antithrombotic therapy increased the risk of major bleeding (RR, 2.17; 95% CI, 1.40-3.35; ARR, 6 more per 1000 patients; 95% CI, 2 more to 12 more; high-certainty evidence). In populations with a high risk for bleeding,²⁵⁹ the use of indefinite antithrombotic therapy instead of a defined duration of anticoagulation led to an increase of 18 more major bleeding events per 1000 patients (95% CI, 6 more to 35 more; high-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged high for PE, DVT, and major bleeding but moderate for mortality because of imprecision, given that the CI around the absolute estimates crossed thresholds that patients would likely consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on mortality. In the subgroup analysis performed for DVT, when using aspirin, the certainty in the evidence was judged moderate because of imprecision.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value on the benefits of risk reduction in VTE recurrence and PTS.³¹¹ However, there is important variability in how individual patients may value the risk of thrombosis vs the risk of bleeding.

We did not identify a cost-effectiveness comparison for nonsurgical provoked VTE. Four Markov model analyses of cost-effectiveness for extended antithrombotic therapy vs limited antithrombotic therapy for VTE treatment were identified. Three analyses showed that the extended strategy was cost-effective compared with limited antithrombotic therapy,^{112,270,271} whereas 1 analysis suggested that longer initial conventional-intensity anticoagulation with warfarin was cost-effective in younger patients, and 3 months of anticoagulation was preferred in elderly patients (≥ 80 years old).²⁷² The panel considered that cost-effectiveness varies with patients, the chronic risk factor(s) contributing to risk of recurrent VTE, and the antithrombotic therapy used.

The panel considered that indefinite treatment was probably feasible but that acceptability varied.

Conclusions and implementation considerations

This recommendation applies to the patient who sustains a VTE related to a transient risk factor, who also has a history of VTE that was unprovoked or provoked by a chronic risk factor (Recommendation 24a) or who has a history of VTE that was provoked by a transient risk factor (Recommendation 24b). These patients need to undergo decisions about initial management (Recommendations 1 to 11) and primary treatment (Recommendations 12 to 14), just as with their first event. If the first event carried a high risk for recurrence (eg, was unprovoked), the ASH guideline panel provided a conditional recommendation in support of indefinite antithrombotic therapy for secondary prevention after completion of the primary treatment phase. In contrast, if the first event carried a lower risk for recurrence (ie, was provoked by a transient risk factor), the panel provided a conditional recommendation favoring discontinuation of anticoagulation after completion of the primary treatment phase. Variables that may impact on decision making for the individual patient, particularly the patient with a first event considered high risk for recurrence, might include whether the second event occurred in the same vascular distribution as the first event, the presence (or absence) of an underlying hypercoagulable state, the development of hemorrhagic complications while on anticoagulant therapy, and/or the clinical severity of the second event (eg, massive PE vs popliteal DVT). For those patients continued on indefinite antithrombotic therapy for secondary prevention, decisions about the optimal antithrombotic strategy for secondary prevention are addressed in Recommendations 20 to 22.

Recommendation 25

For patients with a recurrent unprovoked DVT or PE, the ASH guideline panel *recommends* indefinite antithrombotic therapy over stopping anticoagulation after completion of primary treatment (strong recommendation based on moderate certainty in the evidence of effects $\oplus\oplus\oplus\bigcirc$).

Remarks: For guidance on selection of antithrombotic therapy after completion of primary treatment, see Recommendation 20.

Summary of the evidence

We identified 19 systematic reviews²³⁹⁻²⁵⁷ and 13 RCTs^{88,258,259,261,262,265,267,298,306-310} ($n = 8593$) to inform this recommendation. Trials included adults with objectively confirmed

DVT and/or PE who had been treated with anticoagulants for ≥ 3 months without recurrence, referred to as the “study population” below. Patients were subsequently randomized to receive placebo or continue antithrombotic therapy for ≥ 6 additional months. The mean follow-up varied from 24 to 28 months for different outcomes. The outcomes were measured in both groups immediately at the end of the longer course of anticoagulation. For baseline risks of VTE, we used a prospective cohort study³²⁴ that reported a risk for patients with a recurrent unprovoked VTE of 12 per 100 patient-years. Assuming that 45% of the VTE events are PEs and 55% are DVTs,²⁶⁹ we estimated the risks of PE recurrence to be 5.4 per 100 patient-years and the risks of DVT recurrence to be 6.6 per 100 patient-years for patients with recurrent unprovoked VTE. For the baseline risk of major bleeding, we used data from 2 randomized trials on people with VTE; the risk of major bleeding with placebo during an 18-month or 24-month treatment with anticoagulants was as low as 0.5%³⁰⁶ and as high as 1.5% in 18 months.²⁵⁹ The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/C151C2DC-8A88-9E05-9D73-2FEB6B917C00>.

Benefits

The meta-analysis showed that, compared with discontinuation of anticoagulation, treating patients with indefinite antithrombotic therapy reduced the risk of PE in the study population (RR, 0.29; 95% CI, 0.15-0.56; ARR, 21 fewer per 1000 patients; 95% CI, 25 fewer to 13 fewer; high-certainty evidence), as well as for patients with recurrent unprovoked VTE^{269,324} (ARR, 38 fewer per 1000 patients; 95% CI, 46 fewer to 24 fewer; high-certainty evidence). Indefinite antithrombotic therapy also showed a risk reduction in DVT (RR, 0.20; 95% CI, 0.12-0.34; ARR, 50 fewer per 1000 patients; 95% CI, 56 fewer to 42 fewer; high-certainty evidence). For patients with recurrent unprovoked VTE at 1 year,^{269,324} indefinite antithrombotic therapy also reduced the risk of DVT (ARR, 53 fewer per 1000 patients; 95% CI, 58 fewer to 44 fewer).

There were significant subgroup effects associated with the different antithrombotic interventions on DVT outcome. When using a DOAC for indefinite anticoagulation, the risk of DVT was reduced in the study population (RR, 0.15; 95% CI, 0.10-0.23; ARR, 49 fewer per 1000 patients; 95% CI, 51 fewer to 44 fewer; high-certainty evidence) as well as for patients with recurrent unprovoked VTE^{269,324} (ARR, 56 fewer per 1000 patients; 95% CI, 59 fewer to 51 fewer; high-certainty evidence). When a VKA or LMWH was used for indefinite anticoagulation, we observed a reduction in the risk of DVT in the study population (RR, 0.17; 95% CI, 0.05-0.53; ARR, 54 fewer per 1000 patients; 95% CI, 61 fewer to 30 fewer), as well as for patients with recurrent unprovoked VTE (ARR, 55 fewer per 1000 patients; 95% CI, 63 fewer to 31 fewer; high-certainty evidence).^{269,324} Aspirin also reduced the risk of recurrent DVT in the study population (RR, 0.55; 95% CI, 0.31-0.98; ARR, 64 fewer per 1000 patients; 95% CI, 98 fewer to 3 fewer), as well as for patients with recurrent unprovoked VTE (ARR, 30 fewer per 1000 patients; 95% CI, 46 fewer to 1 fewer; moderate-certainty evidence).^{269,324} Our analysis showed a potential decrease in mortality when using indefinite antithrombotic therapy compared with a defined duration of anticoagulation, without statistical significance (RR, 0.75; 95% CI, 0.49-1.13; ARR, 5 fewer per 1000 patients; 95% CI, 9 fewer to 2 more; moderate-certainty evidence).

Harms and burden

The use of indefinite antithrombotic therapy increased the risk of major bleeding (RR, 2.17; 95% CI, 1.40-3.35; ARR, 6 more per 1000 patients; 95% CI, 2 more to 12 more; high-certainty evidence). In populations with a high risk for bleeding,²⁵⁹ the use of indefinite antithrombotic therapy instead of a defined duration of anticoagulation led to an increase of 18 more major bleeding events per 1000 patients (95% CI, 6 more to 35 more; high-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence was judged high for PE, DVT, and major bleeding but moderate for mortality because of imprecision given that the CI around the absolute estimates crossed thresholds that patients would likely consider important. Therefore, it was not possible to completely rule out a small difference between the alternatives on mortality. In the subgroup analysis performed for DVT, when using aspirin the certainty in the evidence was judged moderate because of imprecision.

Other EtD criteria and considerations

We considered that avoidance of PE, DVT, and major bleeding was critical for patients. Patients placed a high value on the benefits of risk reduction in VTE recurrence and PTS.³¹⁰ However, there is important variability in how individual patients may value the risk of thrombosis vs the risk of bleeding.

We did not identify direct evidence on a cost-effectiveness comparison for nonsurgical provoked VTE. Four Markov model analyses of cost-effectiveness for extended antithrombotic therapy vs limited antithrombotic therapy for VTE treatment were identified. Three analyses showed that the extended strategy was cost-effective compared with the limited antithrombotic therapy,^{112,270,271} whereas 1 analysis suggested that longer initial conventional-intensity anticoagulation with warfarin was cost-effective in younger patients, and 3 months of anticoagulation was preferred in elderly patients (≥ 80 years old).²⁷² The panel considered that cost-effectiveness varies with patients, the chronic risk factor(s) contributing to risk for recurrent VTE, and drug used.

The panel considered that indefinite treatment was probably feasible but that acceptability varies.

Conclusions and implementation considerations

This recommendation applies to the patient who sustains an unprovoked VTE and who also has a history of an unprovoked VTE that was treated with a time-limited course of therapy that had been discontinued prior to the current event. These patients need to undergo decisions about initial management (Recommendations 1 to 11) and primary treatment (Recommendations 12 to 14), just as with their initial event. The ASH guideline panel provided a strong recommendation in favor of indefinite antithrombotic therapy for secondary prevention of recurrent thromboembolism in light of the very high risk of recurrence off anticoagulation. Decisions about the optimal antithrombotic strategy for secondary prevention would be similar to those for a first unprovoked VTE (Recommendations 20 to 22).

Additional management issues

Recommendation 26

For patients with DVT and/or PE with stable CVD who initiate anticoagulation and were previously taking aspirin for cardiovascular risk modification, the ASH guideline panel *suggests* suspending aspirin over continuing it for the duration of anticoagulation therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: A critical review of the indication for aspirin therapy is needed at the time anticoagulant therapy is initiated, considering the increased risk of bleeding vs the potential benefit in terms of cardiovascular prevention. This recommendation does not apply to patients with a recent acute coronary event or coronary intervention.

Summary of the evidence

We identified 13 RCTs ($n = 7928$) to inform this recommendation.³²⁵⁻³³⁷ Trials included PE patients who were previously receiving aspirin for prevention of CVD and had initiated anticoagulation therapy. Patients who received an initial course of anticoagulants were randomized to anticoagulant with aspirin or anticoagulants alone. The mean follow-up time varied from 1 to 2.5 years. The EtD framework is shown online at: <https://guidelines.gradeapro.org/profile/64AF970C-9665-2F07-BFD3-EB4E658C5706>.

Benefits

An assessment of the benefits of aspirin was not relevant to a guideline of VTE treatment and, therefore, was considered outside the scope of this analysis.

Harms and burden

Evidence from included RCTs suggested that treating PE patients who had previously received aspirin for the prevention of CVD with anticoagulation with aspirin increased the risk of major bleeding compared with anticoagulation alone (RR, 1.26; 95% CI, 0.92-1.72; ARR, 7 more per 1000 patients; 95% CI, 2 fewer to 21 more; very-low-certainty evidence). In patient populations with any indication for anticoagulation and/or aspirin,⁹⁸ the use of anticoagulation with aspirin relative to anticoagulation alone led to an increase of 5 more major bleeding events per 1000 patients (95% CI, 2 fewer to 15 more; very-low-certainty evidence).

Certainty in the evidence of effects

The certainty in the evidence from the included RCTs was judged very low for major bleeding because of a serious risk for bias, indirectness, and imprecision. First, there was a lack of allocation concealment and blinding of study participants and personnel across the different studies. Second, the pooled CIs included the null, as well as appreciable benefit and harm. Third, the included trials were conducted for patients without VTE.

Other EtD criteria and considerations

The panel considered that aspirin discontinuation was probably feasible but that acceptability varies.

Conclusions and implementation considerations

Patients may be taking aspirin daily for prevention of CVD at the time of diagnosis with a VTE. For patients taking aspirin for primary prevention of CVD or for stable coronary artery disease, the ASH guideline panel provides a conditional recommendation in favor of suspending aspirin while taking anticoagulant therapy, based on a very low level of certainty in the evidence. For secondary prevention for patients with stable coronary artery disease, studies have found oral anticoagulants to be effective, with a decreased risk for bleeding compared with the combination of an anticoagulant and aspirin.³³⁰⁻³⁸ This recommendation does not apply to patients with a recent acute coronary event or coronary intervention. A similar approach has been advocated for patients who are taking anticoagulant therapy for atrial fibrillation who have concomitant CVD.³³⁹

Research needs relevant to this recommendation include studies to determine which patients should continue antiplatelet therapy when anticoagulant therapy is initiated for the treatment of VTE. In addition, research is needed to determine which anticoagulant agent(s) and dose(s) are safest when coadministered with antiplatelet therapy.

Recommendations 27 and 28

For patients with DVT, with (Recommendation 27) or without (Recommendation 28) increased risk for PTS, the ASH guideline panel *suggests against* the routine use of compression stockings (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks: Although the majority of patients may not benefit from the use of stockings to reduce the risk of PTS, stockings may help to reduce edema and pain associated with DVT in selected patients.

Summary of the evidence

We identified 10 systematic reviews³⁴⁰⁻³⁴⁹ and 6 relevant randomized trials^{260,350-354} ($n = 1393$). All of the identified trials, with the exception of the SOX trial, compared the use of stockings vs no stockings for patients with proximal DVT. Typically, the intervention group received an elastic stocking on the affected leg with an ankle pressure of 30 to 40 mm Hg for 6 to 24 months. Participants were followed for a period of 2 to 5 years and were periodically assessed for the development of PTS. The definition of PTS was variable in the different trials, although the Villalta scale³⁵⁵ was used most frequently. The sample size in the SOX trial³⁵³ ($n = 806$) was larger than in the rest of the trials, and patients with proximal DVT were randomized to elastic stockings with an ankle pressure of 30 to 40 mm Hg or to placebo stockings with an ankle pressure ≤ 5 mm Hg for 2 years. The investigators reported the incidence of PTS at the end of follow-up using different definitions, including the Villalta criteria. The EtD framework is shown online at: <https://guidelines.gradepro.org/profile/88899593-89FA-D803-95A0-B9E113F2B50D> (Recommendation 27) and <https://guidelines.gradepro.org/profile/77202CC8-4CE2-DE7B-8EFF-96F7C0E80DFD> (Recommendation 28).

Benefits

The use of compression stockings has a negligible effect on mortality (RR, 0.99; 95% CI, 0.72-1.36; ARR, 0 fewer per 1000

patients; 95% CI, 13 fewer to 17 more; moderate-certainty evidence). We did observe a nonsignificant reduction in the risk of PE (RR, 0.72; 95% CI, 0.31-1.70; ARR, 4 fewer per 1000 patients; 95% CI, 10 fewer to 10 more; low-certainty evidence); however, this outcome was reported in only 1 trial, and the number of events was very small.

Pooling all identified trials, we observed a nonsignificant reduction in the risk of PTS (RR, 0.62; 95% CI, 0.38-1.01; ARR, 81 fewer per 1000 patients; 95% CI, 132 fewer to 2 more; very-low certainty evidence). However, when we considered only the trials with a low risk for bias, this potential benefit was not observed (RR, 1.01; 95% CI, 0.76-1.33). The same occurred with the risk of DVT. Pooling all trials, we observed a nonsignificant reduction in DVT (RR, 0.56; 95% CI, 0.12-2.70; ARR, 18 fewer per 1000 patients; 95% CI, 35 fewer to 68 more; low-certainty evidence), although this did not hold in the subgroup of trials with a low risk for bias (RR, 1.08; 95% CI, 0.69-1.71).

Harms and burden

We did not identify harmful effects of stockings. However, some patients may experience discomfort, skin breakdown, allergic reaction, or significant cost to acquire the stockings.

Certainty in the evidence of effects

The main limitations of the evidence identified were the risk of bias and the small number of patients studied (imprecision). The effect of compression stockings on PTS and DVT observed in the SOX trial was significantly different from the results of unblinded trials, as demonstrated by the tests for interaction.

Additionally, for all of the outcomes, the number of patients studied and number of events were relatively small, and the CI around the absolute estimates likely crossed the thresholds that patients would consider important.

Other EtD criteria and considerations

There is probably important variability in patients' preferences: although some may experience relief of pain and edema, compression of the leg may be associated with discomfort in others.

We did not find any economic evaluation assessing the cost utility of compression stockings, although we considered that maintaining stockings for a long period of time implied a moderate cost.

Finally, stockings are generally available, although they may not be acceptable for some patients and providers given the uncertainty regarding their effect.

Conclusions and implementation considerations

PTS may develop in up to 30% to 50% of patients following the development of proximal DVT,^{149,150} and it may be severe in 5% to 10% of patients.^{3,150} Some patients may experience symptomatic benefit from wearing compression stockings but, as noted above, there was inconsistent evidence that compression stockings can decrease the risk of developing PTS. Consequently, given the very low level of certainty in the evidence, the ASH guideline panel *suggests against* the routine use of compression stockings for patients with DVT, with or without an increased risk for PTS. Research priorities should focus on the identification of the subsets of patients who would potentially benefit from the use of compression stockings.

What are others saying, and what is new?

There are 4 recent guideline documents concerning the management of patients with VTE. The 2016 guideline and expert panel report on antithrombotic therapy for VTE from the American College of Chest Physicians (ACCP)³⁵⁶ is an update of the 2012 ACCP guidelines.³¹² A second guidance document on the treatment of VTE, endorsed by the Anticoagulation Forum (ACF) Board of Directors, was also published in 2016.³⁵⁷ The European Society of Cardiology has published separate consensus documents on the diagnosis and management of DVT³⁵⁸ and PE.²³⁸ Differences between the ASH guidelines and these documents 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.

As with prior guidelines, the ASH guideline panel has given considerable thought to distinguishing the primary treatment phase of VTE (first 3-6 months) from the secondary prevention phase (indefinite duration following the primary treatment phase; Figure 2). Important decisions concerning which patients should receive indefinite preventive therapy following completion of the primary treatment phase, as well as what antithrombotic therapy should be administered, must have these unique phases of treatment clearly defined. Prior terminology has been confusing, with the primary treatment phase described as “long term” in the 2016 ACCP guidelines and “short term” in the 2016 ACF guidance document; the secondary prevention phase is referred to as “extended” in the 2016 ACCP guidelines and “long term” in the 2016 ACF guidance document. Our choice of terminology reflects the distinct clinical intention of the 2 phases of VTE management, rather than terms reflecting the relative duration of therapy.

New questions addressed in the ASH guidelines include recommendations concerning whether 1 DOAC should be preferred over another for the primary treatment phase (Recommendation 4), whether prognostic scores, D-dimer testing, and/or ultrasound testing should be routinely used to guide decision making concerning continuing therapy after completion of the primary phase of treatment (Recommendations 15 to 17), whether patients receiving rivaroxaban or apixaban for secondary prevention therapy should receive standard-dose or lower-dose therapy (Recommendation 22), and whether patients who have previously sustained a VTE and completed a course of primary treatment, who now sustain a recurrent event associated with a transient risk factor, should receive secondary prevention after completion of the primary treatment phase of therapy (Recommendations 24a and 24b). The ASH guidelines also address the question of whether aspirin should be continued or discontinued during anticoagulation in those patients who sustain a VTE while taking aspirin (Recommendation 26).

The ASH guidelines incorporate the most recent systematic reviews, RCTs, and observational studies, as well as information concerning cost of interventions and health equity, in the final recommendations that have been generated. When appropriate, the panel has also provided suggestions for areas in which future research is needed to address questions important to patients with VTE and their providers.

Limitations of these guidelines

Treatment of VTE in day-to-day practice poses many challenges to clinicians. We acknowledge that not all of them are covered in this guideline. However, the guideline model implemented by ASH can

be easily updated in the future, adding new recommendations to those already published.

Panelists recommended or suggested courses of action based on the evidence available at the moment of development of this guideline. However, new evidence may change the recommendations in the future, especially those based on low- or very-low-certainty evidence.

Finally, the recommendations are meant to inform the decisions of clinicians and patients. They do not, however, replace the careful consideration of the specific clinical circumstances and patients' values and preferences.

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.

Adapting recommendations locally

Although ASH guidelines have a global scope, the recommendations in this article were developed primarily for North America. Likely, resource considerations, feasibility, and acceptability of interventions may vary in different regions.

The “Adolopment” model of guideline adoption, adaptation, and development³⁵⁹ offers an approach to adapt the recommendations of this article to a specific context, taking advantage of the EtD frameworks accompanying each recommendation. Local guideline groups may reuse the evidence collected and appraised on the frameworks. By adding relevant local information, they can generate local recommendations with fewer resources than those required to develop a guideline *de novo*.

Acknowledgment

The authors thank Andrew Kirkman for contributions to the guideline document.

Authorship

Contribution: T.L.O., I.N., and Yuqing Zhang wrote the first draft of this manuscript and revised the manuscript based on authors' suggestions; guideline panel members W.A., R.B., N.P.C., A.C., B.A.H., M.R.J., V.M., S.S., C.T., S.V., P.V., and D.M.W., critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team, I.D.F., A.I., R.N., S.R., H.J.S., W.W., Yuan Zhang, and Yuqing Zhang, contributed evidence summaries to the guidelines; all authors approved of the content; and T.L.O. was chair and I.N. was vice chair of the panel and led the panel meeting.

Conflict-of-interest disclosure: All authors were members of the guideline panel, the systematic review team, or both. They completed disclosure-of interest-forms, which were reviewed by ASH and are available as Supplements 2 and 3. The following disclosure was added after the finalization of the guideline panel's disclosure of interest forms: In January 2020, M.R.J. became part-time chief medical officer for Boston Scientific, for which he receives salary and equity. Embolitech was sold to Surmodics, for which M.R.J. received equity.

ORCID profiles: T.L.O., 0000-0001-6193-4585; R.B., 0000-0003-1727-1133; N.P.C., 0000-0002-9289-7710; A.C., 0000-0002-3595-5697; B.A.H., 0000-0002-9243-0037; M.R.J., 0000-0002-3772-5887; V.M., 0000-0003-0410-8089; D.M.W., 0000-

References

1. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005; 172(8):1041-1046.
2. Jiménez D, Aujesky D, Moores L, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;170(15):1383-1389.
3. Baldwin MJ, Moore HM, Rudarakanchana N, Gohel M, Davies AH. Post-thrombotic syndrome: a clinical review. *J Thromb Haemost*. 2013;11(5): 795-805.
4. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12(8):464-474.
5. Delluc A, Le Mao R, Tromeur C, et al. Incidence of upper-extremity deep vein thrombosis in western France: a community-based study. *Haematologica*. 2019;104(1):e29-e31.
6. Grant JD, Stevens SM, Woller SC, et al. Diagnosis and management of upper extremity deep-vein thrombosis in adults. *Thromb Haemost*. 2012;108(6): 1097-1108.
7. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. 2004;117(1):19-25.
8. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med*. 2014;127(9):829-839.e5.
9. Tagalakos V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med*. 2013;126(9):832.e13-832.e21.
10. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet*. 2003;362(9383):523-526.
11. Boutilier F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ*. 2011;342:d3036.
12. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica*. 2007;92(2):199-205.
13. Rabinovich A, Kahn SR. How I treat the postthrombotic syndrome. *Blood*. 2018;131(20):2215-2222.
14. Pengo V, Lensing AW, Prins MH, et al; Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350(22):2257-2264.
15. Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. *Blood*. 2019;133(5):425-435.
16. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.
17. Zakai NA, McClure LA, Judd SE, et al. Racial and regional differences in venous thromboembolism in the United States in 3 cohorts. *Circulation*. 2014; 129(14):1502-1509.
18. White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. *Ann Intern Med*. 1998;128(9):737-740.
19. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol*. 2000;85(11): 1334-1337.
20. Alonso-Coello P, Oxman AD, Moher 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.
21. Alonso-Coello P, Schünemann HJ, Moher 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. Schünemann H. Principles for Disclosure of Interests and Management of Conflicts in Guidelines: Desirable and Undesirable Action and Consequences. *Ann Intern Med*. 2016;164(10):702.

27. Graham RMM, Wolman DM, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2012
28. 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.
29. Othieno R, Okpo E, Forster R. Home versus in-patient treatment for deep vein thrombosis. *Cochrane Database Syst Rev*. 2018;1:CD003076.
30. Boccalon H, Elias A, Chalé JJ, Cadène A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. *Arch Intern Med*. 2000;160(12):1769-1773.
31. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH; ASTH DVT Study Group. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis*. 2005;19(3):173-181.
32. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg*. 2005;29(6):638-650.
33. Koopman MM, Prandoni P, Piovella F, et al; The Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med*. 1996;334(11):682-687.
34. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med*. 1996;334(11):677-681.
35. Ramacciotti E, Araújo GR, Lastoria S, et al; CLETRAT Investigators. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb Res*. 2004;114(3):149-153.
36. Romera-Villegas A, Cairols-Castellote MA, Vila-Coll R, et al. Early mobilisation in patients with acute deep vein thrombosis does not increase the risk of a symptomatic pulmonary embolism. *Int Angiol*. 2008;27(6):494-499.
37. Lozano F, Trujillo-Santos J, Barrón M, et al; RIETE Investigators. Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. *J Vasc Surg*. 2014;59(5):1362-1367.e1.
38. Rodger MA, Gagné-Rodger C, Howley HE, Carrier M, Coyle D, Wells PS. The outpatient treatment of deep vein thrombosis delivers cost savings to patients and their families, compared to inpatient therapy. *Thromb Res*. 2003;112(1-2):13-18.
39. Spyropoulos AC, Frost FJ, Hurley JS, Roberts M. Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. *Chest*. 2004;125(5):1642-1650.
40. van den Belt AG, Bossuyt PM, Prins MH, Gallus AS, Büller HR; TASMAN Study Group. Replacing inpatient care by outpatient care in the treatment of deep venous thrombosis—an economic evaluation. *Thromb Haemost*. 1998;79(2):259-263.
41. Rodger M, Bredeson C, Wells PS, Beck J, Kearns B, Huebsch LB. Cost-effectiveness of low-molecular-weight heparin and unfractionated heparin in treatment of deep vein thrombosis. *CMAJ*. 1998;159(8):931-938.
42. Frank D, Blättler W. Comparison of ambulatory and inpatient treatment of acute deep venous thrombosis of the leg: subjective and economic aspects [in German]. *Schweiz Med Wochenschr*. 1998;128(36):1328-1333.
43. O'Brien B, Levine M, Willan A, et al. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. *Arch Intern Med*. 1999;159(19):2298-2304.
44. Santamaria A, Juárez S, Reche A, Gómez-Outes A, Martínez-González J, Fontcuberta J; ESFERA Investigators. Low-molecular-weight heparin, bemiparin, in the outpatient treatment and secondary prophylaxis of venous thromboembolism in standard clinical practice: the ESFERA Study. *Int J Clin Pract*. 2006;60(5):518-525.
45. Smith BJ, Weekley JS, Pilotto L, Howe T, Beven R. Cost comparison of at-home treatment of deep venous thrombosis with low molecular weight heparin to inpatient treatment with unfractionated heparin. *Intern Med J*. 2002;32(1-2):29-34.
46. Misky GJ, Manheim JC, Zehnder N, et al. Health care disparities in the acute management of venous thromboembolism based on insurance status in the U.S. *J Thromb Thrombolysis*. 2011;32(4):393-398.
47. Schneider D, Lilienfeld DE, Im W. The epidemiology of pulmonary embolism: racial contrasts in incidence and in-hospital case fatality. *J Natl Med Assoc*. 2006;98(12):1967-1972.
48. Agarwal S, Clark D III, Sud K, Jaber WA, Cho L, Menon V. Gender disparities in outcomes and resource utilization for acute pulmonary embolism hospitalizations in the United States. *Am J Cardiol*. 2015;116(8):1270-1276.
49. Hanemaaijer S, Sodihardjo F, Horikx A, et al. Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands. *Int J Clin Pharm*. 2015;37(6):1128-1135.
50. Douketis JD. Treatment of deep vein thrombosis: what factors determine appropriate treatment? *Can Fam Physician*. 2005;51:217-223.
51. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. *Eur Respir J*. 2013;42(1):134-144.
52. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. *Thromb Res*. 2013;132(5):515-519.
53. Squizzato A, Galli M, Dentali F, Ageno W. Outpatient treatment and early discharge of symptomatic pulmonary embolism: a systematic review. *Eur Respir J*. 2009;33(5):1148-1155.
54. Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review. *Ann Emerg Med*. 2012;60(5):651-662.e4.

55. Janjua M, Badshah A, Matta F, Danescu LG, Yaekoub AY, Stein PD. Treatment of acute pulmonary embolism as outpatients or following early discharge. A systematic review. *Thromb Haemost*. 2008;100(5):756-761.
56. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011;378(9785):41-48.
57. Peacock WF, Coleman CI, Diercks DB, et al. Emergency department discharge of pulmonary embolus patients. *Acad Emerg Med*. 2018;25(9):995-1003.
58. Beer JH, Burger M, Gretener S, Bernard-Bagattini S, Bounameaux H. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. *J Thromb Haemost*. 2003;1(1):186-187.
59. Rodríguez-Cerrillo M, Alvarez-Arcaya A, Fernández-Díaz E, Fernández-Cruz A. A prospective study of the management of non-massive pulmonary embolism in the home. *Eur J Intern Med*. 2009;20(6):598-600.
60. Siragusa S, Arcara C, Malato A, et al. Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. *Ann Oncol*. 2005;16(Suppl 4):iv136-iv139.
61. Peacock WF, Singer AJ. Reducing the hospital burden associated with the treatment of pulmonary embolism. *J Thromb Haemost*. 2019;17(5):720-736.
62. Adam SS, McDuffie JR, Ortel TL, Williams JW Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. *Ann Intern Med*. 2012;157(11):796-807.
63. Almutairi AR, Zhou L, Gellad WF, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants for atrial fibrillation and venous thromboembolism: a systematic review and meta-analyses. *Clin Ther*. 2017;39(7):1456-1478.e36.
64. Canadian Agency for Drugs and Technologies in Health. Rivaroxaban (Xarelto): treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK344331/>. Accessed 15 July 2020.
65. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA*. 2014;312(11):1122-1135.
66. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. *PLoS One*. 2015;10(12):e0144856.
67. Dentali F, Di Minno MN, Gianni M, Ambrosino P, Squizzato A, Ageno W. Non-vitamin K oral anticoagulants in patients with pulmonary embolism: a systematic review and meta-analysis of the literature. *Intern Emerg Med*. 2015;10(4):507-514.
68. Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Dentali F. Direct oral anticoagulants for the treatment of unprovoked venous thromboembolism: a meta-analysis of randomised controlled trials. *Blood Transfus*. 2015;13(3):391-395.
69. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. *BMJ*. 2012;345(7884):e7498.
70. Ganji R, Ala S, Aarabi M, Bagheri B, Salehifar E. Comparison of dabigatran vs. warfarin in acute venous thromboemboly: systematic review. *Iran J Pharm Res*. 2016;15(2):611-617.
71. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review. *Vasc Health Risk Manag*. 2014;10:627-639.
72. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, Suárez-Gea ML, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. *Thromb Res*. 2014;134(4):774-782.
73. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism - a systematic review with indirect comparisons [published correction appears in *Vasa*. 2014;43(6):477]. *Vasa*. 2014;43(5):353-364.
74. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg*. 2014;48(5):565-575.
75. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. *Thromb Res*. 2014;133(6):1145-1151.
76. Loffredo L, Perri L, Del Ben M, Angelico F, Violi F. New oral anticoagulants for the treatment of acute venous thromboembolism: are they safer than vitamin K antagonists? A meta-analysis of the interventional trials. *Intern Emerg Med*. 2015;10(4):499-506.
77. Mumoli N, Cei M, Pesavento R, Campanini M, Dentali F. Are direct oral anticoagulants equally effective in reducing deep vein thrombosis and pulmonary embolism? *Int J Cardiol*. 2015;187:645-647.
78. Petrov VI, Shatalova OV, Gorbatenko VS, Smuseva ON, Maslakov AS. Efficacy and safety of the new oral anticoagulants in the treatment of venous thromboembolic complications: meta-analysis. *Rational Pharmacotherapy in Cardiology*. 2016;12(1):31-39.
79. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. *Cochrane Database Syst Rev*. 2015;(6):CD010956.
80. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. *Cochrane Database Syst Rev*. 2015;(12):CD010957.
81. Senoo K, Kondo Y, Miyazawa K, Isogai T, Chun YH, Kobayashi Y. Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis. *J Cardiol*. 2017;69(5):763-768.
82. Tahir F, Riaz H, Riaz T, et al. The new oral anti-coagulants and the phase 3 clinical trials - a systematic review of the literature. *Thromb J*. 2013;11(1):18.

83. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost.* 2014; 12(3):320-328.
84. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood.* 2014;124(12):1968-1975.
85. Vedovati MC, Becattini C, Germini F, Agnelli G. Efficacy and safety of direct oral anticoagulants after pulmonary embolism: a meta-analysis. *Int J Cardiol.* 2014;177(2):601-603.
86. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013; 369(9):799-808.
87. Agnelli G, Gallus A, Goldhaber SZ, et al; ODIXa-DVT Study Investigators. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation.* 2007;116(2):180-187.
88. EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010; 363(26):2499-2510.
89. Botticelli Investigators, Writing Committee; Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemost.* 2008;6(8):1313-1318.
90. Hokusai-VTE Investigators; Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.
91. Buller HR, Lensing AW, Prins MH, et al; Einstein-DVT Dose-Ranging Study Investigators. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. *Blood.* 2008;112(6):2242-2247.
92. EINSTEIN-PE Investigators; Büller HR, Prins MH, Lensin AW, et al; Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.
93. Nakamura M, Nishikawa M, Komuro I, et al. Apixaban for the treatment of Japanese subjects with acute venous thromboembolism (AMPLIFY-J Study). *Circ J.* 2015;79(6):1230-1236.
94. Piazza G, Mani V, Goldhaber SZ, et al. Magnetic resonance venography to assess thrombus resolution with edoxaban monotherapy versus parenteral anticoagulation/warfarin for symptomatic deep vein thrombosis: a multicenter feasibility study. *Vasc Med.* 2016;21(4):361-368.
95. Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.
96. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352.
97. Yamada N, Hirayama A, Maeda H, et al. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE program [published correction appears in *Thromb J.* 2016;214:11]. *Thromb J.* 2015;13(1):2.
98. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med.* 2010;152(9):578-589.
99. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Real-world medical cost avoidance when new oral anticoagulants are used versus warfarin for venous thromboembolism in the United States. *Clin Appl Thromb Hemost.* 2016;22(1):5-11.
100. Amin A, Jing Y, Trocio J, Lin J, Lingohr-Smith M, Graham J. Evaluation of medical costs associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients. *J Med Econ.* 2014;17(11):763-770.
101. Margolis JM, Deitelzweig S, Kline J, et al. Pulmonary embolism inpatients treated with rivaroxaban had shorter hospital stays and lower costs compared with warfarin. *Clin Ther.* 2016;38(11):2496-2503.
102. Weeda ER, Kohn CG, Peacock WF, et al. Rivaroxaban versus heparin bridging to warfarin therapy: impact on hospital length of stay and treatment costs for low-risk patients with pulmonary embolism. *Pharmacotherapy.* 2016;36(10):1109-1115.
103. Courtney W, Groarke E, Conway J, et al. A direct oral anticoagulant as a cost effective alternative to warfarin for treatment of provoked venous thrombosis. *Ir Med J.* 2016;109(9):466.
104. Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R. Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. *Thromb J.* 2015;13(1):20.
105. Jimenez D, Jimenez S, Martinez-Lopez I, et al. Cost-effectiveness of rivaroxaban in the treatment of venous thromboembolism in Spain. *Pharmacoeconomics - Spanish Research Articles.* 2015;12(4):147-156.
106. Jugrin AV, Ustyugova A, Urbich M, Lamotte M, Sunderland T. The cost-utility of dabigatran etexilate compared with warfarin in treatment and extended anticoagulation of acute VTE in the UK. *Thromb Haemost.* 2015;114(4):778-792.
107. Lanitis T, Leipold R, Hamilton M, et al. Cost-effectiveness of apixaban versus other oral anticoagulants for the initial treatment of venous thromboembolism and prevention of recurrence. *Clin Ther.* 2016;38(3):478-493.e1-16.
108. Law S, Ghag D, Grafstein E, Stenstrom R, Harris D. A pharmacoeconomic study of traditional anticoagulation versus direct oral anticoagulation for the treatment of venous thromboembolism in the emergency department. *CJEM.* 2016;18(5):340-348.
109. Lefebvre P, Coleman CI, Bookhart BK, et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. *J Med Econ.* 2014;17(1):52-64.

110. Maervoet J, Verhamme P, Hainaut P, et al. Cost effectiveness of rivaroxaban versus low molecular weight heparin and vitamin K antagonists for the treatment of deep-vein thrombosis in the Belgian healthcare setting. *Eur J Cardiovasc Med*. 2015;3(1):452-461.
111. Preblich R, Kwong WJ, White RH, Goldhaber SZ. Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study. *Hosp Prac (1995)*. 2015;43(5):249-257.
112. Quon P, Le HH, Raymond V, Mtibaa M, Moshyk A. Clinical and economic benefits of extended treatment with apixaban for the treatment and prevention of recurrent venous thromboembolism in Canada. *J Med Econ*. 2016;19(6):557-567.
113. Rudakova AV. Cost-effectiveness of new oral anticoagulants in the treatment and secondary prevention of venous thromboembolism. *Rational Pharmacotherapy in Cardiology*. 2015;11(5):496-503.
114. Santos IF, Pereira S, McLeod E, Guillermin AL, Chatzitheofilou I. Economic analysis of rivaroxaban for the treatment and long-term prevention of venous thromboembolism in Portugal. *Acta Med Port*. 2014;27(5):615-624.
115. Seaman CD, Smith KJ, Ragni MV. Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: a U.S. perspective. *Thromb Res*. 2013;132(6):647-651.
116. Stevanovic J, De Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the treatment and secondary prevention of venous thromboembolism; a cost-effectiveness analysis for the Netherlands. *PLoS ONE*. 2016;11(10):e0163550.
117. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257-3291.
118. Millar CM, Laffan MA. Drug therapy in anticoagulation: which drug for which patient [published correction appears in *Clin Med (Lond)*. 2017;17(4):347-349]? *Clin Med (Lond)*. 2017;17(3):233-244.
119. Alesh I, Kayali F, Stein PD. Catheter-directed thrombolysis (intrathrombus injection) in treatment of deep venous thrombosis: a systematic review. *Catheter Cardiovasc Interv*. 2007;70(1):143-148.
120. Broholm R, Panduro Jensen L, Baekgaard N. Catheter-directed thrombolysis in the treatment of iliofemoral venous thrombosis. A review. *Int Angiol*. 2010;29(4):292-302.
121. Casey ET, Murad MH, Zumaeta-Garcia M, et al. Treatment of acute iliofemoral deep vein thrombosis. *J Vasc Surg*. 2012;55(5):1463-1473.
122. Du GC, Zhang MC, Zhao JC. Catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone in the treatment of proximal deep vein thrombosis - a meta-analysis. *Vasa*. 2015;44(3):195-202.
123. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med*. 1984;76(3):393-397.
124. Karthikesalingam A, Young EL, Hinchliffe RJ, Loftus IM, Thompson MM, Holt PJ. A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg*. 2011;41(4):554-565.
125. Ng CM, Rivera JO. Meta-analysis of streptokinase and heparin in deep vein thrombosis. *Am J Health Syst Pharm*. 1998;55(19):1995-2001.
126. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev*. 2016;(11):CD002783.
127. Elbasty A, Metcalf J. Safety and efficacy of catheter direct thrombolysis in management of acute iliofemoral deep vein thrombosis: a systematic review. *Vasc Specialist Int*. 2017;33(4):121-134.
128. Li W, Chuanlin Z, Shaoyu M, Yeh CH, Liqun C, Zeju Z. Catheter-directed thrombolysis for patients with acute lower extremity deep vein thrombosis: a meta-analysis. *Rev Lat Am Enfermagem*. 2018;26:e2990.
129. Thomas M, Hollingsworth A, Mofidi R. Endovascular management of acute lower limb deep vein thrombosis: a systematic review and meta-analysis. *Ann Vasc Surg*. 2019;58:363-370.
130. Arnesen H, Heilo A, Jakobsen E, Ly B, Skaga E. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. *Acta Med Scand*. 1978;203(6):457-463.
131. Common HH, Seaman AJ, Rösch J, Porter JM, Dotter CT. Deep vein thrombosis treated with streptokinase or heparin. Follow-up of a randomized study. *Angiology*. 1976;27(11):645-654.
132. Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. *Br J Surg*. 1979;66(12):838-843.
133. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg*. 2002;24(3):209-214.
134. Enden T, Haig Y, Kløw NE, et al; CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.
135. Goldhaber SZ, Hirsch DR, MacDougall RC, Polak JF, Creager MA. Bolus recombinant urokinase versus heparin in deep venous thrombosis: a randomized controlled trial. *Am Heart J*. 1996;132(2 Pt 1):314-318.
136. Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med*. 1990;88(3):235-240.
137. Kakkar VV, Flanc C, Howe CT, O'Shea M, Flute PT. Treatment of deep vein thrombosis. A trial of heparin, streptokinase, and arvin. *BMJ*. 1969;1(5647):806-810.
138. Kiil J, Carvalho A, Saksø P, Nielsen HO. Urokinase or heparin in the management of patients with deep vein thrombosis? *Acta Chir Scand*. 1981;147(7):529-532.

139. Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. *J Lab Clin Med*. 1977;89(5):1018-1029.
140. Schulman S, Granqvist S, Juhlin-Dannfelt A, Lockner D. Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase. *Acta Med Scand*. 1986;219(4):349-357.
141. Schweizer J, Elix H, Altmann E, Hellner G, Forkmann L. Comparative results of thrombolysis treatment with rt-PA and urokinase: a pilot study. *Vasa*. 1998;27(3):167-171.
142. Schweizer J, Kirch W, Koch R, et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol*. 2000;36(4):1336-1343.
143. Tsapogas MJ, Peabody RA, Wu KT, Karmody AM, Devaraj KT, Eckert C. Controlled study of thrombolytic therapy in deep vein thrombosis. *Surgery*. 1973;74(6):973-984.
144. Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Results of a randomized trial. *Chest*. 1990;97(4 suppl):172S-175S.
145. Ugurlu B, Kazaz H, Oto O, Hazan E, Sariosmanoğlu N. Low dose systemic thrombolytic therapy for treatment of deep venous thrombosis. *J Cardiovasc Surg (Torino)*. 2002;43(6):881-885.
146. Vedantham S, Goldhaber SZ, Julian JA, et al; ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377(23):2240-2252.
147. Verhaeghe R, Besse P, Bounameaux H, Marbet GA. Multicenter pilot study of the efficacy and safety of systemic rt-PA administration in the treatment of deep vein thrombosis of the lower extremities and/or pelvis. *Thromb Res*. 1989;55(1):5-11.
148. Su SF, Tian YF, Chen LB, Yan B. Comparison of therapeutic efficacy of anticoagulation and its combination with catheter-directed thrombolysis for deep venous thrombosis of lower extremities [in Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2017;25(5):1509-1513.
149. Roumen-Klappe EM, den Heijer M, Janssen MC, van der Vleuten C, Thien T, Wollersheim H. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. *Thromb Haemost*. 2005;94(4):825-830.
150. Kahn SR, Kearon C, Julian JA, et al; Extended Low-intensity Anticoagulation for Thrombo-embolism (ELATE) Investigators. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost*. 2005;3(4):718-723.
151. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. *Arch Intern Med*. 2002;162(22):2537-2541.
152. Anderson DR, Levine MN. Thrombolytic therapy for the treatment of acute pulmonary embolism. *CMAJ*. 1992;146(8):1317-1324.
153. Arcasoy SM, Kreit JW. Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. *Chest*. 1999;115(6):1695-1707.
154. Bloomer TL, El-Hayek GE, McDaniel MC, et al. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: results of a multicenter registry and meta-analysis. *Catheter Cardiovasc Interv*. 2017;89(4):754-760.
155. Cao Y, Zhao H, Gao W, Wang Y, Cao J. Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism. *Patient Prefer Adherence*. 2014;8:275-282.
156. Capstick T, Henry MT. Efficacy of thrombolytic agents in the treatment of pulmonary embolism. *Eur Resp J*. 2005;26(5):864-874.
157. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311(23):2414-2421.
158. Chen H, Ren C, Chen H. Thrombolysis versus anticoagulation for the initial treatment of moderate pulmonary embolism: a meta-analysis of randomized controlled trials. *Respir Care*. 2014;59(12):1880-1887.
159. Doornik DE, Schrijver AM, Zeebregts CJ, de Vries JP, Reijnen MM. Advancements in catheter-directed ultrasound-accelerated thrombolysis. *J Endovasc Ther*. 2011;18(3):418-434.
160. Gao GY, Yang P, Liu M, et al. Thrombolysis for acute intermediate-risk pulmonary embolism: a meta-analysis. *Thromb Res*. 2015;136(5):932-937.
161. Hao Q, Dong BR, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2018;(12):CD004437.
162. Harris T, Meek S. When should we thrombolysate patients with pulmonary embolism? A systematic review of the literature. *Emerg Med J*. 2005;22(11):766-771.
163. Liu Y, Lu Y, Song J, et al. Recombinant tissue plasminogen activator for hemodynamically stable patients experiencing an acute pulmonary embolism: a meta-analysis. *Thromb Res*. 2014;134(1):50-56.
164. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2015;36(10):605-614.
165. Mostafa A, Briasoulis A, Shokr M, Briasoulis AA, Panaich S, Grines C. Ultrasound accelerated thrombolysis in patients with acute pulmonary embolism: a systematic review and proportion meta-analysis. *Int J Cardiol*. 2016;211:27-30.
166. Nakamura S, Takano H, Kubota Y, Asai K, Shimizu W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. *J Thromb Haemost*. 2014;12(7):1086-1095.
167. Ramakrishnan N. Thrombolysis is not warranted in submassive pulmonary embolism: a systematic review and meta-analysis. *Crit Care Resusc*. 2007;9(4):357-363.
168. Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. *Thromb Res*. 2014;134(6):1265-1271.

169. Serra-Prat M, Jovell AJ, Aymerich M. Efficacy and safety of thrombolytic therapy in pulmonary embolism: meta-analysis of randomized controlled trials [in Spanish]. *Med Clin (Barc)*. 1999;112(18):685-689.
170. Tafur AJ, Shamoun FE, Patel SI, Tafur D, Donna F, Murad MH. Catheter-directed treatment of pulmonary embolism: a systematic review and meta-analysis of modern literature. *Clin Appl Thromb Hemost*. 2017;23(7):821-829.
171. Tardy B, Venet C, Zeni F, Coudrot M, Guyomarc'h S, Mismetti P. Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: results of a meta-analysis involving 464 patients. *Thromb Res*. 2009;124(6):672-677.
172. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. *J Am Coll Cardiol*. 2002;40(9):1660-1667.
173. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110(6):744-749.
174. Worster A, Smith C, Silver S, Brown MD. Evidence-based emergency medicine/critically appraised topic. Thrombolytic therapy for submassive pulmonary embolism? *Ann Emerg Med*. 2007;50(1):78-84.
175. Xu Q, Huang K, Zhai Z, Yang Y, Wang J, Wang C. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: a meta-analysis. *J Thorac Dis*. 2015;7(5):810-821.
176. Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. *Thromb Res*. 2014;133(3):357-363.
177. Jimenez D, Barbero E, Chiluiza D, et al. Efficacy of thrombolytic therapy in patients with massive pulmonary embolism: systematic review and meta-analysis [abstract]. *Am J Respir Crit Care Med*. 2020;201:A3783.
178. Lou BH, Wang LH, Chen Y. A meta-analysis of efficacy and safety of catheter-directed interventions in submassive pulmonary embolism. *Eur Rev Med Pharmacol Sci*. 2017;21(1):184-198.
179. Quezada CA, Bikdeli B, Barrios D, et al. Meta-analysis of prevalence and short-term prognosis of hemodynamically unstable patients with symptomatic acute pulmonary embolism. *Am J Cardiol*. 2019;123(4):684-689.
180. Becattini C, Agnelli G, Salvi A, et al; TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res*. 2010;125(3):e82-e86.
181. Dalla-Volta S, Palla A, Santolucando A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. *J Am Coll Cardiol*. 1992;20(3):520-526.
182. Dotter CT, Seaman AJ, Rösch J, Porter JM. Streptokinase and heparin in the treatment of pulmonary embolism: a randomized comparison. *Vasc Endovascular Surg*. 1979;13(1):42-52.
183. Fasullo S, Scalzo S, Maringhini G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. *Am J Med Sci*. 2011;341(1):33-39.
184. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341(8844):507-511.
185. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. *JAMA*. 1970;214(12):2163-2172.
186. Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. *Chest*. 1990;97(3):528-533.
187. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes García M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227-229.
188. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12(4):459-468.
189. Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol*. 2017;69(12):1536-1544.
190. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129(4):479-486.
191. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest*. 1990;98(6):1473-1479.
192. Liu LH, Lu SJ, Liu Z. The effect of thrombolysis and anticoagulation therapy in patients with sub-massive pulmonary embolism [in Chinese]. *Chongqing Med J*. 2013;42(11):1288-1290.
193. Lu WH, Tang ZZ, Ma Y, Zh Y. The effectiveness and long-term prognosis of thrombolysis plus anticoagulation therapy versus anticoagulation therapy alone in patients with sub-massive pulmonary embolism [in Chinese]. *Clin J Medical Officer*. 2008;36(3):340-342.
194. Marini C, Di Ricco G, Rossi G, Rindi M, Palla R, Giuntini C. Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: a randomized clinical trial. *Respiration*. 1989;54(3):162-173.
195. Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402-1411.
196. Ou YQ. Analysis of the therapeutic effect of urokinase plus sequential anticoagulation for the treatment of sub-massive pulmonary embolism [in Chinese]. *J Hainan Medical College*. 2012;18(7):897-898.
197. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol*. 2013;111(2):273-277.

198. Sun RQ. Efficacy of urokinase combined with low molecular weight heparin and warfarin for the treatment of sub-massive pulmonary embolism [in Chinese]. *Strait Pharmaceutical J.* 2012;24(5):130-131.
199. Taherkhani M, Taherkhani A, Hashemi SR, Faghihi Langroodi T, Sadeghi R, Beyranvand M. Thrombolytic-plus-anticoagulant therapy versus anticoagulant-alone therapy in submassive pulmonary thromboembolism (TVASPE Study): a randomized clinical trial. *J. Tehran Heart Center.* 2014;9(3):104-108.
200. Tibbitt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *BMJ.* 1974;1(5904):343-347.
201. Wei L, Sun FC. Curative effect of thrombolysis and anticoagulant therapy on submassive pulmonary embolism patients. *Int J Respir.* 2012;32(19):1471-1473.
202. Zhang XL, Jiang SH, Jiang LN, Shan FL, Li Z, Qin MH. The effectiveness of low-dose rt-PA thrombolysis in 26 elderly patients with acute sub-massive pulmonary embolism [in Chinese]. *Shandong Yiyao.* 2012;52(3):69-70.
203. Ahmed MA, Abdelsalam SI, Elmorsy RA. Value of thrombolytic therapy for submassive pulmonary embolism patients. *Egypt J Chest Dis Tuberc.* 2018;67(4):413-418.
204. Zhang LY, Gao BA, Jin Z, et al. Clinical efficacy of low dose recombinant tissue-type plasminogen activator for the treatment of acute intermediate-risk pulmonary embolism. *Saudi Med J.* 2018;39(11):1090-1095.
205. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation.* 2006;113(4):577-582.
206. Lin BW, Schreiber DH, Liu G, et al. Therapy and outcomes in massive pulmonary embolism from the Emergency Medicine Pulmonary Embolism in the Real World Registry. *Am J Emerg Med.* 2012;30(9):1774-1781.
207. Kabrhel C, Rosovsky R, Channick R, et al. A multidisciplinary pulmonary embolism response team: initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism. *Chest.* 2016;150(2):384-393.
208. Xenos ES, Davis GA, He Q, Green A, Smyth SS. The implementation of a pulmonary embolism response team in the management of intermediate- or high-risk pulmonary embolism. *J Vasc Surg Venous Lymphat Disord.* 2019;7(4):493-500.
209. Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis [published correction appears in *J Thromb Thrombolysis.* 2019;47(1):41]. *J Thromb Thrombolysis.* 2019;47(1):31-40.
210. Laporte S, Mismetti P, Décousus H, et al; RIETE Investigators. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation.* 2008;117(13):1711-1716.
211. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* 1999;353(9162):1386-1389.
212. Zheng JJ, Zhang ZH, Shan Z, et al. Catheter-directed thrombolysis in the treatment of acute deep venous thrombosis: a meta-analysis. *Genet Mol Res.* 2014;13(3):5241-5249.
213. Robertson L, McBride O, Burdess A. Pharmacomechanical thrombectomy for iliofemoral deep vein thrombosis. *Cochrane Database Syst Rev.* 2016;(11):CD011536.
214. Gong Y, Gu Y, Chen Z, Yu Z, Lv J. Thrombolysis for the treatment of lower extremities deep vein thrombosis [in Chinese]. *J. Chinese Physician.* 2005;7(8):1101.
215. Yu X, Zhou C, Chen X. Using interventional urokinase thrombolysis for the treatment of low extremities deep vein thrombosis [in Chinese]. *J Southern Medical University.* 2009;9:1930-1931.
216. Zhang X, Ren Q, Jiang X, et al. A prospective randomized trial of catheter-directed thrombolysis with additional balloon dilatation for iliofemoral deep venous thrombosis: a single-center experience. *Cardiovasc Intervent Radiol.* 2014;37(4):958-968.
217. Luo Q, Zeng Q. Clinical study of venous filter implantation combined with catheterization thrombolytic therapy for deep vein thrombosis [in Chinese]. *Jiangxi Med J.* 2011;46(4):303-306.
218. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol.* 2009;20(11):1431-1440.
219. Macovei L, Presura RM, Arsenescu Georgescu C. Systemic or local thrombolysis in high-risk pulmonary embolism. *Cardiol J.* 2015;22(4):467-474.
220. Liang NL, Avgerinos ED, Singh MJ, Makaroun MS, Chaer RA. Systemic thrombolysis increases hemorrhagic stroke risk without survival benefit compared with catheter-directed intervention for the treatment of acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord.* 2017;5(2):171-176.e1.
221. Patel P, Arora S, Lahewala S, et al. Thrombolysis (catheter directed/systemic) in pulmonary embolism: predictors and etiologies of readmissions. *Circulation.* 2016;134(suppl 1). Abstract 15283.
222. Geller Bram J, Adusumalli S, Yang L, Groeneveld Peter W, Giri J. Catheter directed thrombolysis versus systemic thrombolysis for the treatment of pulmonary embolism. *Circulation.* 2017;136(suppl 1). Abstract 18461.
223. Chung J, Owen RJ. Using inferior vena cava filters to prevent pulmonary embolism. *Can Fam Physician.* 2008;54(1):49-55.
224. Deso SE, Idakoji IA, Kuo WT. Evidence-based evaluation of inferior vena cava filter complications based on filter type. *Semin Intervent Radiol.* 2016;33(2):93-100.
225. Fox MA, Kahn SR. Postthrombotic syndrome in relation to vena cava filter placement: a systematic review. *J Vasc Interv Radiol.* 2008;19(7):981-985.
226. Garcia D, Ansari M, Cardoso R, et al. Clinical outcomes of retrievable inferior vena cava filter plus anticoagulation versus anticoagulation alone on high-risk patients: a meta-analysis. *J Am Coll Cardiol.* 2016;67(13 suppl):2267.

227. Jiang J, Jiao Y, Zhang X. The short-term efficacy of vena cava filters for the prevention of pulmonary embolism in patients with venous thromboembolism receiving anticoagulation: meta-analysis of randomized controlled trials. *Phlebology*. 2017;32(9):620-627.
228. Wang SL, Lloyd AJ. Clinical review: inferior vena cava filters in the age of patient-centered outcomes. *Ann Med*. 2013;45(7):474-481.
229. Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. *Cochrane Database Syst Rev*. 2010;(2):CD006212.
230. Decousus H, Leizorovicz A, Parent F, et al; Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med*. 1998;338(7):409-415.
231. Mismetti P, Laporte S, Pellerin O, et al; PREPIC2 Study Group. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627-1635.
232. Bertoletti L, Quenet S, Laporte S, et al; RIETE Investigators. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. *Respir Res*. 2013;14(1):75.
233. Otero R, Trujillo-Santos J, Cayuela A, et al; Registro Informatizado de la Enfermedad Tromboembólica (RIETE) Investigators. Haemodynamically unstable pulmonary embolism in the RIETE Registry: systolic blood pressure or shock index? *Eur Respir J*. 2007;30(6):1111-1116.
234. Brown PP, Peyton MD, Elkins RC, Greenfield LJ. Experimental comparison of a new intracaval filter with the Mobin-Uddin umbrella device. *Circulation*. 1974;50(2 suppl):II272-II276.
235. Schulman S, Rhedin AS, Lindmarker P, et al; Duration of Anticoagulation Trial Study Group. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med*. 1995;332(25):1661-1665.
236. Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost*. 1995;74(2):606-611.
237. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA; Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14(7):1480-1483.
238. Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603.
239. Rollins BM, Silva MA, Donovan JL, Kanaan AO. Evaluation of oral anticoagulants for the extended treatment of venous thromboembolism using a mixed-treatment comparison, meta-analytic approach. *Clin Ther*. 2014;36(10):1454-64.e3.
240. Gómez-Outes A, Lecumberri R, Suárez-Gea ML, Terleira-Fernández AI, Monreal M, Vargas-Castrillón E. Case fatality rates of recurrent thromboembolism and bleeding in patients receiving direct oral anticoagulants for the initial and extended treatment of venous thromboembolism: a systematic review. *J Cardiovasc Pharmacol Ther*. 2015;20(5):490-500.
241. Cundiff DK. Clinical evidence for rebound hypercoagulability after discontinuing oral anticoagulants for venous thromboembolism. *Medscape J Med*. 2008;10(11):258.
242. Simes J, Becattini C, Agnelli G, et al; INSPIRE Study Investigators (International Collaboration of Aspirin Trials for Recurrent Venous Thromboembolism). Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation*. 2014;130(13):1062-1071.
243. Streiff MB, Segal JB, Tamariz LJ, et al. Duration of vitamin K antagonist therapy for venous thromboembolism: a systematic review of the literature. *Am J Hematol*. 2006;81(9):684-691.
244. Sindet-Pedersen C, Pallisgaard JL, Olesen JB, Gislason GH, Arevalo LC. Safety and efficacy of direct oral anticoagulants compared to warfarin for extended treatment of venous thromboembolism -a systematic review and meta-analysis. *Thromb Res*. 2015;136(4):732-738.
245. Middeldorp S, Prins MH, Hutten BA. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. *Cochrane Database Syst Rev*. 2014;(8):CD001367.
246. Marik PE, Cavallazzi R. Extended anticoagulant and aspirin treatment for the secondary prevention of thromboembolic disease: a systematic review and meta-analysis. *PLoS One*. 2015;10(11):e0143252.
247. Pinede L, Duhaut P, Cucherat M, Ninet J, Pasquier J, Boissel JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. *J Intern Med*. 2000;247(5):553-562.
248. Sobieraj DM, Coleman CI, Pasupuleti V, Deshpande A, Kaw R, Hernandez AV. Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis. *Thromb Res*. 2015;135(5):888-896.
249. Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. *JAMA*. 2005;294(6):706-715.
250. Castellucci LA, Le Gal G, Rodger MA, Carrier M. Major bleeding during secondary prevention of venous thromboembolism in patients who have completed anticoagulation: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(3):344-348.
251. Bova C, Bianco A, Mascaro V, Nobile CG. Extended anticoagulation and mortality in venous thromboembolism. A meta-analysis of six randomized trials. *Thromb Res*. 2016;139:22-28.
252. Cohen AT, Hamilton M, Bird A, et al. Comparison of the non-VKA oral anticoagulants apixaban, dabigatran, and rivaroxaban in the extended treatment and prevention of venous thromboembolism: systematic review and network meta-analysis [published correction appears in *PLoS One*. 2016;11(9):e0168836]. *PLoS One*. 2016;11(8):e0160064.
253. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ*. 2013;347:f5133.

254. Sardar P, Chatterjee S, Mukherjee D. Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials. *Drugs*. 2013;73(11):1171-1182.
255. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg*. 2014;48(5):565-575.
256. Alotaibi G, Alsaleh K, Wu C, McMurtry MS. Dabigatran, rivaroxaban and apixaban for extended venous thromboembolism treatment: network meta-analysis. *Int Angiol*. 2014;33(4):301-308.
257. Holley AB, King CS, Jackson JL, Moores LK. Different finite durations of anticoagulation and outcomes following idiopathic venous thromboembolism: a meta-analysis. *Thrombosis*. 2010;2010:540386.
258. Agnelli G, Prandoni P, Becattini C, et al; Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med*. 2003;139(1):19-25.
259. Agnelli G, Prandoni P, Santamaria MG, et al; Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med*. 2001;345(3):165-169.
260. Belcaro G, Laurora G, Cesarone MR, De Sanctis MT. Prophylaxis of recurrent deep venous thrombosis. A randomized, prospective study using indobufen and graduated elastic compression stockings. *Angiology*. 1993;44(9):695-699.
261. Couturaud F, Sanchez O, Pernod G, et al; PADIS-PE Investigators. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE Randomized Clinical Trial. *JAMA*. 2015;314(1):31-40.
262. Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S; AUREC-FVIII investigators. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. *Ann Hematol*. 2009;88(5):485-490.
263. Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? *Saudi Med J*. 2004;25(7):848-851.
264. Schulman S, Lockner D, Juhlin-Dannfelt A. The duration of oral anticoagulation after deep vein thrombosis. A randomized study. *Acta Med Scand*. 1985; 217(5):547-552.
265. Schulman S, Wähländer K, Lundström T, Clason SB, Eriksson H; THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349(18):1713-1721.
266. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood*. 2008;112(3):511-515.
267. Vitovec M, Golán L, Roztocil K, Linhart A. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. *Vasa*. 2009;38(3):238-244.
268. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med*. 2010;170(19):1710-1716.
269. Lecumberri R, Alfonso A, Jiménez D, et al; RIETE investigators. Dynamics of case-fatality rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism. *Thromb Haemost*. 2013;110(4):834-843.
270. Coleman CI, Limone BL, Bookhart BK, Mody SH, Nutescu EA. Cost-effectiveness analysis of extended duration anticoagulation with rivaroxaban to prevent recurrent venous thromboembolism. *Thromb Res*. 2014;133(5):743-749.
271. Nguyen GC, Bernstein CN. Duration of anticoagulation for the management of venous thromboembolism in inflammatory bowel disease: a decision analysis. *Am J Gastroenterol*. 2013;108(9):1486-1495.
272. Aujesky D, Smith KJ, Roberts MS. Oral anticoagulation strategies after a first idiopathic venous thromboembolic event. *Am J Med*. 2005;118(6):625-635.
273. Bamber L, Wang MY, Prins MH, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. *Thromb Haemost*. 2013;110(4):732-741.
274. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179(5):417-426.
275. Ensor J, Riley RD, Moore D, Snell KI, Bayliss S, Fitzmaurice D. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. *BMJ Open*. 2016;6(5):e011190.
276. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna Prediction Model. *Circulation*. 2010;121(14):1630-1636.
277. Eichinger S, Heinze G, Kyrle PA. Risk assessment model to predict recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism [abstract]. *Blood*. 2009;114(22). Abstract 452.
278. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna prediction model. *J Thromb Haemost*. 2013;11:115.
279. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna prediction model. *J Am Heart Assoc*. 2014;3(1):e000467.
280. Ensor J, Riley RD, Jowett S, et al; PIT-STOP collaborative group. Prediction of risk of recurrence of venous thromboembolism following treatment for a first unprovoked venous thromboembolism: systematic review, prognostic model and clinical decision rule, and economic evaluation. *Health Technol Assess*. 2016;20(12):i-xxiii, 1-190.
281. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna Prediction Model. *Blood*. 2013;122(21):462.

282. Lazo-Langner A, Abdulrehman J, Taylor EJ, Sharma S, Kovacs MJ. The use of the REVERSE study clinical prediction rule for risk stratification after initial anticoagulation results in decreased recurrences in patients with idiopathic venous thromboembolism. *J Thromb Haemost.* 2013;11:879.
283. Marcucci M, Eichinger S, Iorio A, et al. External validation and updating of the Vienna Prediction Model for recurrent venous thromboembolism using a pooled individual patient data database. *J Thromb Haemost.* 2013;11:879-880.
284. ClinicalTrials.gov. Clinical decision rule validation study to predict low recurrent risk in patients with unprovoked venous thromboembolism (REVERSEII). Identifier NCT00967304. <https://clinicaltrials.gov/ct2/show/NCT00967304>. Accessed 15 July 2020.
285. Raskob GE, Anthonie LWA, Prins MH, Schellong S, Buller HR. Risk assessment for recurrent venous thromboembolism (VTE) after 6-14 months of anticoagulant treatment. *J Thromb Haemost.* 2011;9:857-858.
286. Rodger M, Kovacs M, Le Gal G, Anderson D, Righini M, Beaudoin T. The REVERSE I and II studies: impact of using the Men continue and HERDOO2 clinical decision rule to guide anticoagulant therapy in patients with first unprovoked venous thromboembolism. *J Thromb Haemost.* 2013;11:114.
287. Rodger M, Kovacs MJ, Kahn S, et al. Extended follow-up of the multi-center multi-national prospective cohort study that derived the "Men Continue and HERDOO2" clinical decision rule which identifies low risk patients who may be able to discontinue oral anticoagulants (Oac) 5-7 months after treatment for unprovoked venous thromboembolism (VTE) [abstract]. *Blood.* 2009;114(22). Abstract 451.
288. Rodger MA, Rodger M, Kovacs M. Extended follow-up of the multi-center prospective cohort that derived the 'men continue and HERDOO2' clinical decision rule identifying low risk unprovoked patients. *J Thromb Haemost.* 2011;9:39-40.
289. Tositto A, Iorio A, Marcucci M. Clinical prediction of VTE recurrence in patients with previous unprovoked venous thromboembolism. Results from an individual-level meta-analysis. *Pathophysiol Haemost Thromb.* 2010.
290. Tositto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: the DASH prediction score. *Blood.* 2011;118(21):544.
291. Tositto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost.* 2012;10(6):1019-1025.
292. Tositto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S. Clinical prediction guide to predict thrombosis recurrence after a first unprovoked venous thromboembolism. *J Thromb Haemost.* 2009.
293. Netherlands Trial Register. Cost-effectiveness of tailoring anticoagulant therapy by a VTE recurrence prediction model in patients with venous thromboembolism as compared to care-as-usual: The VISTA study. Trial NL2562 (NTR2680). <https://www.trialregister.nl/trial/2562>. Accessed 15 July 2020.
294. Bruinroop E, Klok FA, Van De Ree MA, Oosterwijk FL, Huisman MV. Elevated D-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: a meta-analysis. *J Thromb Haemost.* 2009;7(4):611-618.
295. Douketis J, Tositto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *BMJ.* 2011;342:d813.
296. Douketis J, Tositto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med.* 2010;153(8):523-531.
297. Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med.* 2008;149(7):481-490, W494.
298. Palareti G, Cosmi B, Legnani C, et al; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355(17):1780-1789.
299. Carrier M, Rodger MA, Wells PS, Righini M, Le Gal G. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost.* 2011;9(6):1119-1125.
300. Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. *Thromb Haemost.* 2014;111(1):172-179.
301. Janakiram M, Sullivan M, Shcherba M, Guo S, Billett HH. A systematic review of the utility of residual vein obstruction studies in primary and secondary venous thrombosis. *Thrombosis.* 2013;2013:247913.
302. Stephenson EJ, Liem TK. Duplex imaging of residual venous obstruction to guide duration of therapy for lower extremity deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2015;3(3):326-332.
303. Tan M, Mos IC, Klok FA, Huisman MV. Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review. *Br J Haematol.* 2011;153(2):168-178.
304. Prandoni P, Prins MH, Lensing AW, et al; AESOPUS Investigators. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med.* 2009;150(9):577-585.
305. Rodger MA, Le Gal G, Anderson DR, et al; REVERSE II Study Investigators. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. *BMJ.* 2017;356:j1065.
306. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708.
307. Ridker PM, Goldhaber SZ, Danielson E, et al; PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;348(15):1425-1434.
308. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med.* 1999;340(12):901-907.

309. Becattini C, Agnelli G, Schenone A, et al; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366(21):1959-1967.
310. Schulman S, Kearon C, Kakkar AK, et al; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709-718.
311. Locadia M, Bossuyt PM, Stalmeier PF, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. *Thromb Haemost*. 2004;92(6):1336-1341.
312. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e419S-e496S.
313. Hansson PO, Sörbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med*. 2000;160(6):769-774.
314. Weitz JI, Lensing AWA, Prins MH, et al; EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222.
315. Brighton TA, Eikelboom JW, Mann K, et al; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367(21):1979-1987.
316. Kearon C, Ginsberg JS, Kovacs MJ, et al; Extended Low-Intensity Anticoagulation for Thrombo-Embolic Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349(7):631-639.
317. Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358(26):2765-2775.
318. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363(26):2487-2498.
319. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776-2786.
320. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807-815.
321. Neumann I, Rada G, Claro JC, et al. Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(10):710-719.
322. Schulman S. How I treat recurrent venous thromboembolism in patients receiving anticoagulant therapy. *Blood*. 2017;129(25):3285-3293.
323. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv*. 2018;2(22):3360-3392.
324. van der Hulle T, Tan M, den Exter PL, et al. Recurrence risk after anticoagulant treatment of limited duration for late, second venous thromboembolism. *Haematologica*. 2015;100(2):188-193.
325. Altman R, Bouillon F, Rouvier J, Raca R, de la Fuente L, Favaloro R. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. *J Thorac Cardiovasc Surg*. 1976;72(1):127-129.
326. Casais P, Meschengieser SS, Sanchez Luceros AG, Bermejo EI, Lazzari MA. Effect of low-dose aspirin on the international normalized ratio variability in patients with mechanical heart valve prostheses. *Pathophysiol Haemost Thromb*. 2002;32(4):155-157.
327. Dale J, Myhre E, Storstein O, Stormorken H, Efskind L. Prevention of arterial thromboembolism with acetylsalicylic acid. A controlled clinical study in patients with aortic ball valves. *Am Heart J*. 1977;94(1):101-111.
328. Farah E, Cadilhac M, Boubaker A, Starkman C, Acar J. Thromboembolic risk in prosthetic valve carriers. Prevention trial. *Scand J Haematol Suppl*. 1981;38:97-119.
329. Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial Fibrillation Aspirin and Anticoagulation. *Arch Intern Med*. 1999;159(12):1322-1328.
330. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347(13):969-974.
331. Huynh T, Thérout P, Bogaty P, Nasimith J, Solymoss S. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. *Circulation*. 2001;103(25):3069-3074.
332. Laffort P, Roudaut R, Roques X, et al. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol*. 2000;35(3):739-746.
333. Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg*. 1997;113(5):910-916.
334. Mirhosseini SJ, Forouzannia SK, Mostafavi Pour Manshadi SM, Ali-Hasan-Al-Saegh S, Naderi N, Sanatkar M. Comparison of aspirin plus heparin with heparin alone on asymptomatic perioperative deep vein thrombosis in candidates for elective off-pump coronary artery bypass graft: a randomized clinical trial. *Cardiol J*. 2013;20(2):139-143.
335. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet*. 1998;351(9098):233-241.

336. Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329(8):524-529.
337. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet*. 2002;360(9327):109-113.
338. Lee SR, Rhee TM, Kang DY, Choi EK, Oh S, Lip GYH. Meta-analysis of oral anticoagulant monotherapy as an antithrombotic strategy in patients with stable coronary artery disease and nonvalvular atrial fibrillation. *Am J Cardiol*. 2019;124(6):879-885.
339. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;50(5):e1-e88.
340. Berntsen CF, Kristiansen A, Akl EA, et al. Compression stockings for preventing the postthrombotic syndrome in patients with deep vein thrombosis. *Am J Med*. 2016;129(4):447.e1-447.e20.
341. Burgstaller JM, Steurer J, Held U, Amann-Vesti B. Efficacy of compression stockings in preventing post-thrombotic syndrome in patients with deep venous thrombosis: a systematic review and metaanalysis. *Vasa*. 2016;45(2):141-147.
342. Giannoukas AD, Labropoulos N, Michaels JA. Compression with or without early ambulation in the prevention of post-thrombotic syndrome: a systematic review. *Eur J Vasc Endovasc Surg*. 2006;32(2):217-221.
343. Jin YW, Ye H, Li FY, Xiong XZ, Cheng NS. Compression stockings for prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Vasc Endovascular Surg*. 2016;50(5):328-334.
344. Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, Nicolaides AN, Geroulakos G. Review on the value of graduated elastic compression stockings after deep vein thrombosis. *Thromb Haemost*. 2006;96(4):441-445.
345. Musani MH, Matta F, Yaekoub AY, Liang J, Hull RD, Stein PD. Venous compression for prevention of postthrombotic syndrome: a meta-analysis. *Am J Med*. 2010;123(8):735-740.
346. Perrin M, Eklöf B. Does prescription of medical compression prevent development of post-thrombotic syndrome after proximal deep venous thrombosis? *Phlebology*. 2016;31(3):160-169.
347. Skervin AL, Thapar A, Franchini AJ, Prandoni P, Shalhoub J, Davies AH. Systematic review and meta-analysis of utility of graduated compression stockings in prevention of post-thrombotic syndrome. *Eur J Vasc Endovasc Surg*. 2016;51(6):838-845.
348. Subbiah R, Aggarwal V, Bashir R. Compression stockings use to prevent post thrombotic syndrome in DVT patients: a meta-analysis of randomized control studies. *J Am Coll Cardiol*. 2015;65(10 suppl):A2054.
349. Tie HT, Luo MZ, Luo MJ, Li K, Li Q, Wu QC. Compression therapy in the prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2015;94(31):e1318.
350. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. *J Vasc Surg*. 2008;47(5):1015-1021.
351. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349(9054):759-762.
352. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med*. 2001;161(17):2105-2109.
353. Kahn SR, Shapiro S, Wells PS, et al; SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383(9920):880-888.
354. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med*. 2004;141(4):249-256.
355. Villalta SBP, Piccioli A, Lensing A, Prins M, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome [abstract]. *Haemostasis*. 1994;24:158a.
356. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report [published correction appears in *Chest* 2016;150(4):988]. *Chest*. 2016;149(2):315-352.
357. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism [published correction appears in *J Thromb Thrombolysis* 2016;41(3):548]. *J Thromb Thrombolysis*. 2016;41(1):32-67.
358. Mazzolai L, Aboyans V, Ageno W, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. *Eur Heart J*. 2018;39(47):4208-4218.
359. 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.
360. Wiercioch W, Nieuwlaar R, Akl EA, et al. Methodology for the American Society of Hematology VTE guidelines: current best practice, innovations, and experiences. *Blood Adv*. 2020;4(10):2351-2365.