CHEST

Antithrombotic Therapy for VTE Disease

Second Update of the CHEST Guideline and Expert Panel Report

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BACKGROUND: This is the 2nd update to the 9th edition of these guidelines. We provide recommendations on 17 PICO (Population, Intervention, Comparator, Outcome) questions, four of which have not been addressed previously.

METHODS: We generate strong and weak recommendations based on high-, moderate-, and low-certainty evidence, using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

RESULTS: The panel generated 29 guidance statements, 13 of which are graded as strong recommendations, covering aspects of antithrombotic management of VTE from initial management through secondary prevention and risk reduction of postthrombotic syndrome. Four new guidance statements have been added that did not appear in the 9th edition (2012) or 1st update (2016). Eight statements have been substantially modified from the 1st update.

CONCLUSION: New evidence has emerged since 2016 that further informs the standard of care for patients with VTE. Substantial uncertainty remains regarding important management questions, particularly in limited disease and special patient populations.

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KEY WORDS: antithrombotic therapy; DVT; guidelines; pulmonary embolism; thrombosis

ABBREVIATIONS: APS = antiphospholipid syndrome; AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; CAT = cancer-associated thrombosis; CDT = catheter-directed thrombolysis; COI = conflict of interest; CVT = cerebral vein thrombosis; DOAC = direct-acting oral anticoagulant; EtD = evidence-to-decision; GCS = graduated compression stockings; GOC = Guidelines Oversight Committee; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; IDDVT = isolated distal DVT; INR = international normalized ratio; ISSPE = isolated subsegmental pulmonary embolism; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PICO = Population, Intervention, Comparator, Outcome; PREPIC = Prévention du Risque d'Embolie Pulmonaire par Interruption Cave; PTS = postthrombotic syndrome; RCT = randomized controlled trial; SVT = superficial venous thrombosis; US = ultrasound; VKA = vitamin K antagonist

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Summary of Recommendations

Initial Management

1. In patients with acute isolated distal DVT of the leg: and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (weak recommendation, moderate-certainty evidence) or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins (weak recommendation, low-certainty evidence).

Remarks: Serial imaging refers to repeating ultrasound once weekly, or with worsening symptoms, for 2 weeks and anticoagulating only if distal thrombi propagate. Patients at high risk for bleeding are more likely to benefit from serial imaging. Evidence suggests uncertainty that anticoagulation is superior to no anticoagulation. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to favor initial anticoagulation over serial imaging.

2. In patients with acute isolated distal DVT of the leg who are treated with serial imaging, we (i) recommend no anticoagulation if the thrombus does not extend (strong recommendation, moderate-certainty evidence), (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (weak recommendation, very low-certainty evidence), and (iii) recommend anticoagulation if the thrombus extends into the proximal veins (strong recommendation, moderate-certainty evidence).

Remarks: Serial imaging refers to repeating ultrasound once weekly, or with worsening symptoms, for 2 weeks and anticoagulating only if distal thrombi propagate. Patients at high risk for bleeding are more likely to benefit from serial imaging. Evidence suggests uncertainty that anticoagulation is superior to no anticoagulation. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to favor initial anticoagulation over serial imaging.

In patients with acute isolated distal DVT of the leg who are treated with anticoagulation, the same anticoagulation regimen as for patients with acute proximal should be used.

3. In patients with subsegmental pulmonary embolism (PE) (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (weak recommendation, low-certainty evidence).

4. In patients who are incidentally found to have asymptomatic PE, we suggest the same initiation and treatment phase anticoagulation as for comparable patients with symptomatic PE (weak recommendation, moderate-certainty evidence).

5. In patients with cerebral vein/venous sinus thrombosis, we recommend anticoagulation therapy for at least the treatment phase (first 3 months) over no anticoagulant therapy (strong recommendation, low-certainty evidence).

Remark: While the formal Evidence to Decision (EtD) assessment warrants a weak recommendation in favor of anticoagulation ("suggest"), the panelists upgraded the guidance to a strong recommendation, placing a very high value on an uncertain but potentially life-preserving benefit.[1]

6. In patients with acute DVT of the leg we suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate-certainty evidence).

7. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically

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administered thrombolytic therapy over no such therapy (weak recommendation, low-certainty evidence).

Remark: Studies of systemically administered thrombolytic therapy have used different agents at varying doses. Due to lack of comparative data between these approaches, the panel does not endorse one agent or dosing strategy over another.

8. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (strong recommendation, low-certainty evidence).

9. In selected patients with acute PE who deteriorate (see remarks) after starting anticoagulant therapy but have yet to develop hypotension and who have an acceptable bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (weak recommendation, low-certainty evidence).

Remark: While the formal EtD assessment warrants a weak recommendation in favor of anticoagulation ("suggest"), the panelists upgraded the guidance to a strong recommendation, placing a very high value on avoiding the potential increase in harm when the magnitude of benefit is variable.[1]

10. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter-directed thrombolysis (CDT) (weak recommendation, low-certainty evidence).

11. In patients with acute PE associated with hypotension who also have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (weak recommendation, low-certainty evidence).

12. In patients with acute DVT of the leg, we recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (strong recommendation, moderate-certainty evidence).

13. In patients with acute proximal DVT of the leg and a contraindication to anticoagulation, we recommend the use of an IVC filter (strong recommendation, moderate-certainty evidence).

14. In patients with low-risk PE we recommend outpatient treatment over hospitalization provided access to medications, ability to access outpatient care, and home circumstances are adequate (strong recommendation, low-certainty evidence).

Remark: While the formal EtD assessment warrants a weak recommendation in favor of anticoagulation ("suggest"), the panelists upgraded the guidance to a strong recommendation, placing a very high value on avoiding the potential increase in risk of harm (including much greater cost) related to hospitalization even though the magnitude of benefit is similar.[1]

15. In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonist (VKA) as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence).

Remark: While the certainty of the evidence is moderate, the panelists chose a strong recommendation, placing a very high value on avoiding the potential increase in harm in the setting of a similar magnitude of benefit.[1]

16. In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over low molecular weight heparin (LMWH) for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence).

Remark: Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with cancer-associated thrombosis (CAT) and a luminal GI malignancy, while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.

17. In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, we suggest adjusted dose VKA (target INR 2.5) over direct oral anticoagulant (DOAC) therapy during the treatment phase (weak recommendation, low-certainty evidence).

Remark: Initiating VKA therapy should include an overlapping period of parenteral anticoagulation.

18. In patients with superficial venous thrombosis (SVT) of the lower limb at increased risk of clot progression to DVT or PE (see text), we suggest the use of anticoagulation for 45 days over no anticoagulation (weak recommendation, moderate-certainty evidence).

19. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over other anticoagulant treatment regimens such as (prophylactic or therapeutic dose) LMWH (weak recommendation, low-certainty evidence).

20. In patients with SVT who refuse or are unable to use parenteral anticoagulation, we suggest rivaroxaban 10 mg daily as a reasonable alternative for fondaparinux 2.5 mg daily (weak recommendation, low-certainty evidence).

Duration of Treatment Phase of Anticoagulation

21. In patients with acute VTE who do not have a contraindication we recommend a 3-month treatment phase of anticoagulation (strong recommendation, moderate-certainty evidence).

Remark: Upon completion of the 3-month treatment phase of therapy, all patients should be assessed for extended-phase therapy.

Extended-Phase Therapy

22. In patients with VTE diagnosed in the setting of a major transient risk factor (see text), we recommend against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence).

23. In patients with VTE diagnosed in the setting of a minor transient risk factor (see text), we suggest against offering extended-phase anticoagulation (weak recommendation, moderate-certainty evidence).

24. In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), we recommend offering extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence).

25. In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, we suggest offering extended-phase anticoagulation with a VKA (weak recommendation, moderate-certainty evidence).

Remarks: The recommendation to offer extended-phase anticoagulation would not automatically imply that all patients with unprovoked VTE receive extended therapy. Patient preference and predicted risk of recurrent VTE or bleeding should also influence the decision to proceed with, or continue, extended-phase anticoagulation therapy.

Patients who receive extended-phase anticoagulation should have this decision reevaluated at least on an annual basis, and at times of significant change in health status.

Extended-phase anticoagulation does not have a predefined stop date. However, studies of extended-phase anticoagulation monitored patients for durations of about 2 to 4 years. Although most patients in these studies did not stop anticoagulation therapy at the end of follow-up, the risk-to-benefit balance of continuing extended anticoagulation therapy beyond this time is uncertain.

26. In patients offered extended-phase anticoagulation, we suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low-certainty evidence).

Remark: Reduced dose refers to apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily.

27. In patients offered extended-phase anticoagulation, we recommend reduced-dose DOAC over aspirin or no therapy (strong recommendation, low-certainty evidence) and suggest rivaroxaban over aspirin (weak recommendation, moderate-certainty evidence).

Remarks: While the formal EtD assessment warrants a weak recommendation in favor of anticoagulation ("suggest"), the panelists upgraded the guidance to a strong recommendation, placing a very high value on an uncertain but potentially life-preserving benefit.[1]

Reduced dose refers to apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily.

Rivaroxaban is the only DOAC to be directly compared to aspirin for secondary prevention of VTE. Several other DOACs, as well as warfarin, are also acceptable for secondary prevention (extended-phase therapy) after VTE.

28. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (weak recommendation, low-certainty evidence).

Remark: Because aspirin has been shown to be much less effective at preventing recurrent VTE than

anticoagulants, and because some anticoagulants confer a similar risk of bleeding to aspirin, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.

Complications of VTE

29. In patients with acute DVT of the leg, we suggest against using compression stockings routinely to prevent post-thrombotic syndrome (PTS) (weak recommendation, low-certainty evidence).

Additional Description of Methods

Terminology

Phases of anticoagulation: Anticoagulant therapy for VTE has been described in several sources and guidelines (including previous editions of this guideline) to consist of phases.[2-6] However, the nomenclature describing these has varied among sources and over time. The CHEST panel underwent a Delphi vote and elected, with > 80% agreement, the following nomenclature to describe the phases of anticoagulation for VTE.

- Initiation phase: This phase describes the initial provision of anticoagulants following VTE diagnosis. It consists of parenteral or high-dose oral anticoagulation, and lasts from approximately 5 to 21 days, depending on the anticoagulant regimen selected.
- Treatment phase: This phase describes the period after initiation, following which treatment is completed for the acute VTE event. It consists of anticoagulants used at standard therapeutic doses. This phase is considered complete following 12 weeks (3 months) of anticoagulation.
- Extended phase: This phase describes the use of anticoagulants, at full or reduced dose, for the goal of secondary prevention (reducing the risk of recurrent VTE events in the future). Unlike the other phases, there is no preplanned stop date for the extended phase. However, the decision to continue extended-phase anticoagulation should be periodically reevaluated, and the decision to use it can change on the basis of an alteration in patient circumstances, values, or preferences. It should also be noted that studies of extended-phase anticoagulation reported outcomes of anticoagulant therapy over periods from about 2 to 4 years. Although anticoagulants were generally not stopped in participants on conclusion of these studies, the balance of risks and benefits of longer durations of treatment is uncertain.

Oral Anticoagulants

Oral direct thrombin inhibitors and factor Xa inhibitors have been developed as alternatives to the older vitamin K antagonists (VKAs) such as warfarin. Several different terms have been used to collectively describe these agents.[7] This guideline will refer to these medications as *direct-acting oral anticoagulants* (DOACs). The order of our presentation of the DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) will be alphabetical. The order of listing should not be interpreted as the guideline panel's order of preference for the use of these agents.

Precipitating Factors for VTE

The presence or absence of identifiable precipitating factors before a VTE event, especially those that are transient, can impact management, particularly the decision to offer extended-phase anticoagulant therapy. Several classification systems and different terminologies have been used to describe and classify precipitating factors.[2,4-6,8] The CHEST panel opted to use the terminology adopted by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis[8]:

- VTE provoked by a major transient risk factor (present within the 3 months before VTE diagnosis)
  - For example, surgery with general anesthesia for greater than 30 min, confinement to bed in hospital (only "bathroom privileges") for at least 3 days with an acute illness, cesarean section, major trauma.
- VTE provoked by a minor transient risk factor (present within the 2 months before VTE diagnosis)
  - For example, surgery with general anesthesia for less than 30 min, admission to hospital for less than 3 days with an acute illness, estrogen therapy, pregnancy, or puerperium, confinement to bed out of hospital for at least 3 days with an acute illness, leg injury associated with reduced mobility for at least 3 days, prolonged car or air travel.
- VTE provoked by a persistent risk factor
  - For example, active cancer, antiphospholipid syndrome.
- Unprovoked VTE

Note that intrinsic patient characteristics that affect susceptibility to VTE, such as sex, the presence of hereditary thrombophilia, ABO blood type, height, leg-to-trunk ratio, age, and so on would not be classified as persistent risk factors, using this system of nomenclature.

Composition and Selection of CHEST Panel Members

The Guidelines Oversight Committee (GOC) at CHEST appointed the editor for the guideline update. The editor then nominated the project executive committee, the chairs, and the remaining panelists (see Acknowledgments). The GOC approved all panelists after review of their qualifications and conflict of interest (COI) disclosures. The 15 panelists include general internists, thrombosis specialists, pulmonologists, hematologists, a methodologist, and a medical librarian.

Throughout guideline development, panelists were required to disclose any potential financial or intellectual conflicts of interest by PICO (Population, Intervention, Comparator, Outcome). Financial and intellectual conflicts of interest were assessed and classified by the GOC as primary (more serious) or secondary (less serious). Panelists with primary COIs were required to abstain from voting on related PICO areas, but could participate in discussions provided they refrained from strong advocacy. A complete listing of COI and its management appears in the Acknowledgments section.

Selection of PICO Questions for the 2nd Update

First, we listed all the PICO questions (PICOs) from AT9 and the 1st update, and then added potential new PICOs proposed by the panel members. The panelists were requested to identify any new clinical question that they thought would be relevant to inform clinical care, and these questions were formatted in a standardized fashion. Next, all panel members voted on whether each PICO should be included in the update. Finally, the full panel reviewed the results of the vote and decided on the final list found in Table 1. The panel selected a

TABLE 1] Structured Clinical Questions

Topic	Population	Intervention(s)	Comparators(s)	Outcomes(s)	Methodology
Whether and how to prescribe anticoagulants to patients with isolated distal DVT	Patients with isolated distal DVT of the leg	Anticoagulation	No anticoagulation (with serial monitoring for propagation)	Recurrent VTE; major bleeding; recurrent DVT; PE; clinically relevant nonmajor bleeding; overall mortality	Systematic review/ meta-analysis
Whether to treat isolated subsegmental PE	Patients with isolated subsegmental PE	Anticoagulation	No anticoagulation	Overall mortality; recurrent VTE; major bleeding	…
Whether to treat an incidentally diagnosed asymptomatic acute PE	Patients with incidentally diagnosed (asymptomatic) PE	Anticoagulation	No anticoagulation	Overall mortality; recurrent VTE; major bleeding	…
Whether to treat cerebral vein thrombosis	Patients with thrombosis of the cerebral veins or venous sinuses	Anticoagulant therapy	No anticoagulant therapy	Overall mortality; disability; new intracranial hemorrhage or PE	Systematic review/ meta-analysis
Thrombolytic and mechanical interventions in acute DVT	Patients with acute DVT	Thrombolytic therapy with or without mechanical interventions	Anticoagulation	Postthrombotic syndrome; bleeding (excluding cerebral and minor bleeds); PE; all-cause mortality; stroke/ intracerebral hemorrhage	Systematic review/ meta-analysis
Thrombolytic therapy in patients with acute PE	Patients with acute PE	Thrombolytic therapy	Anticoagulation alone	Recurrence of PE; recurrence of PE—submassive PE only; major bleeding; major bleeding—submassive PE only; major bleeding—excluding low-certainty studies; all-cause mortality; all-cause mortality—submassive PE only; all-cause mortality—excluding low-certainty studies	Systematic review/ meta-analysis
Catheter-assisted thrombus removal in patients with acute PE	Patients with acute PE	Catheter-assisted thrombus removal	No catheter-assisted thrombus removal	Overall mortality; recurrent VTE; major bleeding	…
IVC filter in addition to anticoagulation in patients with acute VTE	Patients with acute DVT and PE	IVC filter	No IVC filter	…	RCTs
Setting of initial anticoagulation	Patients with low-risk PE	Outpatient treatment with anticoagulants	Inpatient treatment with anticoagulants	Short-term all-cause mortality; long-term all-cause mortality; major bleeding; minor bleeding; recurrent PE	Systematic review/ meta-analysis

(Continued)

TABLE 1] *(Continued)*

Topic	Population	Intervention(s)	Comparators(s)	Outcomes(s)	Methodology
Choice of treatment-phase anticoagulant	Patients with acute VTE	Dabigatran etexilate; oral factor Xa inhibitor	Standard anticoagulation	Recurrent PE; recurrent DVT; recurrent VTE; major bleeding; all-cause mortality	Systematic review/ meta-analysis
DOACs in CAT	Patients with acute VTE in the setting of cancer (cancer-associated thrombosis)	Oral factor Xa inhibitor	LMWH	Recurrent VTE; major bleeding; all-cause mortality; major GI bleeding	Systematic review/ meta-analysis
DOACs in patients with APS	Patients with antiphospholipid syndrome and thrombosis	DOAC	Dose-adjusted VKA	Any thrombosis, arterial thrombosis, venous thrombosis, major bleeding, clinically relevant bleeding, mortality	RCTs
Role of anticoagulation in spontaneous superficial vein thrombosis	Patients with superficial vein thrombosis of the leg	Fondaparinux or LMWH	Placebo or rivaroxaban	VTE; extension or recurrence of SVT; major bleeding; clinically relevant nonmajor bleeding; all-cause mortality	Systematic review/ meta-analysis
Duration of anticoagulation in patients with acute VTE	Patients with VTE	Extended-phase anticoagulation	No extended-phase anticoagulation	Recurrent VTE; major bleeding; all-cause mortality	RCTs
Reduced-dose vs full-dose anticoagulation for extended treatment of VTE	Patients with VTE who have completed the treatment phase of anticoagulant therapy	Reduced dose of DOACs	Aspirin or placebo; full (treatment) dose of DOACs	Recurrent symptomatic VTE (DVT and fatal or nonfatal PE); major or clinically relevant nonmajor bleeding; mortality	Systematic review/ meta-analysis
Aspirin for extended treatment of VTE	Patients with VTE who have completed the treatment phase of therapy and are candidates for extended-phase therapy	Aspirin	No medication (placebo); rivaroxaban	All-cause mortality; VTE-related mortality, recurrent VTE; major bleeding; clinically relevant nonmajor bleeding, stroke, serious adverse events	Systematic review/ meta-analysis
Compression stockings in preventing PTS	Patients with DVT of the leg	GCS	No GCS or placebo stockings	Any PTS of the leg; severe PTS of the leg; recurrent DVT	Systematic review/ meta-analysis

APS = antiphospholipid syndrome; CAT = cancer-associated thrombosis; DOACs = direct-acting oral anticoagulants; GCS = graduated compression stockings; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PTS = postthrombotic syndrome; RCTs = randomized controlled trials; SVT = superficial vein thrombosis; VKA = vitamin K antagonist.

total of 18 PICOs: 14 for updating from AT9 and the 1st update (two prior PICOs were merged) and four new PICOs. For each PICO, we developed standardized questions in the Population, Intervention, Comparator, Outcome format.

Systematic Search

Database-specific strategies were developed to systematically search for evidence for each question. We searched MEDLINE via PubMed for original studies and the Cochrane Library for systematic reviews. For update PICOs, we searched the literature from August 1, 2014 to November 30, 2020. For new PICOs, we searched the literature from 1966 to November 30, 2020. National Library of Medicine Medical Subject Headings and text words were identified for each question. They were combined to create master search strings, which were then tailored for each database to optimize sensitivity and specificity. Searches were limited to English-language publications and human subjects, and by article type (clinical trial, randomized clinical trial, and systematic review). All search strings were peer-reviewed to identify errors. The search process and results for each PICO were documented in a text document. We augmented searches by checking reference lists of published articles and personal files, and with ongoing surveillance of the literature by panel members.

When we identified direct systematic reviews, we assessed their quality according to the Assessment of Multiple Systematic Reviews (AMSTAR 2) tool.[9] We used those that were of highest quality and most up to date as the source of evidence. In the absence of a satisfactory systematic review, we did our own evidence synthesis using the primary studies identified in AT9, the 1st update, and in our updated search.

Study Selection, Data Abstraction, and Data Analysis

The criteria for selecting the evidence were based on the Population, Intervention, Comparator, Outcome elements of the standardized questions and the study design. We followed a standard process of duplicate independent work with agreement checking and disagreement resolution first among the panelists and then, if necessary, involving the chairs. This process was applied to title and abstract screening, full text screening, data abstraction, and risk of bias assessment. We abstracted data on the characteristics of study design, participants, intervention, control, outcomes, funding, and COI. We assessed risk of bias using the Cochrane risk of bias tool in randomized trials.[10]

When existing systematic reviews were not available or were inadequate, we performed meta-analyses when appropriate. For each outcome of interest, we calculated the risk ratios of individual studies and then pooled them and assessed statistical heterogeneity, using the I^2 statistic. We used a fixed-effects model when pooling data from two trials, or when one of the included trials was large relative to the other(s). Otherwise, we used a random-effects model. We used Review Manager (RevMan) version 5.3 software (Nordic Cochrane Center) to perform the meta-analyses and construct forest plots. We calculated absolute effects by applying pooled relative risks to baseline risks, ideally estimated from valid prognostic observational data or, in the absence of the latter, from control group risks.

Evidence-to-Decision Framing

When assessing a prior recommendation from AT9 or the 1st update, the dyad panelists had three potential options: (1) carry forward (endorse) the prior guidance statement, and retain the original evidence profiles and summaries of findings; (2) carry forward (endorse) the prior guidance statement, but update the evidence profiles and summaries of findings, and create an evidence-to-decision (EtD) framework; or (3) create a new guidance statement, produce updated evidence profiles and summaries of findings, and create an EtD framework.

Each dyad worked in conjunction with the methodologist to complete an evidence-to-decision framework, using the EtD tool[11] for each assigned PICO. The assessment of each PICO's problem as a priority was rated "yes" for all 17 PICOs, based on the process of selection of PICOs described above.

The panelists approved a rubric by unanimous vote to rate the magnitude of desirable and undesirable effects, using the following estimated incidences from the evidence profile for that PICO: trivial (fewer than 5 events per 1,000 subjects), small (between 5 and 20 events per 1,000 subjects), moderate (between 21 and 50 events per 1,000 subjects), and large (more than 50 events per 1,000 subjects). When incident estimates differed between outcomes, panelists assigned judgment of magnitude with greater weight on the effects with more importance to patients (eg, death, pulmonary embolism [PE], major bleeding). These estimates were considered together by the panel dyad, along with an assessment of the values of the outcomes, to create an assessment of the balance of favorable and unfavorable effects.

Certainty of evidence was based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Certainty of evidence is defined as the extent to which our confidence in the effect estimate is adequate to support a recommendation. The certainty of evidence is categorized as high, moderate, low, or very low. The rating of the certainty of evidence reflects the strengths and limitations of the body of evidence and was based on the study design, risk of bias, imprecision, inconsistency, indirectness of results, and likelihood of publication bias. Using GRADEpro GDT software,[12] we generated tables to summarize the judgments of the certainty of the evidence and the relative and absolute effects. These tables are available in the online article.

The remaining EtD elements (resources required, cost-effectiveness, equity, acceptability, and feasibility) were assessed by the panel dyads, based on their judgment. Additional literature could be sought to inform these judgments but was not part of the formal literature review selected for the evidence profiles for the PICO.

Drafting of Recommendations

Each EtD was summarized by the assigned panel dyad for the full panel during a virtual meeting. All panelists without conflicts contributed to the discussion, and changes were made to the EtD on the basis of the discussion. The panel dyad then presented one or more proposed guidance statements, and proposed formal remarks, to the panel. Proposed guidance statements and remarks were discussed by all nonconflicted panelists, and the panel chairs created a final voting version of each statement.

Following the GRADE approach, the strength of a recommendation is defined as the extent to which we can be confident that the desirable effects of an intervention outweigh its undesirable effects. The strength of recommendation was categorized as strong (phrased "we recommend" in the guidance statement) or weak (phrased "we suggest" in the guidance statement).

As noted, the dyad of panelists assigned to each PICO could also propose endorsement of preceding guidance statements from AT9 or the 1st update. On panel discussion, endorsements were forwarded for voting. Minor changes in phrasing or formatting could take place to create the voting versions of endorsed guidance statements and formal remarks.

We used a modified Delphi technique[13,14] to achieve consensus on each guidance statement and formal remark. This technique aims to

minimize group interaction bias and to maintain anonymity among respondents. Using an online survey (SurveyMonkey; Momentive, Inc.), panelists without a primary COI voted on whether to approve each guidance statement and formal remark. Each panelist could also provide open-ended feedback on each recommendation with suggested wording edits or general remarks. The same system was used to vote on endorsing guidance statements carried forward from AT9 and the 1st update. To achieve consensus and be included in the final manuscript, each recommendation had to have at least 80% agreement with a response rate of at least 75% of eligible panel members. All recommendations achieved consensus in the first voting round.

The panel chairs prepared the first draft of the full manuscript. We then used an iterative approach that involved review and editing by, and approval from, all panel members for the submission draft of the manuscript. Further revisions to the manuscript were made in response to peer review (detailed below), following the same process.

Peer Review

External reviewers that were not members of the members of the expert panel reviewed the guideline before it was published. The final manuscript was reviewed and approved by the CHEST GOC, the CHEST Board of Regents, and the CHEST journal, using its established peer-review process for submitted manuscripts.

Whether and How to Prescribe Anticoagulants to Patients With Isolated Distal DVT

Evidence and Evidence-to-Decision

The panel dyad reviewed 288 abstracts, from which they selected 28 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 2.[15-20] The panelists determined that the desirable effects of the intervention are moderate, based on a 6% reduction in the rate of recurrent DVT. Undesirable effects were assessed as trivial, and the balance of effects therefore favors the intervention, with a moderate certainty of evidence.

Additional Comments

The following factors may favor choosing anticoagulation:

1. D-dimer is positive (particularly when markedly so without an alternative reason)
2. Thrombosis is extensive (eg, > 5 cm in length, involves multiple veins, > 7 mm in maximum diameter)
3. Thrombosis is close to the proximal veins
4. There is no reversible provoking factor for DVT
5. The patient has active cancer
6. The patient has a history of VTE
7. The patient has inpatient status
8. The patient has COVID-19
9. The patient is highly symptomatic
10. The patient prefers to avoid repeat imaging

The following factors may favor choosing serial imaging:

1. Thrombosis is confined to the muscular veins of the calf (ie, soleus, gastrocnemius)
2. There is a high or moderate risk for bleeding
3. The patient prefers to avoid anticoagulation

If anticoagulant therapy is chosen, the same initiation and treatment-phase regimens should be used as for acute proximal DVT. Duration of anticoagulant therapy for isolated distal DVT is addressed below. If no anticoagulation is chosen, then serial imaging is indicated.

Background

Isolated distal DVT (IDDVT) is defined as a thrombus affecting deep veins of the lower extremity with most proximal extent distal to the popliteal vein. Management of IDDVT has been controversial, as many episodes will resolve without anticoagulant treatment, therefore calling into question whether the risk-to-benefit balance for anticoagulation is favorable.

AT9 included a section covering diagnosis of DVT.[21] It discouraged routine whole-leg ultrasound (US) examinations (ie, including the distal veins) in patients with suspected DVT, thereby reducing how often IDDVT is diagnosed. The rationale for not routinely examining the distal veins in low-risk (low pretest probability or low D-dimer level) patients who have had proximal DVT excluded is that IDDVT is either unlikely to be present or unlikely to cause complications if it is present. This was clearly demonstrated in diagnostic studies in which comparisons of imaging the distal veins vs not imaging the distal veins resulted in similar outcomes despite the option for treatment existing only in the patients in whom the distal veins were studied. In higher risk patients, a repeat US examination of the proximal veins can be done after 1 week to detect possible DVT extension and determine the need for treatment. In addition, false-positive findings for DVT occur more often with US examinations of the distal compared with the proximal veins.[21]

When IDDVT is diagnosed, the two principal management options are to treat the patients with anticoagulant therapy, or to withhold anticoagulant therapy unless extension of their DVT is detected on a follow-up US examination (eg, after 1 and 2 weeks, or sooner if there are progressive symptoms). Because about 10% to 15% of untreated IDDVTs are expected to

TABLE 2] Evidence Profile: Anticoagulation vs No Anticoagulation for Isolated Distal DVT of the Leg

Certainty Assessment							Study Event Rate (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Anticoagulation	No Anticoagulation	Relative (95% CI)	Absolute (95% CI)
Recurrent VTE (follow-up: 3 mo; assessed with: pulmonary angiography, CT imaging, or ventilation-perfusion; DVT: venography or ultrasonography)										
496 (5 studies)	Not serious	Not serious	Not serious	Not serious[a,b]	None	⊕⊕⊕⊕ HIGH	7/243 (2.9%)	23/253 (9.1%)	RR, 0.34 (0.15-0.77)	60 fewer per 1,000 (from 77 fewer to 21 fewer)
Major bleeding (follow-up: 3 mo; assessed with: fall in hemoglobin of 20 g/L or more)										
480 (4 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	1/234 (0.4%)	2/246 (0.8%)	RR, 0.76 (0.13-4.62)	2 fewer per 1,000 (from 7 fewer to 29 more)
Recurrent DVT (follow-up: 3 mo; assessed with: venography or ultrasonography)										
496 (5 studies)	Not serious	Not serious	Not serious	Not serious[a,b]	None	⊕⊕⊕⊕ HIGH	4/243 (1.6%)	20/253 (7.9%)	RR, 0.25 (0.10-0.67)	59 fewer per 1,000 (from 71 fewer to 26 fewer)
PE (follow-up: 3 mo; assessed with: pulmonary angiography, CT imaging, or ventilation-perfusion)										
480 (4 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	2/234 (0.9%)	3/246 (1.2%)	RR, 0.81 (0.18-3.59)	2 fewer per 1,000 (from 10 fewer to 32 more)
All-cause mortality (follow-up: 3 mo)										
430 (3 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	1/211 (0.5%)	0/219 (0.0%)	RR, 3.20 (0.13-77.69)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Mortality related to PE (follow-up: 3 mo)										
496 (3 studies)	…	…	…	…	None	…	0/211 (0.0%)	0/219 (0.0%)	Not estimable	…

Study synthesis was drawn from the Kirkilesis et al[15] (2020) meta-analysis. Individual studies in Kirkilesis et al[15] (2020) include Horner et al[16] (2014), Lagerstedt et al[17] (1985), Nielsen et al[18] (1994), Righini et al[19] (2016), and Schwarz et al[20] (2010). Certainty assessment results, including risk of bias assessments, were drawn from the Kirkilesis et al[15] (2020) meta-analysis. PE = pulmonary embolism; RR = relative risk.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event and a relative risk reduction of 25%.

[b]Large treatment effect.

subsequently extend into the popliteal or more proximal veins, which predicts greater risk, it is not acceptable to neither treat with anticoagulants nor perform surveillance to detect thrombus extension.[4,22] Choice of ultrasound technique is addressed in the previous CHEST guideline.[21]

In both AT9 and the 1st update, the panelists judged that there was high-certainty evidence that anticoagulant therapy was effective for the treatment of proximal DVT and PE, but uncertainty that the benefits of anticoagulation outweigh its risks in patients with IDDVT because of a lower risk of progressive or recurrent VTE. In this update for patients without severe symptoms or risk factors for extension we suggest serial imaging of the deep veins for 2 weeks over anticoagulation; however, for patients with severe symptoms or risk factors for extension we suggest anticoagulation over serial imaging of the deep veins.

Comparison With Prior Versions

The present guidance statement represents a change from AT9 but remains unchanged from the 1st update.[2,4] Additional data available since 2016 suggest that the balance of effects more clearly favors anticoagulation; although serial ultrasound (with anticoagulation only for proximal propagation) remains an option in patients at higher risk for bleeding, or with compatible values and preferences.

Whether to Treat Isolated Subsegmental Pulmonary Embolism

Evidence and Evidence-to-Decision

Formal evidence profiles were not created here or in the 1st update because of the lack of high-quality evidence. The panelists determined that there were no additional high-quality published data to further inform the PICO, and used the evidence as described in the 1st update.[2] The 1st update panel's literature search did not identify any randomized trials (several remain underway). There were no episodes of recurrent VTE in retrospective reports that included about 60 patients with subsegmental PE and no proximal DVT and who were not anticoagulated.[23,24] However, in another retrospective analysis, patients with subsegmental PE appeared to have a similar risk of recurrent VTE during 3 months of anticoagulant therapy as patients with more proximal PE.[25] Given the lack of high-quality evidence, and the endorsement of the prior guidance statement, no evidence-to-decision framework was undertaken for this PICO.

Additional Comments

Imaging and clinical features that suggest a true-positive finding of isolated subsegmental pulmonary embolism (ISSPE), and thus may favor choosing anticoagulation, were delineated in the 1st update:

1. The CT pulmonary angiogram is of high certainty with good opacification of the distal pulmonary arteries
2. There are multiple intraluminal defects
3. Defects involve more proximal subsegmental arteries (ie, are larger)
4. Defects are seen on more than one image
5. Defects are surrounded by contrast rather than appearing to be adherent to the pulmonary artery walls
6. Defects are seen on more than one projection
7. Patients are symptomatic, as opposed to PE being an incidental finding
8. There is a high clinical pretest probability for PE
9. The D-dimer level is elevated, particularly if the increase is marked and otherwise unexplained

Absence of these features suggests a higher likelihood of false-positive imaging and favors refraining from anticoagulation.

Risk factors for recurrent or progressive VTE may also favor choosing anticoagulation or more aggressive surveillance (such as serial venous ultrasound). These include patients who:

1. Are hospitalized or have reduced mobility for another reason
2. Have active cancer (particularly if metastatic or being treated with chemotherapy)
3. Have no reversible risk factor for VTE such as recent surgery
4. Are pregnant

Furthermore, a low cardiopulmonary reserve or marked symptoms that cannot be attributed to another condition favor anticoagulant therapy, whereas a high risk of bleeding favors no anticoagulant therapy. The decision to anticoagulate or not is also expected to be sensitive to patient preferences. Patients who are not anticoagulated should be told to return for reevaluation if symptoms persist or worsen.

Background

ISSPE refers to PE that is confined to the subsegmental pulmonary arteries (ie, no segmental or more proximal involvement). Technological advances in CT pulmonary angiography have increased how often ISSPE is diagnosed (ie, from approximately 5% to more than 10% of PE).[23,24,26,27] It is unclear whether anticoagulant therapy is beneficial in patients with ISSPE because the abnormalities are small and are unlikely to have an adverse effect on cardiopulmonary function and because they may resolve without anticoagulant therapy.[28] In addition, subsegmental PE is more likely to be a false-positive finding.[24,29] Therefore, it may be safe to refrain from providing anticoagulant therapy to patients with ISSPE, if no proximal DVT (itself an indication for anticoagulant therapy) is present.

Comparison With Prior Versions

This PICO was not addressed in AT9 but was added as a new PICO to the 1st update. The panel opted to endorse the statement from the 1st update, having determined that no substantial evidence had emerged during the interval to indicate a need to change the statement.

Whether to Treat an Incidentally Diagnosed Asymptomatic Acute PE

Evidence and Evidence-to-Decision

Formal evidence profiles were not created in the 1st update because of a lack of high-quality evidence. The panelists determined that there were no additional high-quality data to further inform the PICO.[2] Given the lack of high-quality evidence, and the endorsement of the prior guidance statement, no evidence-to-decision framework was undertaken for this PICO.

Background

Asymptomatic PE is diagnosed in about 1% of outpatients and about 4% of inpatients who have contrast-enhanced chest CT scans. Most occurrences of asymptomatic PE are found in patients with known malignancy and are reported on CT scans that are ordered for another indication (eg, cancer staging, surveillance, or treatment response evaluation).[30] About one-half involve the lobar or more central pulmonary arteries, whereas the other one-half are more distal.[30,31] Because most studies of PE treatment have enrolled symptomatic patients only, the optimal management of asymptomatic PE is less certain.

Comparison With Prior Versions

AT9 suggested the same initial and treatment-phase anticoagulation as for similar patients with symptomatic PE, on ensuring that PE is a new finding on CT imaging, or that ultrasound reveals proximal DVT, and the patient is not at high risk for bleeding. The 2nd update panels chose to endorse the AT9 statements.

Whether to Treat Cerebral Vein Thrombosis

Evidence and Evidence-to-Decision

The panel dyad reviewed 1,290 abstracts, from which they selected 62 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 3.[32-34] Because of the small numbers of subjects in the included studies, CIs around benefit and harm estimates are broad. The panelists determined that the desirable effects of the intervention are large, while undesirable effects were assessed as trivial, and the balance of effects therefore favors the intervention, with a low certainty of evidence.

Additional Comments

Trials included in the meta-analysis had a relatively high percentage of patients who had some degree of intracranial hemorrhage before anticoagulation. Despite this, no occurrences of new symptomatic intracranial hemorrhage were observed in patients treated with anticoagulation. Although anticoagulation is suggested even in the presence of hemorrhage and venous infarction, patients with venous infarcts and large parenchymal hematomas may be at unacceptably high risk of hemorrhage extension and the benefits of anticoagulation may not outweigh the potential for harm in these cases. No randomized controlled trial (RCT) evidence reports the use of DOACs among patients with cancer-associated thrombosis (CVT).

Background

CVT, which includes thrombosis of the cerebral veins and sinuses, is uncommon and accounts for less than 0.5% of all strokes. Its incidence is estimated to be 1.3 per 100,000 in the general population, and it disproportionately affects women at a rate of 3:1.[35,36] Treatment of CVT has historically been based largely on indirect evidence derived from the treatment of thrombosis in other locations. Risks associated with anticoagulation for CVT include intracerebral hemorrhage; therefore, understanding the balance of risks and benefits of anticoagulation is key to clinical care. The goal of anticoagulant therapy is to prevent

TABLE 3] Anticoagulation vs No Treatment for Patients With Cerebral Vein Thrombosis

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Anticoagulation	No Treatment	Relative (95% CI)	Absolute (95% CI)
All-cause mortality (follow-up: 90 d)										
79 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	2/40 (5.0%)	7/39 (17.9%)	OR, 0.35 (0.08-1.34)	108 fewer per 1,000 (from 162 fewer to 47 more)
Severe disability (follow-up: 90 d; assessed with: SVT severity scale or Barthel Index)										
79 (2 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	5/40 (12.5%)	12/39 (30.8%)	OR, 0.30 (0.09-1.01)	190 fewer per 1,000 (from 269 fewer to 2 more)
New intracranial hemorrhage or PE (follow-up: 90 d)										
79 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	0/40 (0.0%)	3/39 (7.7%)	OR, 0.10 (0.00-2.28)	69 fewer per 1,000 (from – to 83 more)

Study synthesis was drawn from the Al-Rawahi et al[32] (2018) meta-analysis. Individual studies in Al-Rawahi et al[32] (2018) include Einhaupl et al[33] (1991) and de Bruijn and Stam[34] (1999). Certainty assessments were conducted by the authors, referencing risk of bias assessments in Al-Rawahi et al[32] (2018). PE = pulmonary embolism; SVT = superficial venous thrombosis.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[b]CIs around relative and absolute estimates of effects include both appreciable benefit and appreciable harm.

propagation of the CVT leading to worsening neurologic outcomes, as well as to prevent embolism resulting in PE.[37]

Either dose-adjusted heparin or low-molecular-weight heparin (LMWH) can be used for the initial treatment of patients with CVT.[37] Parenteral therapy should be continued until the patient has stabilized clinically. For patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options, such as endovascular thrombectomy or local intrathrombus infusion of a thrombolytic agent, together with IV heparin, may be considered.[38,39] Patients who have stabilized can be switched from heparin to oral anticoagulation. The treatment phase of oral anticoagulation is less well defined than for DVT and PE, with studies undertaking treatment phases of 3 to 12 months. Extended-phase anticoagulation may be considered in the absence of hormonal or other provocation or in the presence of persisting risk factors for recurrent VTE; although CVT appears to have an overall lower risk of recurrence than DVT or PE.[37]

Comparison With Prior Versions

Neither the AT9 chapter on venous thrombosis nor the 1st update addressed this PICO; however, it was addressed in the stroke chapter of the AT9 guideline.[40] The present guidance statement is largely similar.

Thrombolytic and Mechanical Interventions in Acute DVT

Evidence and Evidence-to-Decision

The panel dyad reviewed 279 abstracts, from which they selected 45 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 4.[41-61] The panelists determined that the desirable effects of the intervention are moderate. While in absolute numeric terms postthrombotic syndrome (PTS) reduction would qualify as a large desirable effect, there is no difference in the more important end points of PE (as represented in Fig 1), VTE recurrence and death. Further, overall quality of life is not improved despite reduction in PTS. Undesirable effects were assessed as moderate as well, due to an increased risk of bleeding, and a nonsignificant trend suggesting a possible increase in the risk of stroke. Overall, the panelists rated the balance of effects as probably favoring the comparison, with a moderate certainty of evidence.

Background

Thrombolysis can be delivered by systemic IV infusion, by infusion through a catheter placed at the location of the DVT (catheter-directed thrombolysis [CDT]), or as one part of a multicomponent intervention that uses catheter-based devices to disrupt or remove existing clots in combination with thrombolytic infusion (pharmacomechanical thrombus removal). Several devices using different methods for the mechanical component of the intervention exist.[42] The potential benefit of any of these therapies is more rapid resolution of a thrombus when compared with anticoagulation alone (where thrombus dissolution depends on the patient's intrinsic thrombolytic system). It has also been hypothesized that such therapies may provide long-term benefit by reducing the incidence or severity of PTS. These potential benefits must be weighed against the greater expense, need for hospitalization, invasiveness, and higher risk of bleeding.

At the time of AT9, there was one small randomized trial[58] comparing the effect of CDT vs anticoagulant alone on the development of PTS, and another larger randomized trial (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis [CaVenT] study) assessing short-term (eg, venous patency and bleeding) but not long-term (eg, PTS) outcomes.[62,63] At the time of the 1st update, the CaVenT study had further reported that CDT reduced PTS, did not alter quality of life, and appeared to be cost-effective.[59,64-66] Since the 1st update, the larger, ATTRACT trial was published, along with additional reports of outcomes in patient subgroups, and an extended follow-up report.[67] Overall, ATTRACT revealed minimal long-term benefits of CDT when compared with patients receiving anticoagulation alone. Risks of interventional therapies include an increased risk of intracranial bleeding, any bleeding, the need for transfusion, and a greater than twofold increase in major bleeding overall.[67] Inferior vena cava (IVC) filter placement frequently accompanies interventional therapies, which introduces additional risks.

Comparison With Prior Versions

Since the 1st update, the certainty of the evidence has improved and validates the statement made in the 1st update. The panel therefore opted to make no change to the recommendation from the 1st update, apart from minor rewording.

TABLE 4] Evidence Profile: Any Thrombolysis/Clot Removal Strategy vs Anticoagulation Alone for Treatment of Acute DVT

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Any Thrombolysis	Anticoagulation Alone	Relative (95% CI)	Absolute (95% CI)
Postthrombotic syndrome (follow-up: range, 6 mo-5 y)										
1,393 (6 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	383/771 (52.9%)	329/622 (52.9%)	RR, 0.78 (0.66-0.93)	116 fewer per 1,000 (from 180 fewer to 37 fewer)
Postthrombotic syndrome (follow-up: range, 5 y-indefinite)										
211 (2 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	41/104 (39.4%)	75/107 (70.1%)	RR, 0.56 (0.43-0.73)	308 fewer per 1,000 (from 400 fewer to 189 fewer)
Major bleeding (excluding cerebral and minor bleeds)										
1,943 (19 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	72/1,073 (6.7%)	20/870 (2.3%)	RR, 2.45 (1.58-3.78)	33 more per 1,000 (from 13 more to 64 more)
PE (follow-up: range, 1-30 d; assessed with: standard imaging techniques)										
1,124 (7 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	14/627 (2.2%)[c]	8/497 (1.6%)	RR, 1.02 (0.41-2.54)	0 fewer per 1,000 (from 9 fewer to 25 more)
All-cause mortality (follow-up: range, 1-30 d)										
1,220 (10 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	5/677 (0.7%)	7/543 (1.3%)	RR, 0.76 (0.31-1.89)	3 fewer per 1,000 (from 9 fewer to 11 more)

(Continued)

TABLE 4] *(Continued)*

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Any Thrombolysis	Anticoagulation Alone	Relative (95% CI)	Absolute (95% CI)
Early stroke/intracerebral hemorrhage										
1,943 (19 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	3/1,073 (2.3%)	0/870 (0.0%)	RR, 1.92 (0.34-10.86)	0 fewer per 1,000 (from 0 fewer to 0 fewer)

Study synthesis was drawn from the Broderick et al[41] (2021) meta-analysis, except for early bleeding (1- to 30-day follow-up), which includes results of Vedantham et al[42] (2017) (see Fig 1). Additional data on breakdown of VTE between PE and DVT not included in the original publication were provided by original study author via communication dated June 15, 2020. Individual studies in Broderick et al[41] (2021) include Tsapogas et al[43] (1973), Elliot et al[44] (1979), Ugurlu et al[45] (2002), Verhaege et al[46] (1989), Schweizer et al[47] (2000), Goldhaber et al[48] (1990), Schulman et al[49] (1986), Marder et al[50] (1977), Goldhaber et al[51] (1996), Turpie et al[52] (1990), Kakkar et al[53] (1969), Kil et al[54] (1981), Arnesen et al[55] (1978), Common et al[56] (1976), Schweizer et al[57] (1998), Elsharawy and Elzayat[58] (2002), Enden et al[59] (2012) (CaVenT), Notten et al[60] (2020) (CAVA), and Comerota et al[61] (2019) (ATTRACT). Certainty assessment results, including risk of bias assessments, were drawn from the Broderick et al[41] (2021) meta-analysis for bleeding, intermediate and late postthrombotic syndrome. Certainty assessments for the remaining outcome measures were conducted by the authors with risk of bias assessments drawn from Broderick et al[41] (2021). PE = pulmonary embolism; RR = risk ratio.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[b]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

[c]Includes results of Vedantham et al[42] (2017) study. Authors provided additional breakout of 10-day PE-only events not reported in the original study findings (3 of 336 for any thrombolysis; 3 of 355 for anticoagulation alone). E-mail communication between S. Vedantham and S. Woller, June 15, 2020.

Thrombolytic Therapy in Patients With Acute PE

Evidence and Evidence-to-Decision

The panel dyad reviewed 423 abstracts, from which they selected 29 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 5.[68–85,86] The panelists determined that the desirable effects of the intervention are small in magnitude, whereas the undesirable effects are moderate. Overall, the panelists rated the balance of effects as probably favoring the comparison, with a low certainty of evidence.

Additional Comments

Patients with PE without hypotension include a broad spectrum of presentations. At the mild end of the spectrum are those who have minimal symptoms and minimal cardiopulmonary impairment. At the other end of the spectrum are those with severe symptoms and more marked cardiopulmonary impairment (even though systolic BP is > 90 mm Hg). The largest trial of normotensive patients with "submassive PE" randomized 1,006 patients with PE and right ventricular dysfunction to tenecteplase and heparin or to heparin therapy alone (with placebo).[86] The most notable findings of this study were that thrombolytic therapy prevented cardiovascular collapse but increased major (including intracranial) bleeding; these benefits and harms were finely balanced, with no convincing net benefit from thrombolytic therapy. An additional finding was that "rescue thrombolytic therapy" appeared to be of benefit in patients who developed cardiovascular collapse after initially being treated with anticoagulant therapy alone. In fact, the principal component of the benefit of immediate thrombolysis was a reduction in the rate of rescue thrombolytic therapy. It is therefore possible that a similar benefit could occur from providing rescue thrombolysis only to those who decompensate, rather than subjecting a larger number of patients to the risk of immediate thrombolysis.

This observation leads to the question of whether it is better to wait and offer rescue therapy only to those patients who deteriorate, as it is still not possible to confidently identify which normotensive patients will derive net benefit from this therapy at presentation. We therefore suggest that patients without hypotension who are at the severe end of the spectrum be treated with aggressive anticoagulation, close monitoring, and other supportive measures, and not with thrombolytic therapy unless decompensation, manifested by hypotension,

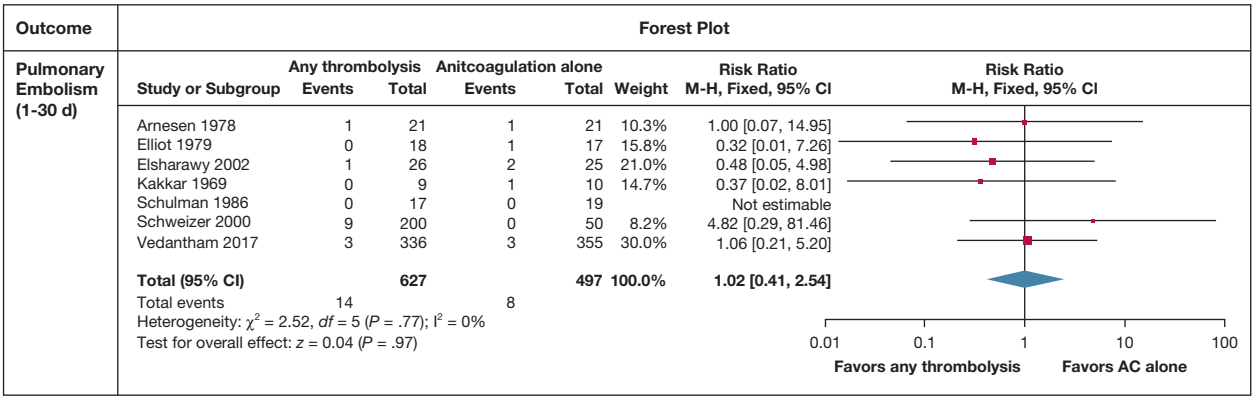

Figure 1 – *Forest plot of pooled estimates: any thrombolysis clot removal strategy vs anticoagulation alone for treatment of acute DVT—early pulmonary embolism (1-30 days). AC = anticoagulation; M-H = Mantel-Haenszel. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

occurs, at which point the risk-to-benefit balance of thrombolysis is more justifiable. Deterioration that has not resulted in hypotension may also prompt the use of thrombolytic therapy. For example, there may be a progressive increase in heart rate, a decrease in systolic BP (which remains > 90 mm Hg), an increase in jugular venous pressure, worsening gas exchange, signs of shock (eg, cold sweaty skin, reduced urine output, confusion), progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers.

Background

Systemic thrombolytic therapy accelerates resolution of PE as evidenced by more rapid lowering of pulmonary artery pressure, increases in arterial oxygenation, and resolution of perfusion defects on imaging. Thrombolytic therapy increases bleeding.[4] The net mortality benefit of thrombolytic therapy in patients with acute PE, however, has been uncertain and depends on an individual patient's risk of dying from acute PE and risk of bleeding. Patients with the highest risk of dying from PE and the lowest risk of bleeding would be predicted to obtain the greatest net benefit from thrombolytic therapy. Patients with the lowest risk of dying from PE and the highest risk of bleeding would be predicted to obtain the least net benefit from thrombolytic therapy and are likely to be harmed.

AT9 recommendations for the use of thrombolytic therapy in acute PE were based on low-certainty evidence.[4,87] At that time, trials had enrolled only about 800 patients and had a high risk of bias. At the time of the 1st update, two additional small, randomized trials[72,74] and a much larger trial[86] had evaluated systemic thrombolytic therapy in about 1,200 patients with acute PE. The findings of these studies were combined with those of earlier studies in several meta-analyses.[88–92] These data increased the certainty of the evidence from low to moderate for recommendations about the use of systemic thrombolytic therapy in acute PE, but this did not substantially change the recommendations in the 1st update. Similarly, interval data since the 1st update have increased the precision of the estimates of benefits and harms, but without a meaningful change in their balance.

Comparison With Prior Versions

Although there has been additional evidence that has increased the precision of estimates since the AT9 and 1st update statements were drafted, the evidence continues to support the same clinical guidance. Therefore, the panel has made no meaningful change in the guidance statement for the 2nd update.

Consistent with AT9, and the 1st update, we continue to suggest that patients with acute PE with hypotension (ie, systolic BP < 90 mm Hg for 15 min) and without high bleeding risk be treated with thrombolytic therapy.

Catheter-Assisted Thrombus Removal in Patients With Acute PE

Evidence and Evidence-to-Decision

Formal evidence profiles were not created in the 1st update because of a lack of high-quality evidence. The panelists determined that there were no additional high-quality data to further inform the PICO. Given the lack of high-quality evidence, and the endorsement of the prior guidance statement, no evidence-to-decision framework was undertaken for this PICO.

TABLE 5] Evidence Profile: Thrombolytic Therapy vs Heparin for Patients With Acute Pulmonary Embolism

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Thrombolytic Therapy	Heparin	Relative (95% CI)	Absolute (95% CI)
Recurrent PE (follow-up: range, 7 d-12 mo; assessed with: standard imaging techniques)										
1,898 (10 studies)	Very serious[a]	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW	19/946 (2.0%)	37/952 (3.9%)	OR, 0.51 (0.29-0.89)	19 fewer per 1,000 (from 27 fewer to 4 fewer)
Recurrent PE—submassive PE only (follow-up: range, 7 d-12 mo; assessed with: standard imaging procedures)										
1,707 (8 studies)	Serious[b]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ LOW	7/849 (0.8%)	21/858 (2.4%)	OR, 0.39 (0.17-0.86)	15 fewer per 1,000 (from 20 fewer to 3 fewer)
Major bleeding (follow-up: range, 7 d-12 mo; assessed with: ISTH criteria)										
1,897 (12 studies)	Very serious[a]	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW	98/946 (10.4%)	36/951 (3.8%)	OR, 2.90 (1.95-4.31)	65 more per 1,000 (from 33 more to 107 more)
Major bleeding—submassive PE only (follow-up: range, 7 d-12 mo; assessed with: ISTH criteria)										
1,669 (8 studies)	Serious[b]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE	70/828 (8.5%)	22/841 (2.6%)	OR, 3.35 (2.06-5.45)	56 more per 1,000 (from 26 more to 102 more)
Major bleeding (excluding low-quality studies) (follow-up: range, 7 d-12 mo; assessed with: ISTH and Cochrane risk of bias tool for study quality)										
1,842 (10 studies)	Serious[b]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE	93/919 (10.1%)	33/923 (3.6%)	OR, 3.00 (1.99-4.53)	64 more per 1,000 (from 33 more to 108 more)
All-cause mortality (follow-up: range, 7 d-12 mo)										
2,167 (17 studies)	Very serious[a]	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW	30/1,081 (2.8%)	53/1,086 (4.9%)	OR, 0.57 (0.37-0.87)	20 fewer per 1,000 (from 30 fewer to 6 fewer)
All-cause mortality—submassive PE only (follow-up: range, 7 d-12 mo)										
1,841 (10 studies)	Serious[b]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ LOW	21/914 (2.3%)	36/927 (3.9%)	OR, 0.60 (0.36-1.01)	15 fewer per 1,000 (from 24 fewer to 0 fewer)

(Continued)

TABLE 5] (Continued)

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Thrombolytic Therapy	Heparin	Relative (95% CI)	Absolute (95% CI)
All-cause mortality (excluding low-quality studies) (follow-up: range, 7 d-12 mo; assessed with: low-quality studies assessed using Cochrane risk of bias tool)										
2,054 (13 studies)	Serious[b]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ LOW	29/1,025 (2.8%)	43/1,029 (4.2%)	OR, 0.66 (0.42-1.06)	14 fewer per 1,000 (from 24 fewer to 2 more)

Outcomes were analyzed for all patients with PE and for the subgroup of patients with submassive PE (eg, normotensive patients). Study synthesis was drawn from the Hao et al[68] (2018) meta-analysis. Individual studies in Hao et al[68] (2018) include Fasullo et al[69] (2011), Taherkhani et al[70] (2014), Goldhaber et al[71] (1993), Sharifi et al[72] (2013), Becattini et al[73] (2010), Kline et al (2014),[74] Konstantinides et al[75] (2002), Dalla-Volta et al[76] (1992), Levine et al[77] (1990), Kucher et al[78] (2014), Jerjes-Sanchez et al[79] (1995), Ly et al[80] (1978), Tibbutt et al[81] (1974), Dotter et al[82] (1979), Wenger[83] (1970) (UPETSG), PIOPED Investigators[84] (1990), Marini et al[85] (1988), and Meyer et al[86] (2014). Certainty assessment results, including risk of bias assessments for overall measures of all-cause mortality, recurrence of pulmonary emboli, and major bleeding, were drawn from Hao et al[68] (2018). Certainty assessments for subanalysis (submassive PE and high-quality studies only) were completed by the authors with individual study risk of bias assessments drawn from Hao et al[68] (2018).
ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism.
[a]High risk of selection, performance and detection bias in most included studies.
[b]Risk of selection, performance or detection bias in most included studies.
[c]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

Additional Comments

Small randomized trials of ultrasound-assisted CDT vs anticoagulation alone revealed more rapid improvement of right ventricular parameters and a low reported risk of procedure-related bleeding, but these studies were small and did not assess patient-important efficacy outcomes.[78,93–97] An older randomized trial of 34 patients with massive PE found that infusion of recombinant tissue plasminogen activator into a pulmonary artery as opposed to a peripheral vein did not accelerate thrombolysis, but caused more frequent bleeding at the catheter insertion site.[98] Studies describing the use of a rheolytic catheter reported significant rates of bradycardia, which has been added as a warning for this device.[99] No randomized trials or observational studies have compared contemporary CDT with systemic thrombolytic therapy. Evidence for the use of CDT compared with anticoagulation alone, CDT compared with systemic thrombolytic therapy, and CDT without thrombolytic therapy is of low certainty, therefore, our recommendations are weak. Patients with high-risk PE and a high risk for bleeding are particularly challenging. Catheter-assisted thrombus removal may carry a lower risk of bleeding than systemic thrombolysis, but the evidence to support this is limited.

Background

Interventional catheter-based treatments for acute PE include CDT if there is not a high risk of bleeding, or catheter-based treatment without thrombolytic therapy if there is a high risk of bleeding.

CDT: The most important limitation of systemic thrombolytic therapy is that it increases bleeding, including intracranial bleeding. Because CDT uses a lower dose of thrombolytic drug it is expected to cause less bleeding at remote sites such as the brain or GI tract.[5,100–103] CDT, however, may be similarly effective to systemic thrombolytic therapy because it achieves a high local concentration of thrombolytic drug in addition to the ability to mechanically disrupt a thrombus. Thrombolytic therapy in CDT is usually infused over many hours or a small number of days. In emergency situations, systemic thrombolytic therapy can be given while CDT is being arranged, and mechanical thrombus fragmentation and aspiration can then be performed as an adjunct to systemic thrombolysis, or as additional therapy if systemic thrombolysis is ineffective.

Catheter-based Thrombus Removal Without Thrombolytic Therapy: Catheter-based (mechanical-only) techniques for thrombus removal involve thrombus fragmentation using various types of catheters, some of which are designed specifically for this purpose.[100,104] Fragmentation results in distal displacement of a thrombus, with or without suctioning and removal of some of the thrombus through the catheter. Mechanical methods alone are used when thrombus removal is indicated but there is a high risk of bleeding that precludes thrombolytic therapy. No randomized controlled trial has evaluated catheter-based thrombus removal of PE without thrombolytic therapy.

Comparison With Prior Versions

For patients who require thrombolytic therapy and do not have a high risk of bleeding, the 1st update panel favored systemic thrombolytic therapy over CDT because, compared with anticoagulation alone, there was a higher certainty of evidence in support of systemic thrombolytic therapy than for CDT. Although additional small prospective trials have been published since the 1st update, the evidence was insufficient to meaningfully change the guidance statements, which the panel voted to endorse.

IVC Filter in Addition to Anticoagulation in Patients With Acute VTE

Evidence and Evidence-to-Decision

The panel dyad reviewed 155 abstracts, from which they selected 35 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 6.[105] The dyad determined that there were no additional high-quality data to further inform the PICO and used the evidence profile from the 1st update.[2] Given the use of the preceding evidence profile and endorsement of the prior guidance statement, no evidence-to-decision framework was undertaken for this PICO.

Additional Comments

IVC filters are overused, especially in the United States.[106] Although most filters are now designed to be retrieved, many remain in patients for extended durations or permanently, even when the original reason for filter placement has resolved.[107] The recommendation in AT9 was primarily based on findings of the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) randomized trial, which showed that placement of a permanent IVC filter increased DVT, decreased PE, and did not influence combined VTE or mortality.[108,109] At the time of the 1st update, several registries had suggested that IVC filters can reduce early mortality in patients with acute VTE, although the certainty of evidence for this benefit was low.[110–114] The PREPIC2 randomized trial found that placement of an IVC filter for 3 months did not reduce recurrent PE, including fatal PE, in anticoagulated patients with PE and DVT who had additional risk factors for recurrent VTE.[105] The 1st update panel decided against combining the results of the PREPIC and PREPIC2 studies because of differences in the type of filter used, the duration of filter placement, and differences in the length of follow-up.

Given the known risks of harm and significant uncertainty of benefit of IVC filters,[115] the panel continues to endorse a conservative approach to their placement by suggesting use only in patients with acute VTE (eg, diagnosed in the preceding 1 month) in whom anticoagulants are contraindicated. In these patients, the IVC filter should be promptly removed when anticoagulant therapy has been instituted. Institutions that place IVC filters should use a system to monitor patients who have received IVC filters and ensure that regular reassessment for removal takes place.[116] Because it is uncertain if there is benefit to placement of an IVC filter in anticoagulated patients with severe PE (eg, with hypotension), our recommendation against insertion of an IVC filter in patients with acute PE who are anticoagulated may not apply to this select subgroup of patients.

Background

Placement of a filter device in the IVC is performed percutaneously under angiographic guidance. Many different devices exist, and most modern devices are designed to be retrievable by a percutaneous approach like that used for device placement. The rationale for IVC filters is to prevent emboli from the lower extremities from reaching the lungs. Settings in which IVC filter placement has been posited as potentially valuable include acute VTE when anticoagulants cannot be given (eg, active bleeding), progressive VTE despite adequate anticoagulation, as an adjunct to anticoagulation in patients with more significant PE burden, and as a prophylactic intervention in the periprocedural period.[106] Filters carry risks, such as fracture, device embolization, strut penetration, and increased probability for DVT.[107] Filters do not eliminate the risk for PE.[105]

Comparison With Prior Versions

Given the absence of significant interval new evidence, the 2nd update panel chose to endorse the preceding

TABLE 6] Evidence Profile: Temporary Inferior Vena Caval Filter vs No Temporary Inferior Vena Caval Filter in Addition to Anticoagulation for Acute DVT or Pulmonary Embolism[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (No. of Studies); Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Temporary Inferior Vena Caval Filter in Addition to Anticoagulation	With Temporary Inferior Vena Caval Filter	Relative Effect (95% CI)	Risk With No Temporary Inferior Vena Caval Filter in Addition to Anticoagulation	Risk Difference With Temporary Inferior Vena Caval Filter (95% CI)
All-cause mortality (critical outcome)											
399 (1 study); 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	⊕⊕⊕◯ MODERATE[c,d] due to imprecision	12/199 (6%)	15/200 (7.5%)	RR, 1.25 (0.6-2.6)	60 per 1,000	15 more per 1,000 (from 24 fewer to 96 more)
Recurrent PE (critical outcome)											
399 (1 study); 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	⊕⊕⊕◯ MODERATE[c,d] due to imprecision	3/199 (1.5%)	6/200 (3%)	RR, 2.00 (0.51-7.89)	15 per 1,000	15 more per 1,000 (from 7 fewer to 104 more)
Major bleeding (critical outcome)											
399 (1 study); 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	⊕⊕⊕◯ MODERATE[c,d] due to imprecision	10/199 (5%)	8/200 (4%)	RR, 0.80 (0.32-1.98)	50 per 1,000	10 fewer per 1,000 (from 34 fewer to 49 more)

Mismetti et al[105] (2015) (PREPIC2). PE = pulmonary embolism; RR = relative risk.

[a]All patients received full-dose anticoagulant therapy according to guidelines for at least 6 mo.

[b]Filter removal was attempted in 164 patients and successful for 153 (93.3%).

[c]CI includes values suggesting no effect and values suggesting either benefit or harm.

[d]Small number of events.

statements following an updated review of the evidence. The evidence profile pertaining to patients with a contraindication to anticoagulation was not updated from AT9.[4]

Setting of Initial Anticoagulation

Evidence and Evidence-to-Decision

The panel dyad reviewed 294 abstracts, from which they selected 14 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 7.[117–119] The panelists determined that the desirable effects of the intervention are trivial, based on absence of difference in any principal outcome; however, a lack of difference in outcomes would nonetheless favor the intervention, based on improved convenience and lower cost. The undesirable effects were rated as small. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a low certainty of evidence.

Background

Home treatment is more convenient and less expensive than hospital treatment and is preferred by most patients.[120] Studies have focused on identifying patients with acute PE and a low probability of complications that would require hospital management.[121] Treatment of acute PE with a DOAC that does not require initial heparin therapy (eg, apixaban or rivaroxaban) facilitates treatment without hospital admission, making outpatient therapy more accessible and less complicated for patients.[122]

Clinical decision rules such as the Pulmonary Embolism Severity Index, either the original form with a score < 85 or the simplified form with a score of 0, can help to identify low-risk patients who are suitable for treatment at home.[123–128] However, we consider clinical prediction rules as aids to decision-making and do not require patients to have a predefined score (eg, low-risk Pulmonary Embolism Severity Index score) to be considered for treatment at home. The presence of right ventricular dysfunction or increased cardiac biomarker levels should discourage treatment out of the hospital.[5,127,129–135]

The recommendation in AT9 was based on two trials that randomized patients with acute PE to receive LMWH for only 3 days in the hospital[136] or entirely at home[118] compared with being treated with LMWH in the hospital for a longer period, in addition to 15 observational studies, nine of which were prospective, that evaluated treatment of acute PE out of the hospital.[4]

At the time of the 1st update, no further randomized trials had been published, although several additional prospective and retrospective observational studies had been completed and included in meta-analyses.[137–139]

Comparison With Prior Versions

The 1st update guidance statement was consistent with AT9 but was modified to state that appropriately selected patients may be treated entirely at home, rather than just be discharged early. The 2nd update's guidance is consistent with the 1st update, but the strength of the recommendation and level of evidence have been increased requisite with development of the medical literature during the interval.

Choice of Treatment-Phase Anticoagulant

Evidence and Evidence-to-Decision

The panel dyad reviewed 977 abstracts, from which they selected 64 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 8[140–142] and Table 9.[140,141,143–146] For the comparison of oral direct thrombin inhibitor vs standard anticoagulation, the panelists determined that the desirable effects of the intervention are small in magnitude, whereas the undesirable effects are trivial. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a high certainty of evidence. For the comparison of oral factor Xa inhibitor vs standard anticoagulation, the panelists determined that the desirable effects of the intervention are small in magnitude, whereas the undesirable effects are trivial. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a moderate certainty of evidence.

Additional Comments

The 1st update panel's overall assessment of the relative efficacy and risk of bleeding with different anticoagulant agents was that the DOACs, compared with VKA therapy, have similar efficacy in reducing the risk of VTE with a lower risk of overall and especially intracranial bleeding, although possibly a higher risk for GI bleeding with dabigatran, edoxaban, and rivaroxaban. Direct comparison between DOACs is very limited but suggests that apixaban may carry a lower risk of bleeding than other DOACs.[146–158]

Pooled evidence and interval reports indicate that the risk reduction for recurrent VTE with all of the DOACs appears to be similar to the risk reduction with VKA; although there has been limited direct comparison

TABLE 7] Evidence Profile: Outpatient Treatment vs Inpatient Treatment for Low-Risk Pulmonary Embolism

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Outpatient Treatment	Inpatient Treatment	Relative (95% CI)	Absolute (95% CI)
All-cause mortality (follow-up: range, 7-10 d)										
451 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	0/222 (0.0%)	1/229 (0.4%)	RR, 0.33 (0.01 to 7.98)	3 fewer per 1,000 (from 4 fewer to 30 more)
All-cause mortality (follow-up: 90 d)										
451 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	1/222 (0.5%)	1/229 (0.4%)	RR, 0.98 (0.06 to 15.58)	0 fewer per 1,000 (from 4 fewer to 64 more)
Major bleeding (follow-up: 14 d)										
445 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	2/222 (0.9%)	0/223 (0.0%)	RR, 4.91 (0.24 to 101.57)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Major bleeding (follow-up: 90 d)										
445 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	3/222 (1.4%)	0/223 (0.0%)	RR, 6.88 (0.36 to 132.14)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Recurrent PE (follow-up: 90 d)										
445 (2 studies)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	1/222 (0.5%)	0/223 (0.0%)	RR, 2.95 (0.12 to 71.85)	0 fewer per 1,000 (from 0 fewer to 0 fewer)

Study synthesis was drawn from the Yoo et al[117] (2019) meta-analysis. Individual studies in Yoo et al[117] (2019) include Aujesky et al[118] (2011) and Frank Peacock et al[119] (2018). Certainty assessment results, including risk of bias assessments, were drawn from the Yoo et al[117] (2020) meta-analysis. PE = pulmonary embolism; RR = risk ratio.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[b]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

TABLE 8] Evidence Profile: Oral Direct Thrombin Inhibitors vs Standard Anticoagulation for Treatment Phase for Acute VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Dabigatran Etexilate	Standard Anticoagulation[a]	Relative (95% CI)	Absolute (95% CI)
Recurrent PE (follow-up: 6 mo; assessed with: standard imaging techniques)										
1,602 (1 study)[b]	Not serious[c]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	16/795 (2.0%)	16/807 (2.0%)	RR, 1.02 (0.51-2.02)	0 fewer per 1,000 (from 10 fewer to 20 more)
Recurrent VTE (follow-up: 6 mo; assessed with: standard imaging techniques)										
1,602 (1 study)[b]	Not serious[c]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	23/795 (2.9%)	25/807 (3.1%)	RR, 0.93 (0.53-1.63)	2 fewer per 1,000 (from 15 fewer to 20 more)
DVT (follow-up: 6 mo; assessed with: standard imaging techniques)										
1,602 (1 study)[b]	Not serious[c]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	7/795 (0.9%)	9/807 (1.1%)	RR, 0.79 (0.30-2.11)	2 fewer per 1,000 (from 8 fewer to 12 more)
Major bleeding (follow-up: 6 mo; assessed with: ISTH criteria)										
1,527 (1 study)[b]	Not serious[c]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	4/759 (0.5%)	8/768 (1.0%)	RR, 0.51 (0.15-1.67)	5 fewer per 1,000 (from 9 fewer to 7 more)

Study synthesis was drawn from the Robertson et al[140,141] (2015) meta-analysis. Individual studies include Schulman et al[142] (2011) (RE-COVER I and RE-COVER II). Results of the Robertson et al[140,141] (2015) meta-analysis were updated by the authors to reflect the relative risk ratio calculation for measurement of relative effect as reflected in Figure 2. Certainty assessment results, including risk of bias assessments, drawn from the Robertson et al[140,141] (2015) meta-analysis. Forest plots for the overall synthesis are included in Figure 2. ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism; RR = risk ratio.

[a]Defined as therapeutic parenteral anticoagulation overlapped with warfarin per recommendations.

[b]The data from the two RECOVER studies were taken from one pooled analysis and are therefore shown as one study.

[c]Risk of bias was "unclear" for random sequence generation, but we did not consider it sufficient to downgrade the quality of evidence.

TABLE 9] Evidence Profile: Oral Factor Xa vs Standard Anticoagulation for Treatment Phase for Acute VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Oral Factor Xa	Standard Anticoagulation	Relative (95% CI)	Absolute (95% CI)
Recurrent PE (assessed with: standard imaging techniques)										
4,588 (3 studies)	Not serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE	45/2,293 (2.0%)	51/2,295 (2.2%)	RR, 0.89 (0.60-1.32)	2 fewer per 1,000 (from 9 fewer to 7 more)
Recurrent VTE (assessed with: standard imaging techniques)										
6,374 (4 studies)	Not serious[a]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	84/3,193 (2.6%)	99/3,181 (3.1%)	RR, 0.85 (0.63-1.13)	5 fewer per 1,000 (from 12 fewer to 4 more)
DVT (assessed with: standard imaging techniques)										
4,588 (3 studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	18/2,293 (0.8%)	25/2,295 (1.1%)	RR, 0.72 (0.39-1.32)	3 fewer per 1,000 (from 7 fewer to 3 more)
All-cause mortality										
4,896 (2 studies)	Not serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕⊕◯ MODERATE	58/2,452 (2.4%)	50/2,444 (2.0%)	RR, 1.16 (0.80-1.68)	3 more per 1,000 (from 4 fewer to 14 more)
Major bleeding (assessed with: ISTH criteria)										
4,586 (3 studies)	Not serious[a]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	30/2,293 (1.3%)	33/2,293 (1.4%)	RR, 0.91 (0.56-1.48)	1 fewer per 1,000 (from 6 fewer to 7 more)

Study synthesis was drawn from the Robertson et al[140,141] (2015) meta-analysis updated to include more recent study (Nakamura et al[143] (2015). Individual studies in the final meta-analysis include Agnelli et al[144] (2013) (AMPLIFY), EINSTEIN-PE Investigators et al[145] (2012), Hokusai-VTE Investigators et al[146] (2013), and Nakamura et al[143] (2015). Results of the Robertson et al[140,141] (2015) meta-analysis were updated by the authors to reflect the relative risk ratio calculation for measurement of relative effect. Certainty assessment results, including risk of bias assessments, were drawn from the Robertson et al[140,141] (2015) meta-analysis updated by the authors for assessment of Nakamura et al[143] (2015). Forest plots for the overall final synthesis are included in Figure 3. ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism; RR = risk ratio.

[a]Risk of bias was "unclear" for random sequence generation. However, we did not consider it sufficient to downgrade the quality of evidence.

[b]Statistical heterogeneity was found for this outcome and could not be explained

[c]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

between agents.[147] The risk of bleeding with DOACs, and particularly intracranial bleeding, is less with DOACs than with VKA therapy.[147,149,154,159,160] On the basis of patients with atrial fibrillation, GI bleeding may be higher with dabigatran, edoxaban, and rivaroxaban than with VKA therapy, although this had not been seen in patients with VTE.[149,154,155,159,161] However, on the basis of indirect comparisons and studies reporting on DOACs for the treatment of cancer-associated thrombosis, the risk of bleeding may be lower with apixaban than with other DOACs.[147,162–165] Specific reversal agents for DOACs have been approved (yet even before the availability of these, the risk that a major bleed will be fatal appears to be no higher for DOACs than for VKA therapy).[147,149,151]

Background

In the past, the only option for the treatment phase of VTE was the use of VKA following parenteral overlap with heparin. In 2009 the first direct oral anticoagulant (the direct thrombin inhibitor dabigatran etexilate) was demonstrated to be safe and effective (Fig 2) for the treatment of VTE.[166] Shortly thereafter a second class of DOACs, the activated factor X inhibitors (Fig 3), were approved.[144,146,153,167] In comparison with VKA, DOACs are comparatively easier to manage in the treatment phase, have few potential drug interactions, few alimentary limitations, and do not require routine laboratory monitoring or dose adjustment.[168]

The recommendations in AT9 were based on comparisons of VKA with LMWH that were performed in the preceding two decades and with two of the DOACs (dabigatran[166] and rivaroxaban[153]) that had been published more recently. The AT9 panel suggested VKA therapy or LMWH over the DOACs because only two randomized trials had compared a DOAC (dabigatran[166] and rivaroxaban[153]) with VKA therapy, and none had compared a DOAC with long-term LMWH. At the time of the 1st update, four new randomized trials were available that compared a DOAC (with[146,152] or without[144,153] initial heparin therapy) with VKA therapy (with initial heparin therapy) for the initial and treatment phases of VTE therapy.[144,146,153,154,166]

Comparison With Prior Versions

The AT9 panel suggested VKA therapy or LMWH over the DOACs. With additional interval evidence, the 1st update panel suggested DOACs over VKA or LMWH in the absence of compelling indications for the latter. In the 2nd update, the panel maintained the guidance from the 1st update, but increased the GRADE of the recommendation, based on interval evidence and results from real-world registries using DOACs.

DOACs in Cancer-Associated Thrombosis

Evidence and Evidence-to-Decision

The panel dyad reviewed 428 abstracts, from which they selected 33 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 10[164,169–171] and Table 11.[164,169–172] The panelists determined that the desirable effects of the intervention are large in magnitude whereas the undesirable effects are moderate. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a high certainty of evidence.

Additional Comments

The panelists discussed the comparative effectiveness and safety of DOACs when compared with LMWH. Consensus existed that, because of the comparative risk for bleeding among patients with cancer and because there appeared to be a difference in the rates of individual DOACs when compared with LMWH, a remark would be added to the guidance statement. Pooled risk estimates comparing DOACs with LMWH for the outcome of major GI bleeding are found in Figure 4.

Background

In patients with VTE and cancer (cancer-associated thrombosis [CAT]) there is a higher risk for recurrence as well as a higher risk for major bleeding than in patients with VTE without cancer.[173] In comparison with extended-duration LMWH, warfarin demonstrated lower efficacy than LMWH and comparable safety, leading to guidance favoring LMWH in patients with CAT.[2] However, extended-duration injections are burdensome[174] and can be costly. More recent prospective studies have compared oral factor Xa inhibitors with LMWH to determine comparative efficacy and safety.[172] These studies enrolled patients with active cancer and randomized them to receive either a DOAC (using the standard dosing for initiation and treatment-phase therapy) or the LMWH dalteparin. Outcomes were reported at 6 months for all studies except one (reported at 12 months).[164] Notable heterogeneity of patients enrolled in the respective studies included stage and type of malignancy.[164,165,169,170] It was observed in some

TABLE 10] Evidence Profile: Drug-Specific Direct-Acting Oral Anticoagulants vs Low-Molecular-Weight Heparin for Treatment of VTE in Patients With Cancer

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)
Major GI bleeding—edoxaban/rivaroxaban vs LMWH (follow-up: range, 6-12 mo)										
1,452 (2 studies)	Not serious[a,b]	Not serious	Not serious	Serious[c]	None	⊕⊕⊕◯ MODERATE	28/725 (3.9%)	10/727 (1.4%)	RR, 2.81 (1.37-5.74)	25 more per 1,000 (from 5 more to 65 more)
Major GI bleeding—apixaban vs LMWH (follow-up: 6 mo)										
1,442 (2 studies)	Not serious[a]	Not serious	Not serious	Very serious[c,d]	None	⊕⊕◯◯ LOW	11/721 (1.5%)	10/721 (1.4%)	RR, 1.11 (0.47-2.58)	2 more per 1,000 (from 7 fewer to 22 more)

The meta-analysis was generated by the authors. Individual studies for comparison of edoxaban or rivaroxaban vs LMWH include Raskob et al[164] (2018) and Young et al[169] (2018). Individual studies for comparison of apixaban vs LMWH include Agnelli et al[170] (2020) and McBane et al[171] (2020). Certainty assessments, including risk of bias assessments, were conducted by the authors. Forest plots for the final synthesis are included in Figure 4. DOACs = direct-acting oral anticoagulants; LMWH = low-molecular-weight heparin; RR = risk ratio.

[a]Performance bias due to the absence of blinding participants and personnel on three studies [Raskob et al[164] (2018), McBane et al[171] (2020), and Agnelli et al[170] (2020)].

[b]Selection/detection bias in one study [Young et al[169] (2018)].

[c]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[d]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

TABLE 11] Evidence Profile: Direct-Acting Oral Anticoagulants vs Low-Molecular-Weight Heparin for Treatment of VTE in Patients With Cancer

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)
Recurrent VTE (follow-up: 6 mo; assessed with: standard imaging techniques)										
2,894 (4 studies)	Not serious[a,b]	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	75/1,446 (5.2%)	119/1,448 (8.2%)	RR, 0.62 (0.43-0.91)	31 fewer per 1,000 (from 47 fewer to 7 fewer)
Major bleeding (follow-up: 6 mo; assessed with: ISTH or European Medicines Agency definition)										
2,894 (4 studies)	Not serious[a,b]	Not serious	Not serious	Serious[c]	None	⊕⊕⊕◯ MODERATE	62/1,446 (4.3%)	48/1,448 (3.3%)	RR, 1.31 (0.83-2.08)	10 more per 1,000 (from 6 fewer to 36 more)

Study synthesis was drawn from the Giustozzi et al[172] (2020) meta-analysis. Individual studies in the final meta-analysis include Raskob et al[164] (2018) (Hokusai VTE), Young et al[169] (2018) (SELECT-D), McBane et al[171] (2020) (ADAM VTE), and Agnelli et al[170] (2020) (Caravaggio). Certainty assessments, including risk of bias assessments, were conducted by the authors. DOACs = direct-acting oral anticoagulants; ISTH = International Society on Thrombosis and Haemostasis; LMWH = low-molecular-weight heparin; RR = risk ratio.

[a]Performance bias due to the absence of blinding participants and personnel on three studies [Raskob et al[164] (2018), McBane et al[171] (2020), and Agnelli et al[170] (2020)].

[b]Selection and detection bias on one study [Young et al[169] (2018)].

[c]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

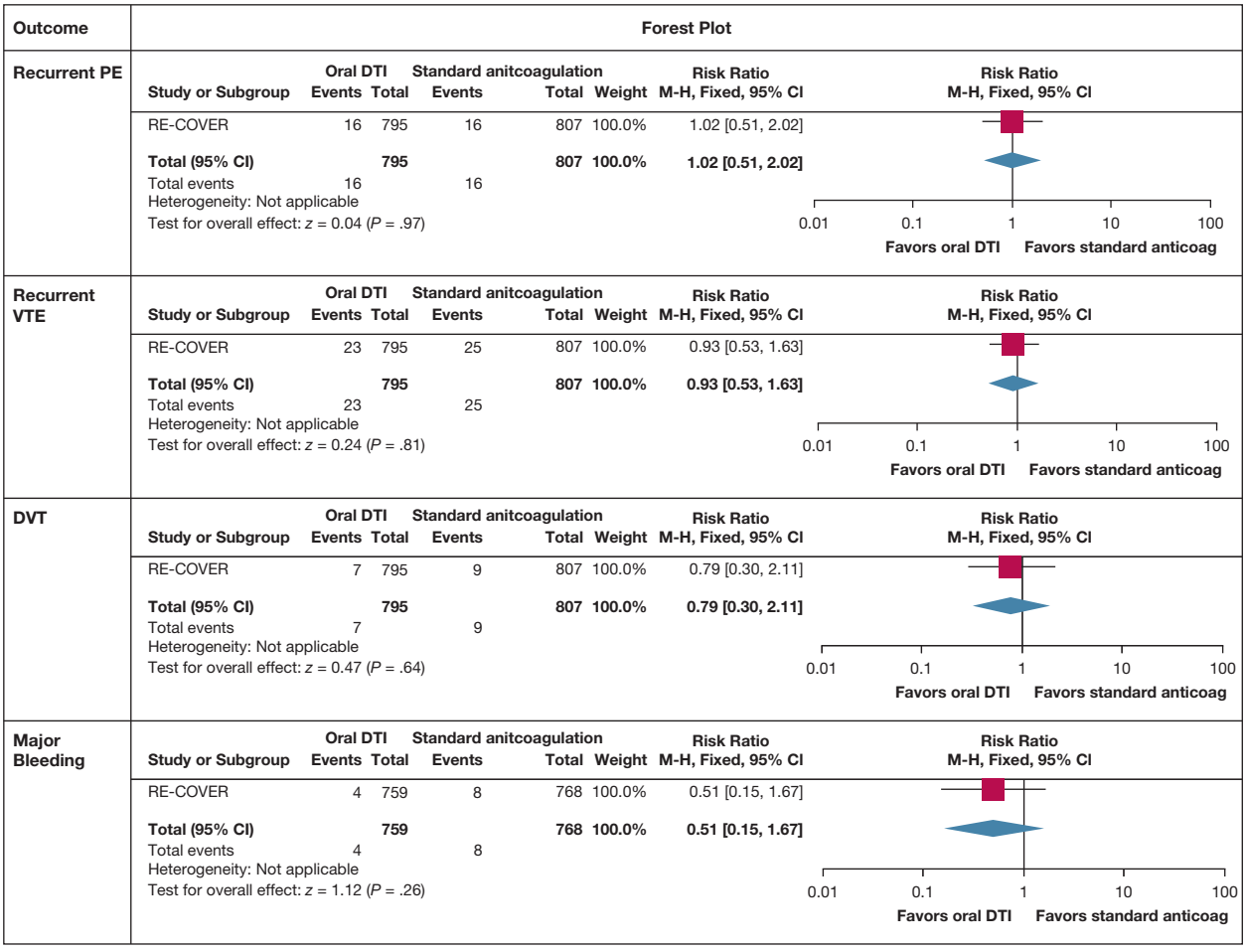

Figure 2 – *Forest plot of pooled estimates: oral direct thrombin inhibitors vs standard anticoagulation for treatment phase for acute VTE. DTI = direct thrombin inhibitor; M-H = Mantel-Haenszel; PE = pulmonary embolism. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

studies[164,169] that the rate of GI bleeding was higher among patients with a cancer diagnosis of luminal GI malignancy; however, this was not the case in other studies.[165,170]

AT9 suggested LMWH over VKA in patients with cancer for the following reasons: there was moderate-certainty evidence that LMWH is more effective than VKA in patients with cancer; there was a substantial rate of recurrent VTE in patients with VTE and cancer who are treated with VKA; it is often more difficult to keep patients with cancer who are taking VKA in the therapeutic range; LMWH is reliable in patients who have difficulty with oral therapy (eg, vomiting); and LMWH is easier to withhold or adjust than VKA if invasive interventions are required or thrombocytopenia develops. At the time of the 1st update, one new randomized trial was available that compared LMWH (tinzaparin) with warfarin for the first 6 months of treatment in 900 cancer patients with VTE.[175]

Comparison With Prior Versions

AT9 and the 1st update suggested LMWH over VKA in patients with cancer. In the 2nd update, considering substantial new RCT evidence comparing oral factor Xa inhibitors with LMWH, the guidance statement has been modified to recommend oral factor Xa inhibitors over LMWH; with a remark regarding the safety advantage of LMWH in comparison with edoxaban and rivaroxaban in patients with luminal GI malignancies.

DOACs in Patients With Antiphospholipid Syndrome

Evidence and Evidence-to-Decision

The panel dyad reviewed 921 abstracts, from which they selected 27 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 12.[176–180] The panelists determined that the desirable effects of the intervention are small in magnitude, whereas the

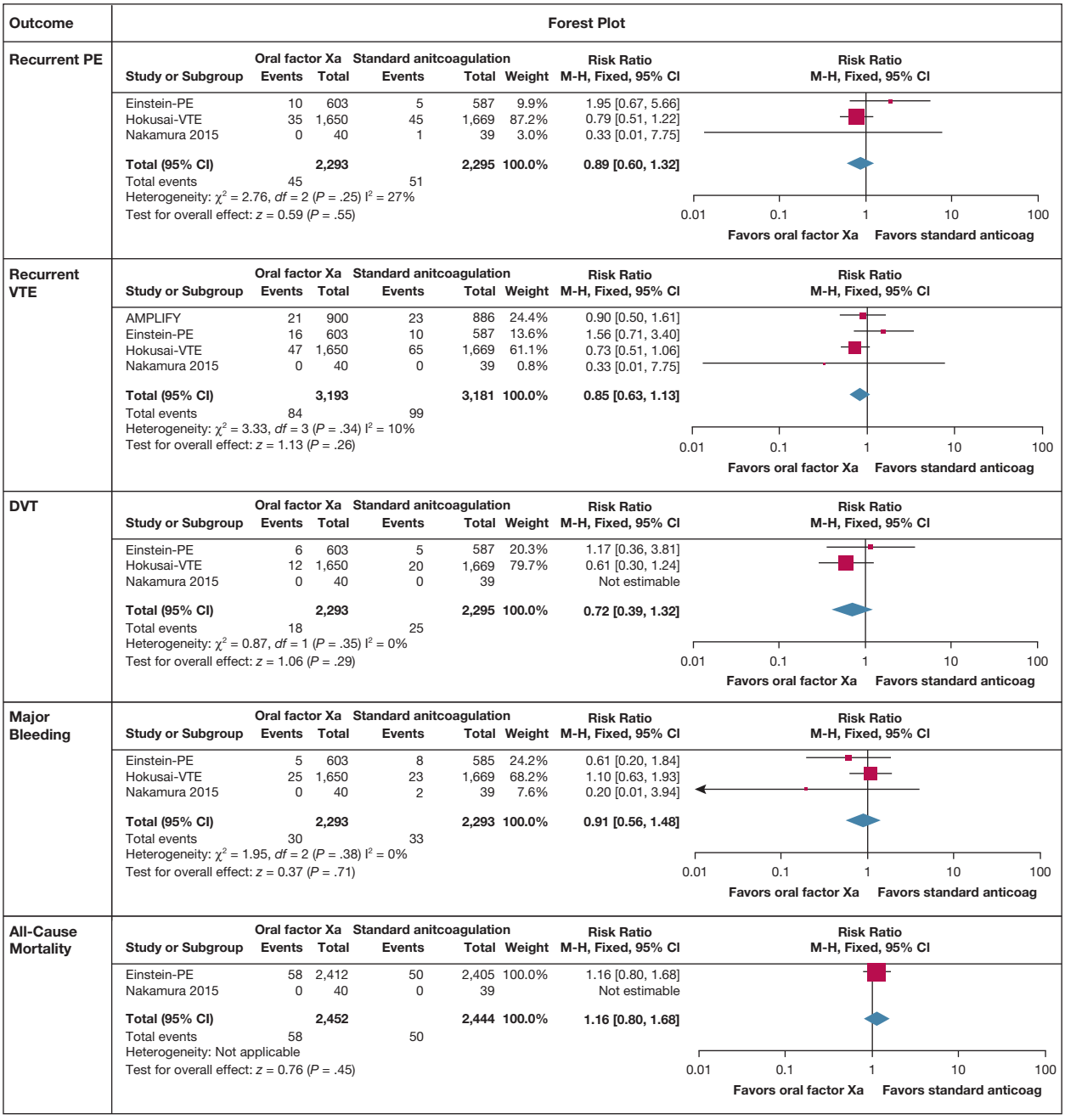

Figure 3 – *Forest plot of pooled estimates: oral factor Xa vs standard anticoagulation for treatment phase for acute VTE. M-H = Mantel-Haenszel; PE = pulmonary embolism. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

undesirable effects are large. Overall, the panelists rated the balance of effects as probably favoring the comparison, with a low certainty of evidence. Pooled risk estimates comparing DOACs with dose-adjusted VKAs for patient-important outcomes are found in Figure 5.

Additional Comments

If a patient with triple-positive antiphospholipid syndrome (APS) presents with VTE, then VKA is favored over DOAC therapy. If such a patient is initiated on a DOAC, then panel consensus exists for transitioning to VKA therapy. Among patients who experience new or progressive thrombosis while receiving standard intensity VKA, it is not recommended to transition to a DOAC. For these patients other treatment options may include increasing the target INR range, standard treatment dose low-molecular-weight heparin, transitioning to fondaparinux, or the addition of antiplatelet therapy.

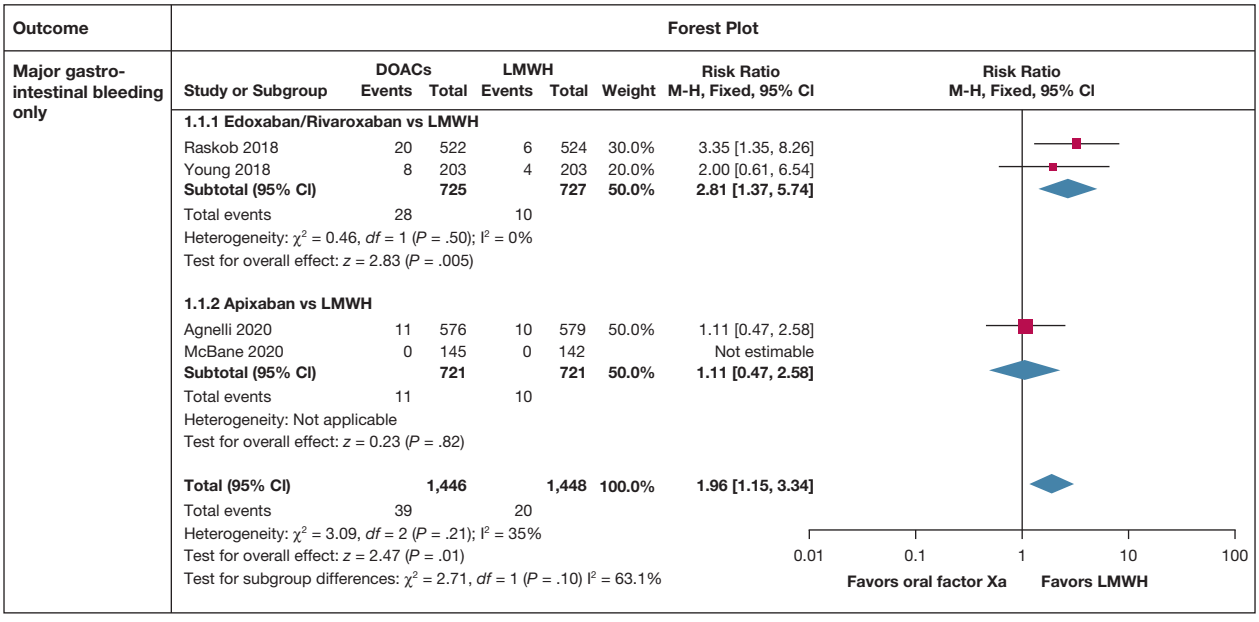

Figure 4 – *Forest plot of pooled estimates: direct-acting oral anticoagulants vs low-molecular-weight heparin for the treatment of VTE in patients with cancer. DOACs = direct-acting oral anticoagulants; LMWH = low-molecular-weight heparin; M-H = Mantel-Haenszel. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

Background

Thrombotic APS is an uncommon acquired autoimmune-mediated thrombophilia that predisposes patients to thrombosis in the arterial, venous, and microvascular circulation, and is characterized by the presence of persistent antibodies.[181] Thrombotic APS is treated with therapeutic anticoagulation and, because of an estimated high risk for recurrent thrombosis,[182] recommendations exist to continue anticoagulation indefinitely.[183] DOACs have been compared with VKA in small prospective RCTs for the outcome of recurrent thrombosis and major bleeding.[179,180] The choice of anticoagulant is complicated not only by limited data, but by the heterogeneity of APS; including presentation with thrombosis in different vascular beds and varying antibody isotypes (eg, "single positive" vs "double positive" vs "triple positive," the latter defined as positive for lupus anticoagulant, anti-cardiolipin, and anti-β_2-glycoprotein-I antibodies).[181]

Comparison With Prior Versions

Neither AT9 nor the 1st update addressed this PICO.

Role of Anticoagulation in Spontaneous Superficial Vein Thrombosis

Evidence and Evidence-to-Decision

The panel dyad reviewed 252 abstracts, from which they selected 26 full texts for review. Studies selected for abstraction and synthesis are detailed in Tables 13 through 16.[184–188] The panelists determined that the desirable effects of the intervention are small in magnitude whereas the undesirable effects are trivial. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a moderate certainty of evidence.

Additional Comments

Although more expensive in some jurisdictions, anticoagulants have greater efficacy and similar safety when compared with conservative therapy and nonsteroidal antiinflammatory medications. The Comparison of Arixtra in Lower Limb Superficial Thrombophlebitis With Placebo (CALISTO) study compared fondaparinux (2.5 mg/d for 45 days) with placebo in 3,000 patients with SVT (≥ 5 cm in length), and found that fondaparinux was effective at reducing VTE, recurrent SVT, extension of SVT, and the need for venous surgery, and was associated with a low risk of bleeding.[185] In an open-label RCT that enrolled 485 patients with SVT in a supragenual vein segment of at least 5 cm in length, subjects were randomized to fondaparinux 2.5 mg once daily or to rivaroxaban 10 mg once daily. Rivaroxaban met the prespecified margin for noninferiority in efficacy, with 3% vs 2% of patients experiencing progression of SVT, DVT, PE, or death.[188]

TABLE 12] Evidence Profile: Direct-Acting Oral Anticoagulants vs Dose-Adjusted Vitamin K Antagonists for Preventing Thrombotic Events in Patients With Antiphospholipid Syndrome

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	DOACs	Dose-Adjusted VKAs	Relative (95% CI)	Absolute (95% CI)
Any thrombosis (follow-up: 6 mo)										
219 (2 studies)	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	⊕◯◯◯ VERY LOW	4/106 (3.8%)	0/113 (0.0%)	RR, 10.41 (0.57-188.77)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Any thrombosis (follow-up: 36 mo; assessed with: adjudication)										
190 (1 study)	Not serious	Not serious	Not serious	Very serious[b,c]	None	⊕⊕◯◯ LOW	12/95 (12.6%)	6/95 (6.3%)	RR, 2.00 (0.78-5.11)	63 more per 1,000 (from 14 fewer to 260 more)
Arterial thrombosis (follow-up: 6 mo)										
219 (2 studies)	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	⊕◯◯◯ VERY LOW	3/106 (2.8%)	0/113 (0.0%)	RR, 8.10 (0.43-153.09)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Arterial thrombosis (follow-up: 36 mo; assessed with: adjudication)										
190 (1 study)	Not serious	Not serious	Not serious	Very serious[b,c]	None	⊕⊕◯◯ LOW	11/95 (11.6%)	3/95 (3.2%)	RR, 3.67 (1.06-12.73)	84 more per 1,000 (from 2 more to 370 more)
Venous thrombosis (follow-up: 6 mo)										
219 (2 studies)	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	⊕◯◯◯ VERY LOW	1/106 (0.9%)	0/113 (0.0%)	RR, 3.47 (0.14-83.34)	0 fewer per 1,000 (from 0 fewer to 0 fewer)
Venous thrombosis (follow-up: 36 mo; assessed with: adjudication)										
190 (1 study)	Not serious	Not serious	Not serious	Very serious[b,c]	None	⊕⊕◯◯ LOW	2/95 (2.1%)	3/95 (3.2%)	RR, 0.67 (0.11-3.90)	10 fewer per 1,000 (from 28 fewer to 92 more)

(Continued)

TABLE 12] *(Continued)*

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	DOACs	Dose-Adjusted VKAs	Relative (95% CI)	Absolute (95% CI)
Major bleeding (follow-up: 6 mo)										
366 (3 studies)	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	⊕◯◯◯ VERY LOW	2/176 (1.1%)	2/190 (1.1%)	RR, 1.07 (0.16-7.15)	1 more per 1,000 (from 9 fewer to 65 more)
Major bleeding (follow-up: 36 mo)										
190 (1 study)	Not serious	Not serious	Not serious	Very serious[b,c]	None	⊕⊕◯◯ LOW	6/95 (6.3%)	7/95 (7.4%)	RR, 0.86 (0.30-2.46)	10 fewer per 1,000 (from 52 fewer to 108 more)
All-cause mortality (follow-up: 6 mo)										
258 (2 studies)	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	⊕◯◯◯ VERY LOW	4/126 (3.2%)	4/132 (3.0%)	RR, 1.07 (0.30-3.83)	2 more per 1,000 (from 21 fewer to 86 more)
All-cause mortality (follow-up: 36 mo)										
190 (1 study)	Not serious	Not serious	Not serious	Very serious[b,c]	None	⊕⊕◯◯ LOW	5/95 (5.3%)	3/95 (3.2%)	RR, 1.67 (0.41-6.78)	21 more per 1,000 (from 19 fewer to 183 more)

Study synthesis of 6-mo results was drawn from the Sanchez-Redondo et al[176] (2019) meta-analysis. Individual studies in Sanchez-Redondo et al[176] (2019) include Cohen et al[177] (2016), Goldhaber et al[178] (2016), and Pengo et al[179] (2018). Separately reported 36-mo study results were drawn directly from Ordi-Ros et al[180] (2019). Results of the Sanchez-Redondo et al[176] (2019) meta-analysis were adjusted by the authors to reflect Mantel-Haenszel with a fixed effect. Certainty assessments were conducted by the authors referencing risk of bias assessments in Sanchez-Redondo et al[176] (2019). Forest plots for the adjusted final synthesis of 6-mo results are included in Figure 5. DOACs = direct-acting oral anticoagulants; RR = risk ratio; VKA = vitamin K antagonist.

[a]Two or more risk factors identified for bias.

[b]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[c]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

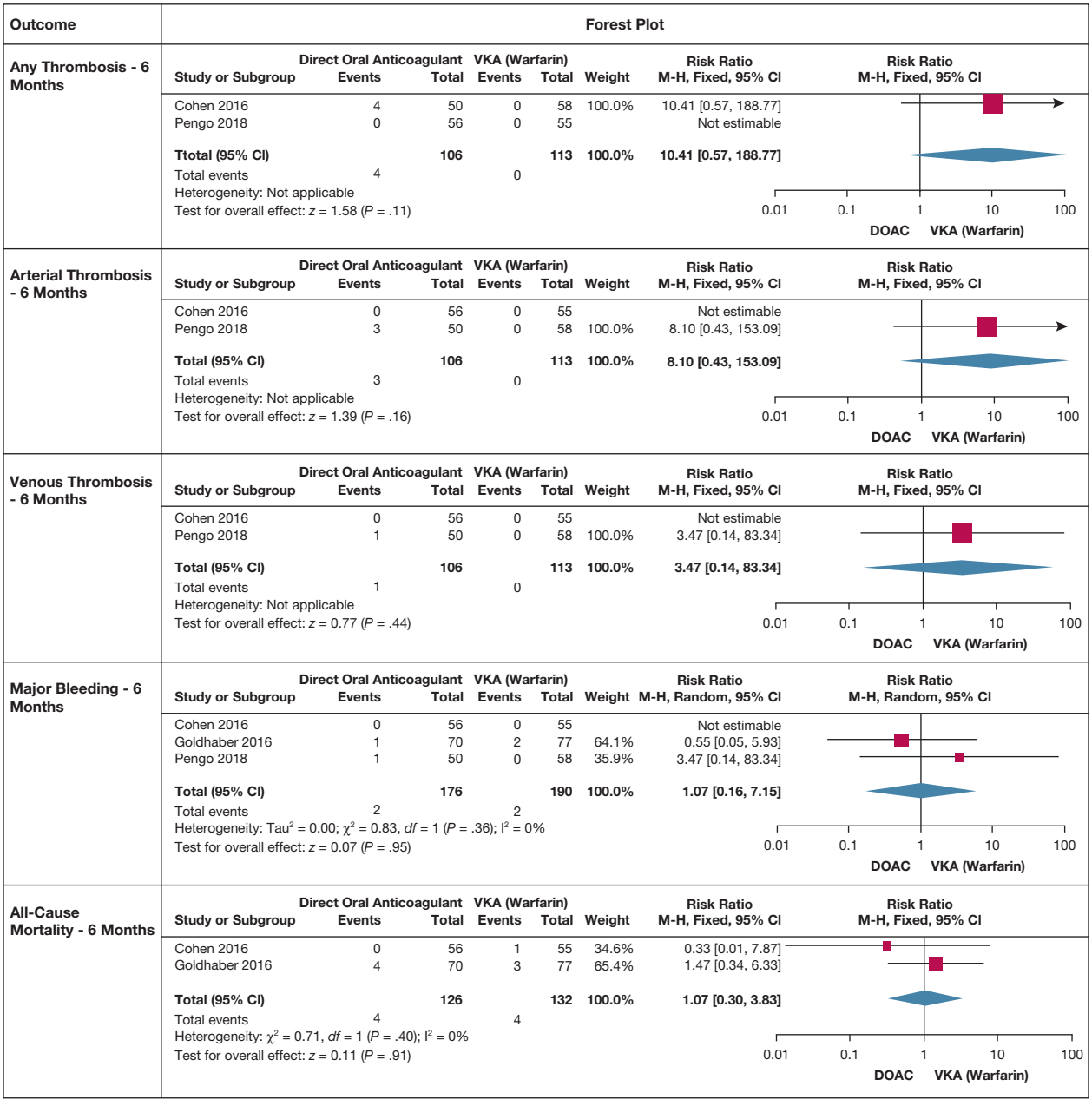

Figure 5 – *Forest plot of pooled estimates: direct-acting oral anticoagulants vs dose-adjusted vitamin K antagonists for preventing thrombotic events in patients with antiphospholipid syndrome. DOACs = direct-acting oral anticoagulants; M-H = Mantel-Haenszel; VKAs = vitamin K antagonists. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

Factors that favor the use of anticoagulant therapy in patients with SVT include the following:

1. Extensive SVT
2. Involvement above the knee, particularly if close to the saphenofemoral junction
3. Severe symptoms
4. Involvement of the greater saphenous vein
5. History of VTE or SVT
6. Active cancer
7. Recent surgery

Nonanticoagulant therapies for SVT include graduated compression stockings (eg, 83% of patients in the CALISTO study),[185] oral nonsteroidal antiinflammatory agents (which may reduce symptoms), and surgical therapies, including ligation of the saphenofemoral junction or stripping of thrombosed superficial veins. Anticoagulant therapy generally is not used to treat SVT that occurs in association with an IV infusion (ie, infusion thrombophlebitis).

Given the high prevalence of concomitant proximal DVT in patients with SVT and the need to treat such

TABLE 13] Evidence Profile: Fondaparinux vs Placebo for Treatment of Superficial Vein Thrombosis of the Leg

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Fondaparinux	Placebo	Relative (95% CI)	Absolute (95% CI)
PE (follow-up: 47 d; assessed with: standard imaging techniques)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a,b]	None	⊕⊕⊕◯ MODERATE	0/1,502 (0.0%)	5/1,500 (0.3%)	RR, 0.09 (0.01-1.64)	3 fewer per 1,000 (from 3 fewer to 2 more)
DVT (follow-up: 47 d; assessed with: standard imaging techniques)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	3/1,502 (0.2%)	18/1,500 (1.2%)	RR, 0.17 (0.05-0.56)	10 fewer per 1,000 (from 11 fewer to 5 fewer)
DVT or PE (follow-up: 47 d; assessed with: standard imaging techniques)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	3/1,502 (0.2%)	20/1,500 (1.3%)	RR, 0.15 (0.04-0.50)	11 fewer per 1,000 (from 13 fewer to 7 fewer)
Extension of superficial thrombophlebitis (follow-up: 47 d; assessed with: standard imaging techniques)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	4/1,502 (0.3%)	51/1,500 (3.4%)	RR, 0.08 (0.03-0.22)	31 fewer per 1,000 (from 33 fewer to 27 fewer)
Recurrence of superficial thrombophlebitis (follow-up: 47 d; assessed with: standard imaging techniques)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	5/1,502 (0.3%)	24/1,500 (1.6%)	RR, 0.21 (0.08-0.54)	13 fewer per 1,000 (from 15 fewer to 7 fewer)
All-cause mortality (follow-up: 47 d)										
3,002 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	2/1,502 (0.1%)	1/1,500 (0.1%)	RR, 2.00 (0.18-22.00)	1 more per 1,000 (from 1 fewer to 14 more)
Major bleeding (follow-up: 47 d)										
2,987 (1 study)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	1/1,499 (0.1%)	1/1,488 (0.1%)	RR, 0.99 (0.06-15.86)	0 fewer per 1,000 (from 1 fewer to 10 more)

Study synthesis was drawn from the Di Nisio et al[184] (2018) meta-analysis. Individual studies in Di Nisio et al[184] (2018) include Decousus et al[185] (2010) (CALISTO). Certainty assessments were drawn from Di Nisio et al[184] (2018), except for separate PE and DVT outcome measures that were generated by the authors. PE = pulmonary embolism; RR = risk ratio.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[b]CIs around relative and absolute estimates of effects include both appreciable benefit and appreciable harm.

TABLE 14] Evidence Profile: Prophylactic Low-Molecular-Weight Heparin vs Placebo for Treatment of Superficial Vein Thrombosis of the Leg

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Prophylactic LMWH	Placebo	Relative (95% CI)	Absolute (95% CI)
VTE end of treatment (follow-up: 12 d; assessed with: standard imaging techniques)										
222 (1 study)	Serious[a]	Not serious	Not serious	Serious[b,c]	None	⊕⊕◯◯ LOW	1/110 (0.9%)	4/112 (3.6%)	RR, 0.25 (0.03-2.24)	27 fewer per 1,000 (from 35 fewer to 44 more)
VTE 3-mo follow-up (follow-up: 97 d)										
222 (1 study)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	6/110 (5.5%)	5/112 (4.5%)	RR, 1.22 (0.38-3.89)	10 more per 1,000 (from 28 fewer to 129 more)
Extension or recurrence (or both) of superficial thrombophlebitis (follow-up: range, 12-97 d)										
222 (1 study)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	16/110 (14.5%)	37/112 (33.0%)	RR, 0.44 (0.26-0.74)	185 fewer per 1,000 (from 244 fewer to 86 fewer)
Major bleeding (follow-up: 97 d)										
222 (1 study)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	0/110 (0.0%)	0/112 (0.0%)	Not estimable	…

Study synthesis was drawn from the Di Nisio et al[186] (2018) meta-analysis. Individual studies in Di Nisio et al[186] (2018) include Quenet et al[187] (STENOX Group) (2003). Certainty assessments were drawn from Di Nisio et al[186] (2018), except for the assessment of the VTE end-of-treatment outcome measure, which was generated by the authors. LMWH = low-molecular-weight heparin; RR = risk ratio.

[a]Unclear random sequence generation and incomplete outcomes data.

[b]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[c]CIs around relative and absolute estimates of effects include both appreciable benefit and appreciable harm.

TABLE 15] Evidence Profile: Therapeutic Low-Molecular-Weight Heparin vs Placebo for Treatment of Superficial Vein Thrombosis of the Leg

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Therapeutic LMWH	Placebo	Relative (95% CI)	Absolute (95% CI)
VTE at end of treatment (follow-up: 12 d; assessed with: standard imaging techniques)										
218 (1 study)	Serious[a]	Not serious	Not serious	Serious[b,c]	None	⊕⊕◯◯ LOW	1/106 (0.9%)	4/112 (3.6%)	RR, 0.26 (0.32-2.33)	26 fewer per 1,000 (from 24 fewer to 48 more)
VTE at 3-mo follow-up (follow-up: 97 d)										
218 (1 study)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	4/106 (3.8%)	5/112 (4.5%)	RR, 0.85 (0.23-3.06)	7 fewer per 1,000 (from 34 fewer to 92 more)
Extension or recurrence (or both) of superficial thrombophlebitis (follow-up: 97 d; assessed with: standard imaging techniques)										
218 (1 study)	Serious[a]	Not serious	Not serious	Not serious	Serious[b]	⊕⊕◯◯ LOW	16/106 (15.1%)	37/112 (33.0%)	RR, 0.46 (0.27-0.77)	178 fewer per 1,000 (from 241 fewer to 76 fewer)
Major bleeding (follow-up: 97 d)										
218 (1 study)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	0/106 (0.0%)	0/112 (0.0%)	Not estimable	…

Study synthesis was drawn from the Di Nisio et al[186] (2018) meta-analysis. Individual studies in Di Nisio et al[186] (2018) include Quenet et al[187] (STENOX Group) (2003). Certainty assessments were drawn from Di Nisio et al (2018),[186] except for the assessment of the VTE end-of-treatment outcome measure, which was generated by the authors. LMWH = low-molecular-weight heparin; RR = risk ratio.

[a]Unclear random sequence generation and incomplete outcomes data.

[b]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[c]CIs around relative and absolute estimates of effects include both appreciable benefit and appreciable harm.

TABLE 16] Evidence Profile: Fondaparinux vs Rivaroxaban for Treatment of Superficial Vein Thrombosis of the Leg

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Fondaparinux	Rivaroxaban	Relative (95% CI)	Absolute (95% CI)
Recurrence of superficial thrombophlebitis (follow-up: 90 d)										
472 (1 study)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	3/236 (1.3%)	4/236 (1.7%)	RR, 0.75 (0.17-3.31)	4 fewer per 1,000 (from 14 fewer to 39 more)
Recurrent VTE (follow-up: 90 d; assessed with: standard imaging techniques)										
472 (1 study)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	1/236 (0.4%)	3/236 (1.3%)	RR, 0.33 (0.03-3.18)	9 fewer per 1,000 (from 12 fewer to 28 more)
Major bleeding (follow-up: 45 d; assessed with: ISTH criteria)										
471 (1 study)	Not serious	Not serious	Not serious	Very serious[a]	None	⊕⊕◯◯ LOW	0/235 (0.0%)	0/236 (0.0%)	Not estimable	…
All-cause mortality (follow-up: 90 d)										
472 (1 study)	Not serious	Not serious	Not serious	Very serious[a,b]	None	⊕⊕◯◯ LOW	0/236 (0.0%)	1/236 (0.4%)	RR, 0.33 (0.01-8.14)	3 fewer per 1,000 (from 4 fewer to 30 more)

Study synthesis was drawn from the Di Nisio et al[186] (2018) meta-analysis. Individual studies in Di Nisio et al[186] (2018) include Beyer-Westendorf et al[188] (2017). Certainty assessments were generated by the authors. ISTH = International Society on Thrombosis and Haemostasis; RR = risk ratio.

[a]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative risk reduction of 25%.

[b]CIs around relative and absolute estimates of effects include both appreciable benefit and appreciable harm.

patients with higher doses of anticoagulant therapy (ie, therapeutic doses), patients with clinically suspected SVT above the knee should have ultrasonography to exclude proximal DVT. Ultrasound can also help with the diagnosis of SVT if the clinical presentation is uncertain.

Background

SVT has been less well studied than DVT but is estimated to occur more often.[189] It usually affects the lower limbs; often involves a varicose vein; and is associated with chronic venous insufficiency, malignancy, thrombophilia, pregnancy or estrogen therapy, obesity, sclerotherapy, long-distance travel, and a history of VTE. In addition, SVT may be unprovoked.[184] Although traditionally considered a benign disease, a number of studies indicate that the consequences of SVT may be more serious.[190] A prospective study of 3,002 patients with acute SVT of the greater saphenous vein with extent $>$ 5 cm found that 5.9% of patients experienced symptomatic extension of SVT, and extension to DVT or PE at 77 days in the absence of anticoagulants.[185]

With greater appreciation of the seriousness of SVT, investigators have evaluated anticoagulant therapy, often in prophylactic or intermediate doses, to reduce acute symptoms, extension, recurrence, and progression to VTE.

Comparison With Prior Versions

The 1st update panel favored fondaparinux over LMWH when anticoagulants were chosen for SVT.[4] The 2nd update panel maintained this statement, but added a statement supporting low-dose rivaroxaban, based principally on interval evidence from an RCT.[188]

Duration of Anticoagulation in Patients With Acute VTE

Evidence and Evidence-to-Decision

The panel dyad reviewed 1,361 abstracts, from which they selected 37 full texts for review. On review of the evidence, the dyad identified several systematic reviews/meta-analyses that addressed the question but determined that all had substantial limitations, and thus performed a new pooled analysis that included 15 RCTs and is detailed in Table 17.[153,167,191–202] The panelists determined that both the desirable and undesirable effects of the intervention are moderate in magnitude. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a moderate certainty of evidence.

Additional Comments

An updated review of evidence regarding the decision to offer extended-phase anticoagulation to patients with unprovoked VTE was performed, as the most common and difficult decision about whether to stop anticoagulants after a time-limited course or to use extended therapy is for patients with a first unprovoked proximal DVT or PE. In this subgroup of patients, several approaches have been studied to attempt to more precisely refine the predicted risk for recurrent VTE, and to select patients most likely to have a favorable risk-to-benefit balance if provided extended-phase therapy. Yet the decision remains challenging, as not all patients who sustain an initial event will go on to have a future event, making individualized assessment of the risk-to-benefit balance of extended-phase treatment difficult. Current risk assessment systems are imperfect at predicting the risk of thrombosis in the absence of extended-phase therapy, or the risk of bleeding with extended-phase therapy. Pooled risk estimates comparing extended-phase (indefinite period) with time-limited anticoagulation for patient-important outcomes are found in Figures 6 and 7. Studies validating these risk models, however, have been performed or are underway, yet await further validation preferably in pooled analyses before they can inform patients and physicians on the optimal risk-to-benefit balance in individual cases.

The 2nd update panel focused its literature review and assessment on the question of identifying patients who should be offered extended-phase therapy on completion of the treatment phase. The updated guidance statements focus on three patient subgroups: VTE provoked by a major transient risk factor (eg, surgery with general anesthesia for greater than 30 min, confinement to bed in hospital [only "bathroom privileges"] for at least 3 days with an acute illness, cesarean section); VTE provoked by a minor transient risk factor (eg, surgery with general anesthesia for less than 30 min, admission to hospital for less than 3 days with an acute illness, estrogen therapy, pregnancy or puerperium, confinement to bed out of hospital for at least 3 days with an acute illness, leg injury associated with reduced mobility for at least 3 days); and unprovoked VTE. Patients with a minor transient risk factor represent a group with the closest balance between the risk of recurrent thrombosis without extended-phase anticoagulation, and the risk of bleeding if receiving extended-phase anticoagulation. The panel favored a suggestion against offering extended-phase anticoagulation, but this decision is highly informed by

TABLE 17] Evidence Profile: Extended-Phase Anticoagulation (Indefinite Period) vs Time-Limited Anticoagulation for Prevention of Subsequent Provoked or Unprovoked VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Anticoagulation for Indefinite Period (Extended Phase)	Anticoagulation for Definite Period (Time-Limited, Treatment Phase)	Relative (95% CI)	Absolute (95% CI)
Recurrent VTE (follow-up: range, 7-48 mo; assessed with: objective diagnosis)										
6,665 (14 studies)	Not serious[a]	Serious[b]	Not serious	Not serious[c]	None	⊕⊕⊕◯ MODERATE	154/3,352 (4.6%)	370/3,313 (11.2%)	RR, 0.43 (0.28-0.67)	64 fewer per 1,000 (from 80 fewer to 37 fewer)
Recurrent VTE (< 100% unprovoked)—VKA intervention (follow-up: range, 11-48 mo; assessed with: objective diagnosis)										
9,47 (4 studies)	Serious[d]	Serious[b]	Not serious	Serious[e]	None	⊕◯◯◯ VERY LOW	41/478 (8.6%)	78/469 (16.6%)	RR, 0.51 (0.26-1.01)	81 fewer per 1,000 (from 123 fewer to 2 more)
Recurrent VTE (< 100% unprovoked)—DOAC intervention (follow-up: range, 7-18 mo; assessed with: objective diagnosis)										
4,208 (3 studies)	Not serious[a]	Not serious	Not serious	Not serious[c]	None	⊕⊕⊕⊕ HIGH	25/2,123 (1.2%)	152/2,085 (7.3%)	RR, 0.17 (0.11-0.26)	61 fewer per 1,000 (from 65 fewer to 54 fewer)
Major bleeding (follow-up: range, 7-48 mo; assessed with: ISTH criteria)										
6,665 (14 studies)	Not serious[a]	Not serious	Not serious	Not serious[c]	None	⊕⊕⊕⊕ HIGH	46/3,352 (1.4%)	20/3,313 (0.6%)	RR, 1.98 (1.18-3.32)	6 more per 1,000 (from 1 more to 14 more)
Major bleeding (< 100% unprovoked)—VKA intervention (follow-up: range, 11-48 mo; assessed with: ISTH criteria)										
947 (4 studies)	Serious[d]	Not serious	Not serious	Serious[e]	None	⊕⊕◯◯ LOW	16/478 (3.3%)	5/469 (1.1%)	RR, 2.91 (1.12-7.56)	20 more per 1,000 (from 1 more to 70 more)
Major bleeding (< 100% unprovoked)—DOAC intervention (follow-up: range, 7-18 mo; assessed with: ISTH criteria)										
4,208 (3 studies)	Not serious[a]	Not serious	Not serious	Serious[c,f]	None	⊕⊕⊕◯ MODERATE	8/2,123 (0.4%)	4/2,085 (0.2%)	RR, 1.97 (0.29-13.64)	2 more per 1,000 (from 1 fewer to 24 more)
All-cause mortality (follow-up: range, 7-48 mo)										
6,665 (14 studies)	Not serious[a]	Not serious	Not serious	Not serious[c]	None	⊕⊕⊕⊕ HIGH	65/3,352 (1.9%)	77/3,313 (2.3%)	RR, 0.83 (0.58-1.21)	4 fewer per 1,000 (from 10 fewer to 5 more)

(Continued)

TABLE 17] *(Continued)*

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Anticoagulation for Indefinite Period (Extended Phase)	Anticoagulation for Definite Period (Time-Limited, Treatment Phase)	Relative (95% CI)	Absolute (95% CI)
All-cause mortality (< 100% unprovoked)—VKA intervention (follow-up: range, 11-48 mo)										
947 (4 studies)	Serious[d]	Not serious	Not serious	Serious[e]	None	⊕⊕◯◯ LOW	31/478 (6.5%)	32/469 (6.8%)	RR, 0.94 (0.52-1.71)	4 fewer per 1,000 (from 33 fewer to 48 more)
All-cause mortality (< 100% unprovoked)—DOAC intervention (follow-up: range, 7-18 mo)										
4,208 (3 studies)	Not serious[a]	Not serious	Not serious	Serious[c,f]	None	⊕⊕⊕◯ MODERATE	8/2,123 (0.4%)	18/2,085 (0.9%)	RR, 0.46 (0.20-1.04)	5 fewer per 1,000 (from 7 fewer to 0 fewer)

Analysis includes all patients with VTE and a subgroup of studies enrolling patients with both unprovoked VTE and VTE in the setting of transient risk factors. Meta-analysis was generated by the authors, using the following studies: Eischer et al[191] (2009) (AUREC), Farraj[192] (2004), Kearon et al[193] (2000), Couturaud et al[194] (2019) (PADIS-DVT), Couturaud et al[195] (2015) (PADIS-PE), Ridker et al[196] (2003) (PREVENT), Agnelli et al[197] (2001) (WODIT-DVT), Agnelli et al[167] (2013) (AMPLIFY-EXT), Siragusa et al[198] (2008) (DACUS), Schulman et al[199] (1997) (DURAC), EINSTEIN Investigators[153] (2010), Levine et al[200] (1995), Schulman et al[201] (2013) (RE-SONATE), and Agnelli et al[202] (2003) (WODIT-PE). VKA subgroup analysis includes Siragusa et al[198] (2008) (DACUS), Schulman et al[199] (1997) (DURAC), Levine et al[200] (1995), and Agnelli et al[202] (2003) (WODIT-PE). DOAC subanalysis includes Agnelli et al[167] (2013) (AMPLIFY-EXT), EINSTEIN Investigators (2010),[153] and Schulman et al[201] (2013) (RE-SONATE). Certainty assessments, including risk of bias assessments, were conducted by the authors. Forest plots for the overall synthesis are included in Figure 6. Forest plots of subanalyses of VKA and DOACs in studies with < 100% unprovoked study populations are included in Figure 7. DOAC = direct-acting oral anticoagulant; ISTH = International Society on Thrombosis and Haemostasis; RR = risk ratio; VKA = vitamin K antagonist.

[a]Significant majority of studies and study population rated as low risk of study bias.

[b]I^2 > 60%. Variation across study populations in risk factors related to VTE recurrence include variation in definition of provoked/unprovoked, number of prior VTE events, presence of factor VIII, and population demographics.

[c]Large sample size (> 4,000).

[d]Majority of overall study population from moderate to high risk of bias studies.

[e]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[f]CIs around relative and absolute estimates include appreciable benefit and appreciable harm.

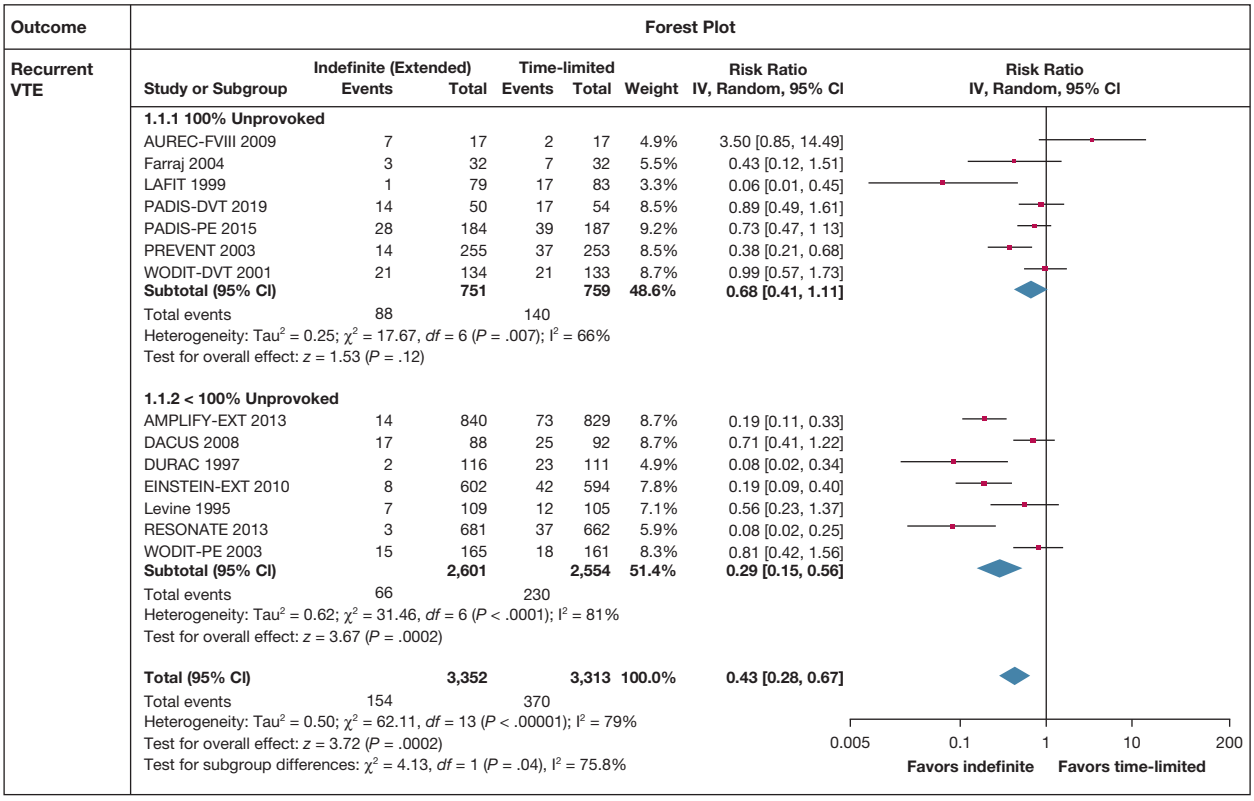

Figure 6 – *Forest plot of pooled estimates: extended-phase anticoagulation (indefinite period) vs time-limited anticoagulation for prevention of subsequent provoked or unprovoked VTE. IV = inverse-variance. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

the values and preferences of the patient. Other guidelines have made weak recommendations (suggestions) for the opposite.[6,203] Panelist discussion surrounding these discrepant recommendations included (a) avoidance of prescribing anticoagulation and the concomitant certain potential harm, however uncertain benefit (b) acknowledgment that studies of extended-phase anticoagulation monitored patients for durations of about 2 to 4 years, further limiting evidence for anticoagulation among such patients, and (c) updated guidance from others[204] that endorsed an approach analogous to that favored by the panelists. Recurrent unprovoked VTE is not separately specified, as the same guidance would apply as for patients with an initial unprovoked VTE. In patients offered extended-phase treatment, use of a DOAC receives a stronger recommendation than use of VKA, principally driven by lower risk of bleeding.

It should be noted that trials assessing outcomes of patients receiving extended-phase anticoagulation assessed outcomes for up to approximately 4 years of follow-up. Although participants in these trials generally did not discontinue anticoagulants at the conclusion of follow-up, the risk-to-benefit balance of continuing anticoagulants beyond this period is less certain. Choice of anticoagulant during extended-phase therapy may be simply the continuation of that anticoagulant chosen for the treatment phase. However, over the course of extended-phase therapy individual patient circumstance or preference may change such that continuing the selected anticoagulant may become less favorable. In this case the panelists agreed that electing continuation of anticoagulation with an alternative anticoagulant is appropriate.

Background

Duration of anticoagulation refers both to the length of the initiation and treatment phases of anticoagulant therapy, as detailed in the introduction above, as well as the decision to offer extended-phase therapy. The 2nd update panel opted against an updated review of evidence for the duration of the initiation and treatment phases, although members chose to combine several statements from the 1st update into a single new guidance statement, to improve clarity.

AT9 recommendations on how long VTE should be treated were based on comparisons of four durations of

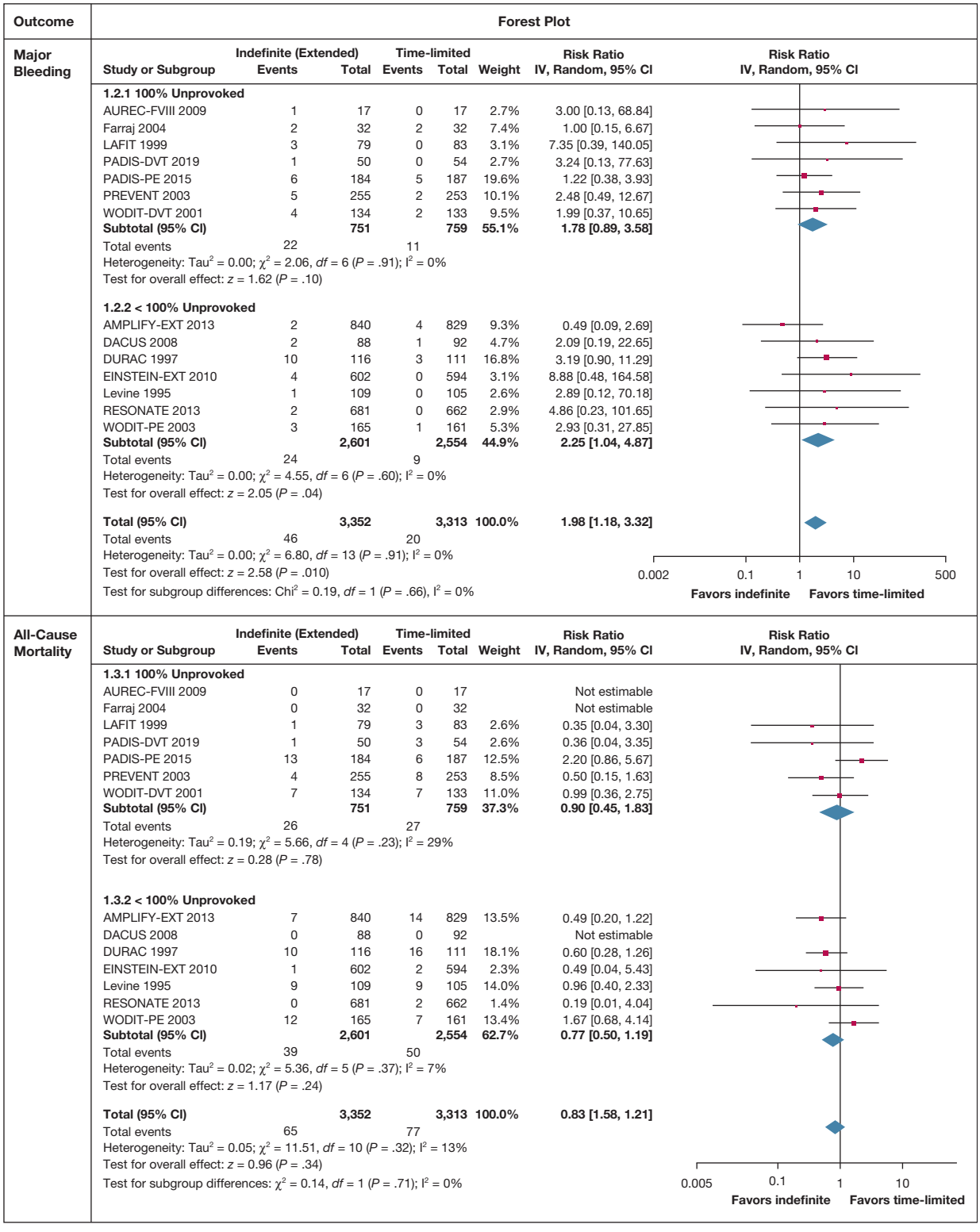

Figure 6 – *Continued*

treatment: (1) 4 or 6 weeks; (2) 3 months; (3) longer than 3 months but still a time-limited course of therapy (usually 6 or 12 months); or (4) extended (also termed "indefinite"; no scheduled stopping date) therapy.[4] These four options were assessed in three subgroups of VTE patients with different estimated risks of recurrence after stopping anticoagulant therapy: (1) VTE provoked by surgery (a major transient risk factor; 3% recurrence at 5

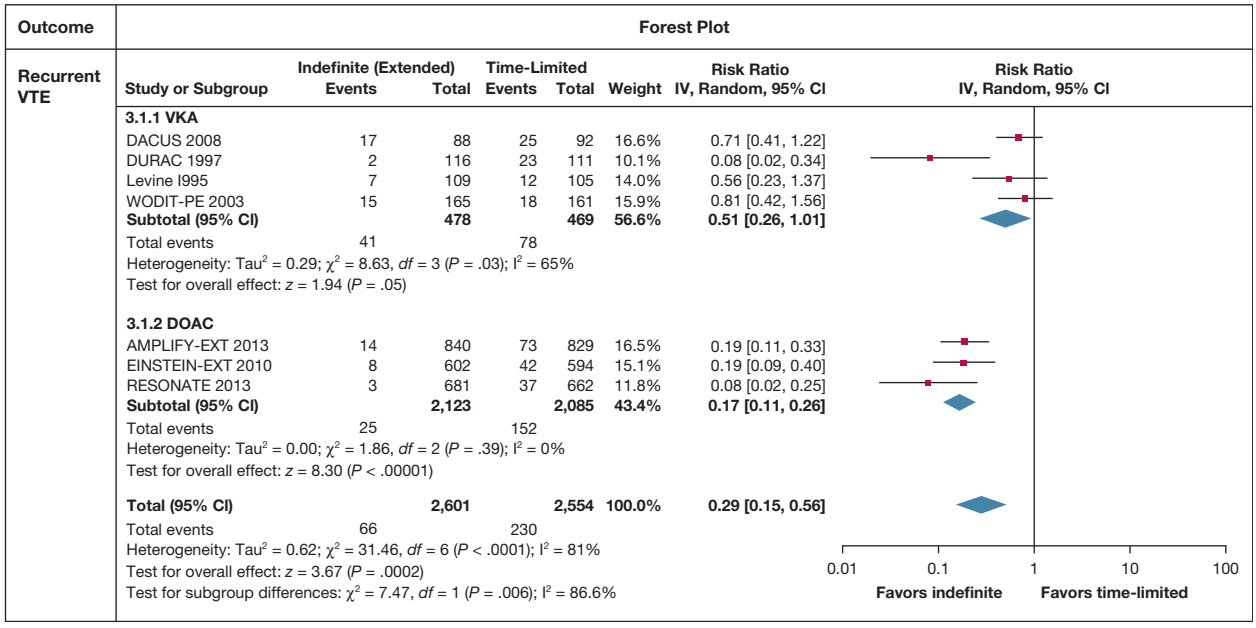

Figure 7 – *Forest plot of pooled estimates: extended-phase anticoagulation (indefinite period) vs time-limited anticoagulation for prevention of subsequent provoked or unprovoked VTE: vitamin K antagonist and direct-acting oral anticoagulant subanalyses of studies with < 100% unprovoked study population. DOAC = direct-acting oral anticoagulant; IV = inverse-variance; VKA = vitamin K antagonist. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

years)[205]; (2) VTE provoked by a nonsurgical transient risk factor (eg, estrogen therapy, pregnancy, leg injury, flight of > 8 h; 15% recurrence at 5 years)[205]; and (3) unprovoked (also termed "idiopathic") VTE, that is, not meeting criteria for provocation by a transient risk factor or by cancer (30% recurrence at 5 years).[206,207] Recurrence risk was further stratified by estimating the risk of recurrence after (1) an isolated distal DVT was one-half that after a proximal DVT or PE[208,209] and (2) a second unprovoked proximal DVT or PE was 50% higher (1.5-fold) than after a first unprovoked event.[209,210]

For the decision about whether to stop treatment at 3 months or to treat indefinitely ("extended treatment"), the AT9 panel categorized a patient's risk of bleeding while receiving anticoagulant therapy as low (no bleeding risk factors; 0.8% annualized risk of major bleeding), moderate (one bleeding risk factor; 1.6% annualized risk of major bleeding), or high (two or more bleeding risk factors; 6.5% annualized risk of major bleeding).[4] At the time of the 1st update, four additional studies were available: two that compared two time-limited durations of anticoagulant therapy[195,211] and two comparing extended DOAC treatment with stopping therapy (placebo).[167,201]

Comparison With Prior Versions

AT9 included a complex set of recommendations that addressed multiple lengths of treatment-phase anticoagulation, including separate guidance statements for DVT and PE, as well as statements covering the decision to offer extended-phase therapy.[4] The 1st update panel endorsed the statements from AT9, considering the interval evidence further confirmatory of the guidance; the only alteration was to change a weak to strong recommendation in favor of extended therapy in patients with a second unprovoked VTE who had a moderate risk of bleeding.[2] In the 2nd update, the panel considered the concept of different time-limited courses of anticoagulant therapy to be unchanged by interval evidence and voted to carry forward relevant statements without new formal evidence review. However, the 2nd update panel determined that the multiple statements relevant to differing time-limited (treatment-phase) periods of therapy could be more clearly combined into a single statement covering both DVT and PE. Likewise, guidance regarding selection of patients for extended-phase therapy also applies to both those with DVT and/or PE.

Reduced-Dose vs Full-Dose Anticoagulation for Extended Treatment of VTE

Evidence and Evidence-to-Decision

The panel dyad reviewed 114 abstracts, from which they selected 14 full texts for review. Studies selected for abstraction and synthesis are detailed in

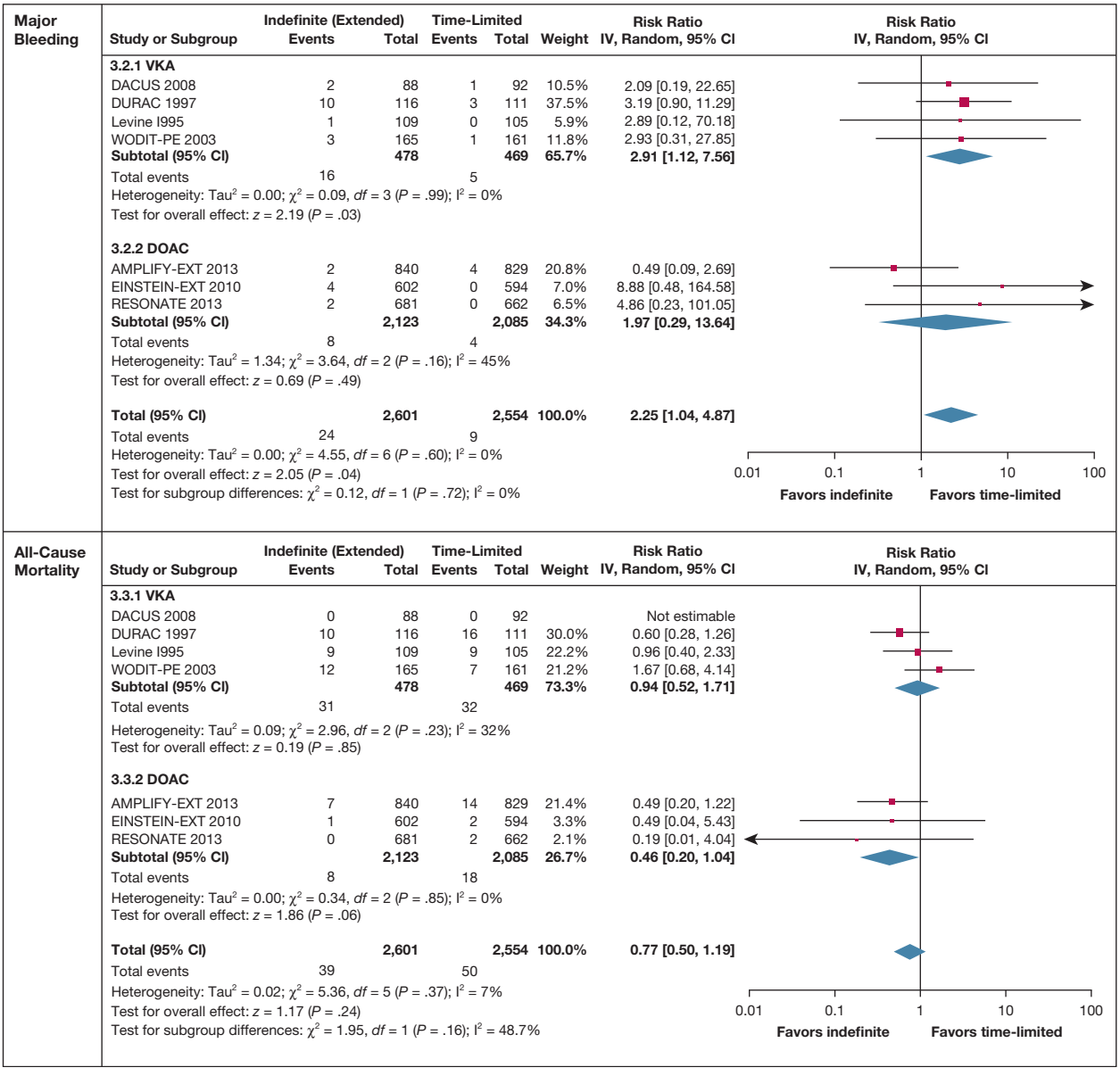

Figure 7 – *Continued*

Tables 18 and 19.[167,212,213] For the comparison of DOAC vs aspirin or placebo, the panelists determined that the desirable effects of the intervention (reduced dose) are large in magnitude whereas the undesirable effects are moderate. Overall, the panelists rated the balance of effects as favoring the intervention, with a low certainty of evidence. For the comparison of reduced-dose vs full-dose DOAC, the panelists determined that the desirable effects of the intervention are trivial in magnitude whereas the undesirable effects are small. Overall, the panelists rated the balance of effects as favoring neither the intervention nor the comparison, with a very low certainty of evidence.

Background

The decision to offer extended-phase anticoagulation for secondary prevention of VTE is sensitive to the risk of both recurrent thrombosis without treatment, and the risk for bleeding on extended-phase treatment.[2] Reduced doses of anticoagulants, as well as low-dose aspirin, have been studied as approaches that might be effective in preventing VTE recurrence with a reduced risk for

TABLE 18] Evidence Profile: Reduced vs Full Dose of Direct-Acting Oral Anticoagulants in Extended Phase of Treatment for VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Reduced Dose of DOACs	Full Dose of DOACS	Relative (95% CI)	Absolute (95% CI)
Recurrent symptomatic VTE (DVT and fatal or nonfatal PE) (follow-up: 12 mo; assessed with: DVT and fatal or nonfatal PE event)										
3,887 (2 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	31/1,967 (1.6%)	27/1,920 (1.4%)	Not estimable	2 more per 1,000 (from 5 fewer to 12 more)
Major or clinically relevant nonmajor bleeding event (follow-up: 12 mo; assessed with: major events [ISTH]; nonmajor events [per individual study criteria])										
3,887 (2 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	54/1,967 (2.7%)	71/1,920 (3.7%)	Not estimable	10 fewer per 1,000 (from 18 fewer to 2 more)

Study synthesis drawn from the Vasanthamohan et al[212] (2018) meta-analysis. Individual studies in Vasanthamohan et al[212] (2018) include Agnelli et al[167] (2013) (AMPLIFY-EXT) and Weitz et al[213] (2017) (EINSTEIN CHOICE). Certainty assessment results, including risk of bias assessments, were drawn from Vasanthamohan et al[212] (2018). DOACs = direct-acting oral anticoagulants; ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism.
[a]Downgraded by Vasanthamohan et al[212] (2018) given the wide CIs resulting from the small number of studies and lack of detected risk difference between intervention and control.

TABLE 19] Evidence Profile: Reduced-Dose Direct-Acting Oral Anticoagulants vs Aspirin or Placebo for Extended Phase of Treatment for VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Reduced Dose of DOACs	Aspirin or Placebo	Relative (95% CI)	Absolute (95% CI)
Recurrent symptomatic VTE (DVT and fatal or nonfatal PE) (follow-up: 12 mo; assessed with: DVT and fatal or nonfatal PE event)										
3,927 (2 studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH	31/1967 (1.6%)	123/1960 (6.3%)	Not estimable	46 fewer per 1,000 (from 54 fewer to 34 fewer)
Major or clinically relevant nonmajor bleeding event (follow-up: 12 mo; assessed with: major events [ISTH]; nonmajor events [per individual study criteria])										
3,927 (2 studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ MODERATE	54/1967 (2.7%)	45/1960 (2.3%)	Not estimable	4 more per 1,000 (from 4 fewer to 18 more)

Study synthesis drawn from the Vasanthamohan et al[212] (2018) meta-analysis. Individual studies in Vasanthamohan et al[212] (2018) include Agnelli et al[167] (2013) (AMPLIFY-EXT) and Weitz et al[213] (2017) (EINSTEIN CHOICE). Certainty assessment results, including risk of bias assessments, were drawn from Vasanthamohan et al[212] (2018). DOACs = direct-acting oral anticoagulants; ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism.
[a]Downgraded by Vasanthamohan et al[212] (2018) given the wide CIs and lack of detected risk difference between intervention and control.

bleeding.[167,214,215] By improving the risk-to-benefit balance of extended-phase anticoagulation through reducing the risk for bleeding, the decision to offer this therapy is simplified, and the eligible population might increase.

Comparison With Prior Versions

Neither AT9 nor the 1st update addressed this PICO.

Aspirin for Extended Treatment of VTE

Evidence and Evidence-to-Decision

The panel dyad reviewed 129 abstracts, from which they selected nine full texts for review. Studies selected for abstraction and synthesis are detailed in Tables 20 and 21.[213,216–218] For the comparison of aspirin with no aspirin, the panelists determined that the desirable effects of the intervention are trivial in magnitude whereas the undesirable effects are small. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a moderate certainty of evidence. For the comparison of rivaroxaban with aspirin, the panelists determined that the desirable effects of the intervention are large in magnitude whereas the undesirable effects are moderate. Overall, the panelists rated the balance of effects as probably favoring the intervention, with a moderate certainty of evidence. Pooled risk estimates comparing aspirin with rivaroxaban and placebo for patient-important outcomes are found in Figures 8 and 9.

Additional Comments

On the basis of direct and indirect comparisons, we expect the net benefit of extended anticoagulant therapy in patients with unprovoked VTE to be substantially greater than the benefits of extended aspirin therapy.[214,219] Consequently, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin (which may also include a small reduction in arterial thrombosis risk). These benefits must be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients with VTE stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started. Although payor status affects direct patient costs it has been estimated that continued anticoagulation may be associated with lower overall clinical costs yet perhaps higher total health care costs.[220]

TABLE 20] Evidence Profile: Rivaroxaban vs Aspirin for Extended Phase of Treatment for VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Rivaroxaban	Aspirin	Relative (95% CI)	Absolute (95% CI)
Recurrent VTE (follow-up: 12 mo; assessed with: standard imaging procedures)										
921 (1 study)	Not serious	Not serious	Not serious	Serious[a,b]	Not serious	⊕⊕⊕◯ MODERATE	15/921 (1.6%)	26/468 (5.6%)	RR, 0.29 (0.16-0.55)	39 fewer per 1,000 (from 47 fewer to 25 fewer)
Major bleeding (follow-up: 12 mo; assessed with: ISTH criteria)										
921 (1 study)	Not serious	Not serious	Not serious	Serious[a,b]	Not serious	⊕⊕⊕◯ MODERATE	6/921 (0.7%)	1/468 (0.2%)	RR, 3.05 (0.37-25.25)	4 more per 1,000 (from 1 fewer to 52 more)

Study synthesis was drawn from the Robertson et al[216] (2017) meta-analysis. Individual studies in Robertson et al[216] (2017) include Weitz et al[213] (2017) (EINSTEIN CHOICE). Results of the Robertson et al[216] (2017) meta-analysis were adjusted by the authors to reflect Mantel-Haenszel with a fixed effect. Certainty assessment results, including risk of bias assessments, were drawn from Robertson et al[216] (2017). Forest plots for the adjusted final synthesis are included in Figure 8. ISTH = International Society on Thrombosis and Haemostasis; RR = risk ratio.
[b]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

TABLE 21] Evidence Profile: Aspirin vs Placebo for Extended Phase of Treatment for VTE

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Aspirin	Placebo	Relative (95% CI)	Absolute (95% CI)
All-cause mortality (follow-up: range, 2-4 y)										
1,224 (2 studies)	Serious[a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE	22/616 (3.6%)	23/608 (3.8%)	RR, 0.95 (0.53-1.68)	2 fewer per 1,000 (from 18 fewer to 26 more)
VTE-related mortality (follow-up: range, 2-4 y)										
1,224 (2 studies)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	2/616 (0.3%)	2/608 (0.3%)	RR, 0.98 (0.14-6.93)	0 fewer per 1,000 (from 3 fewer to 20 more)
Recurrent VTE (follow-up: range, 2-4 y; assessed with: standard imaging practices)										
1,224 (2 studies)	Serious[a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE	85/616 (13.8%)	116/608 (19.1%)	RR, 0.72 (0.56-0.93)	53 fewer per 1,000 (from 84 fewer to 13 fewer)
Major bleeding (follow-up: range, 2-4 y; assessed with: ISTH criteria)										
1,224 (2 studies)	Serious[a]	Not serious	Not serious	Serious[b,c]	None	⊕⊕◯◯ LOW	9/616 (1.5%)	7/608 (1.2%)	RR, 1.28 (0.48-3.41)	3 more per 1,000 (from 6 fewer to 28 more)
Stroke (assessed with: ischemic, hemorrhagic, or TIA)										
1,224 (2 studies)	Serious[a]	Not serious	Not serious	Serious[b,c]	None	⊕⊕◯◯ LOW	7/616 (1.1%)	6/608 (1.0%)	RR, 1.15 (0.39-3.42)	1 more per 1,000 (from 6 fewer to 24 more)

Study synthesis was drawn from the Robertson et al[216] (2017) meta-analysis. Individual studies in Robertson et al[216] (2017) include Brighton et al[217] (2012) (ASPIRE) and Becattini et al[218] (2012) (WARFASA). Results of the Robertson et al[216] (2017) meta-analysis were updated by the authors to reflect risk ratio calculation for measurement of relative effect. Certainty assessment results, including risk of bias assessments, were drawn from Robertson et al[216] (2017). Forest plots for the adjusted final synthesis are included in Figure 9. ISTH = International Society on Thrombosis and Haemostasis; RR = risk ratio; TIA = transient ischemic attack.

[a]Selection bias (WARFASA study).

[b]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[c]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

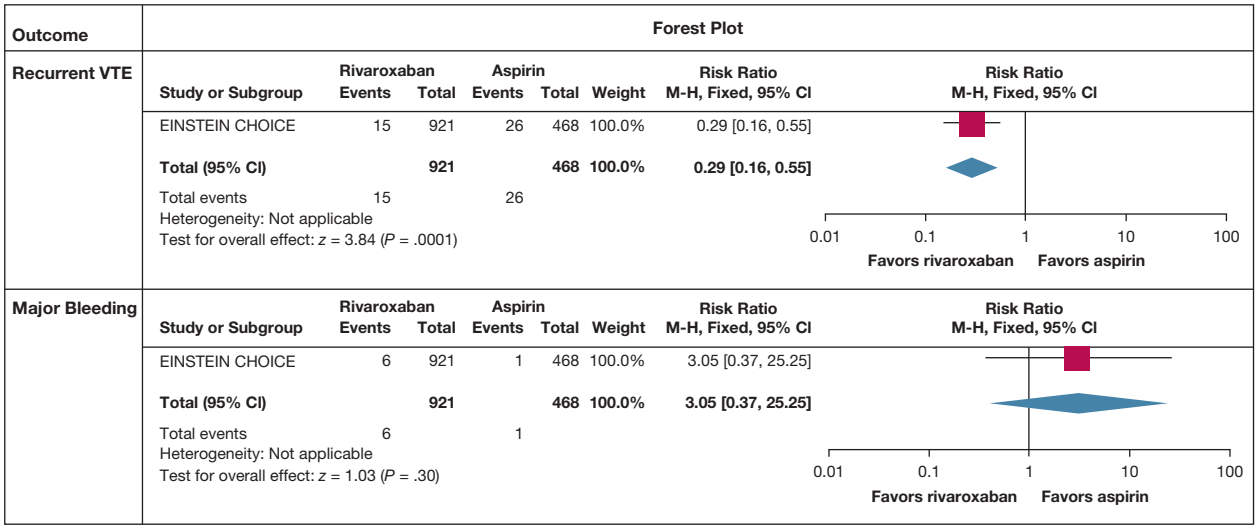

Figure 8 – *Forest plot of pooled estimates: rivaroxaban vs aspirin for extended phase of treatment for VTE. M-H = Mantel-Haenszel. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

Background

Extended anticoagulant therapy is estimated to reduce recurrent VTE by more than 80%, and extended DOAC therapy is associated with a risk of bleeding similar to that of aspirin.[219,221] Comparatively, it has been estimated that aspirin will reduce the risk of recurrent VTE by about one-third.[214] If patients with a first unprovoked VTE decline extended anticoagulant therapy because they have risk factors for bleeding or because they have a lower than average risk of recurrence, the net benefit of aspirin therapy is expected to be less than in the trials that evaluated aspirin for extended treatment of VTE. The direct comparison of anticoagulant therapy with aspirin demonstrated superiority of anticoagulation with no difference in major bleeding.[213]

At the time of the 1st update, two randomized trials had compared aspirin with placebo for the prevention of recurrent VTE in patients with a first unprovoked proximal DVT or PE and who have completed 3 to 18 months of anticoagulant therapy.[214,217,218]

Comparison With Prior Versions

AT9 did not address whether there was a role for aspirin, or antiplatelet therapy generally, in the treatment of VTE. The 1st update panel suggested that aspirin be considered for patients who stop anticoagulation but remarked that aspirin should not be considered a substitute for extended anticoagulation, due to lower efficacy. The 2nd update panel voted to endorse the 1st update statement and added a second guidance statement to reflect the additional evidence directly comparing rivaroxaban with aspirin for extended therapy.

Compression Stockings in Preventing Postthrombotic Syndrome

Evidence and Evidence-to-Decision

The panel dyad reviewed 197 abstracts, from which they selected 53 full texts for review. Studies selected for abstraction and synthesis are detailed in Table 22.[222–225] The panelists determined that the desirable effects of the intervention are moderate in magnitude whereas the undesirable effects are small. Overall, the panelists rated the balance of effects as probably favoring the comparison, with a low certainty of evidence.

Additional Comments

The SOX trial found that routine use of graduated compression stockings did not reduce leg pain during the 3 months after DVT diagnosis.[226] Follow-up at 6 and 24 months demonstrated no benefit for graduated compression stockings (GCS) in the reduction of PTS or for the outcome of severe PTS symptoms. This finding, however, does not mean that graduated compression stockings will not reduce acute symptoms of DVT or chronic symptoms in those who have developed PTS. No evidence exists that the use of GCS following DVT reduces risk for recurrent DVT. Pooled risk estimates

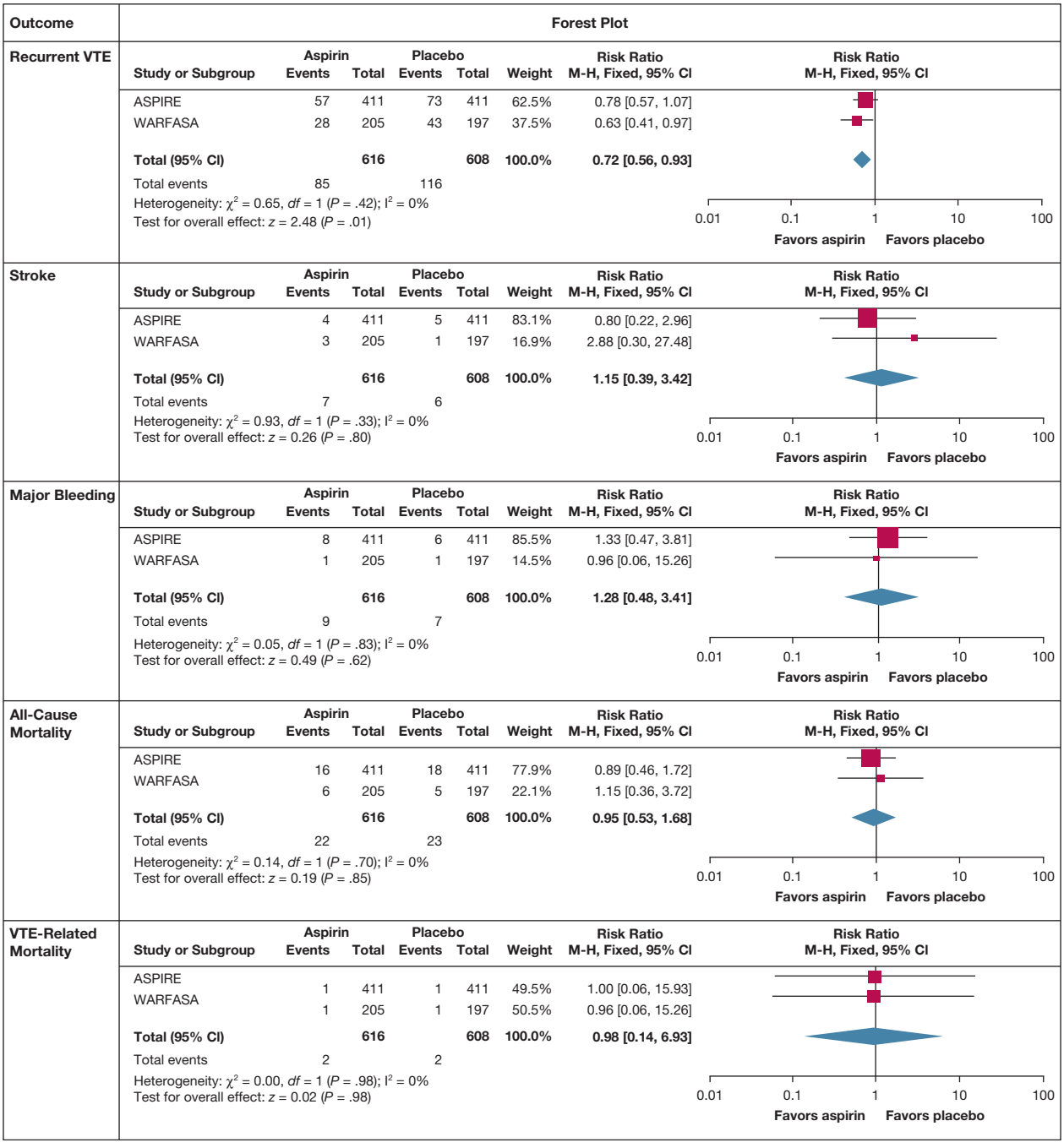

Figure 9 – *Forest plot of pooled estimates: aspirin vs placebo for extended phase of treatment for VTE. M-H = Mantel-Haenszel. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

comparing GCS with no GCS for patient-important outcomes are found in Figure 10.

Background

Small studies of limited quality[222–224] formerly informed the recommendations regarding the benefits of graduated compression stockings for the prevention of postthrombotic syndrome before a landmark study of nearly 400 patients in 2014.[226] Heterogeneity of results exist when pooling the smaller studies with the 2014 study. A reduction in the outcome of either any PTS or the outcome of severe PTS at 36 months was suggested

TABLE 22] Evidence Profile: GCS vs No GCS or Placebo for Prevention of Postthrombotic Syndrome of the Leg

Certainty Assessment							No. of Patients (%)		Effect	
Participants (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	GCS	No GCS or Placebo	Relative (95% CI)	Absolute (95% CI)
Any PTS of the leg (follow-up: range, 6-37 mo; assessed with: Villalta scale or Brandjes criteria)										
1,246 (4 studies)	Serious[a]	Very serious[b]	Not serious	Not serious	None	⊕◯◯◯ VERY LOW	245/631 (38.8%)	294/615 (47.8%)	RR, 0.71 (0.44 to 1.16)	139 fewer per 1,000 (from 268 fewer to 76 more)
Severe PTS of the leg (follow-up: range, 6-37 mo; assessed with: Villalta scale or Brandjes criteria)										
1,246 (4 studies)	Serious[a]	Very serious[b]	Not serious	Very serious[c,d]	None	⊕◯◯◯ VERY LOW	44/631 (7.0%)	54/615 (8.8%)	RR, 0.74 (0.34 to 1.65)	23 fewer per 1,000 (from 58 fewer to 57 more)
Recurrent DVT (follow-up: range, 6-37 mo; assessed with: standard imaging techniques)										
1,043 (3 studies)	Serious[a]	Not serious	Not serious	Very serious[c,d]	None	⊕◯◯◯ VERY LOW	59/525 (11.2%)	64/518 (12.4%)	RR, 0.92 (0.66 to 1.27)	10 fewer per 1,000 (from 42 fewer to 33 more)

Meta-analysis was generated by the authors, using the following studies: Prandoni et al[222] (2004), Jayaraj and Meissner[223] (2015), Brandjes et al[224] (1997), and Kahn et al[225] (2014). In reporting recurrent DVT, results from Kahn et al[225] (2014) include all VTE events. Certainty assessments were conducted by the authors. Forest plots for the final synthesis are included in Figure 10. GCS = graduated compression stockings; PTS = postthrombolytic syndrome; RR = risk ratio.

[a]Selection bias due to lack of allocation concealment.

[b]Combined $I^2 > 60\%$.

[c]Total number of events not sufficient to meet optimal information size criteria given the control group event rate and a relative-risk reduction of 25%.

[d]CIs around both the relative and absolute effects include both appreciable benefit and appreciable harm.

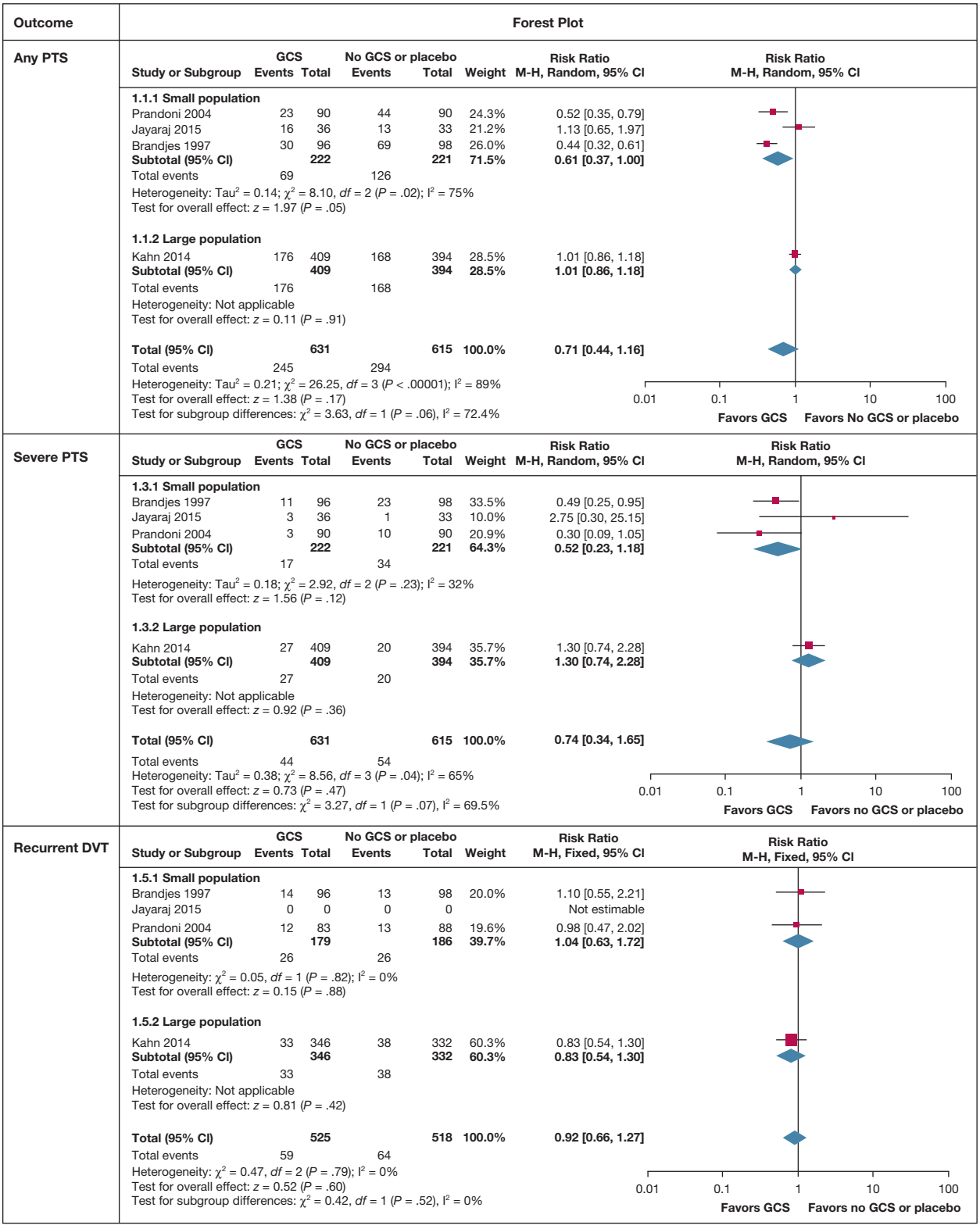

Figure 10 – *Forest plot of pooled estimates: GCS vs no GCS or placebo for prevention of postthrombotic syndrome of the leg. GCS = graduated compression stockings; M-H = Mantel-Haenszel; PTS = postthrombotic syndrome. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

TABLE 23] Conflict of Interest Grid

PICO Question	Description of COI			
	Lisa Baumann Kreuziger, MD, MS	Henri Bounameaux, MD	Kevin Doerschug, MD	Geert-Jan Geersing, MD
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated distal DVT?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated subsegmental pulmonary embolism?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with incidentally diagnosed asymptomatic acute pulmonary embolism?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with cerebral vein or cerebral venous sinus thrombosis?	None	None	None	None
Should thrombolytic, mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute DVT?	None	None	None	None
Should systemic thrombolytic therapy vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should an inferior vena cava filter (permanent or retrievable) be used in addition to anticoagulant therapy vs anticoagulant therapy alone in patients with acute pulmonary embolism?	None	None	None	None
Should treatment in hospital vs outpatient treatment be provided to patients with acute pulmonary embolism?	None	None	None	None
Should standard anticoagulation (heparinoid transitioned to an oral VKA inhibitor) vs DOAC be provided for treatment-phase therapy in patients with acute VTE?	None	None	None	None
In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 mo) anticoagulant therapy (strong recommendation, moderate-certainty evidence)	None	None	None	None
Should low molecular weight heparin vs oral factor Xa inhibitor be provided for treatment-phase therapy in patients with acute VTE in the setting of cancer (cancer-associated thrombosis)?	None	None	None	None

(Continued)

TABLE 23] *(Continued)*

PICO Question	Description of COI			
	Lisa Baumann Kreuziger, MD, MS	Henri Bounameaux, MD	Kevin Doerschug, MD	Geert-Jan Geersing, MD
Should standard anticoagulation (heparinoid transitioned to an oral VKA inhibitor) vs DOAC be provided for treatment- and extended-phase therapy in patients with acute VTE in the setting of antiphospholipid syndrome?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be provided to patients with acute superficial venous thrombosis of the lower extremities?	None	None	None	None
Should extended-phase anticoagulant therapy vs no extended-phase anticoagulant therapy be provided to patients with VTE who have completed the treatment phase of therapy?	None	None	None	None
Should reduced-dose factor Xa inhibitor (apixaban or rivaroxaban) vs full-dose factor Xa inhibitor (apixaban or rivaroxaban) be provided to patients with VTE who have been selected to receive extended-phase anticoagulant therapy?	None	None	None	None
Should aspirin vs anticoagulant therapy be provided to patients with VTE who have been selected to receive extended-phase therapy?	None	None	None	None
Should graduated compression stockings vs no graduated compression stockings be provided to patients with acute DVT to reduce the risk of postthrombotic syndrome?	None	None	None	None
All disclosures	Funds for patient enrollment in research to institution from Daiichi Sankyo	Medical consultancy for Bayer Global, Switzerland	Legal consultancy sepsis, airway management, rapid response, and code blue management	Research grants to institution from Bayer Global, Boehringer Ingelheim, BMS/Pfizer, Daiichi Sankyo

PICO Question	Description of COI			
	Menno V. Huisman, MD, PhD	Clive Kearon, MD, PhD†	Christopher S. King, MD	Andrew J. Knighton, PhD, CPA
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated distal DVT?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated subsegmental pulmonary embolism?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with incidentally diagnosed asymptomatic acute pulmonary embolism?	None	None	None	None

(Continued)

TABLE 23] *(Continued)*

PICO Question	Description of COI			
	Menno V. Huisman, MD, PhD	Clive Kearon, MD, PhD[†]	Christopher S. King, MD	Andrew J. Knighton, PhD, CPA
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with cerebral vein or cerebral venous sinus thrombosis?	None	None	None	None
Should thrombolytic, mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute DVT?	None	None	None	None
Should systemic thrombolytic therapy vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should an inferior vena cava filter (permanent or retrievable) be used in addition to anticoagulant therapy vs anticoagulant therapy alone in patients with acute pulmonary embolism?	None	None	None	None
Should treatment in hospital vs outpatient treatment be provided to patients with acute pulmonary embolism?	None	None	None	None
Should standard anticoagulation (heparinoid transitioned to an oral VKA inhibitor) vs DOAC be provided for treatment-phase therapy in patients with acute VTE?	None	None	None	None
In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 mo) anticoagulant therapy (strong recommendation, moderate-certainty evidence)	None	None	None	None
Should low-molecular-weight heparin vs oral factor Xa inhibitor be provided for treatment-phase therapy in patients with acute VTE in the setting of cancer (cancer-associated thrombosis)?	None	None	None	None
Should standard anticoagulation (heparinoid transitioned to an oral VKA inhibitor) vs DOAC be provided for treatment- and extended-phase therapy in patients with acute VTE in the setting of antiphospholipid syndrome?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be provided to patients with acute superficial venous thrombosis of the lower extremities?	None	None	None	None

(Continued)

TABLE 23] *(Continued)*

PICO Question	Description of COI			
	Menno V. Huisman, MD, PhD	Clive Kearon, MD, PhD†	Christopher S. King, MD	Andrew J. Knighton, PhD, CPA
Should extended-phase anticoagulant therapy vs no extended-phase anticoagulant therapy be provided to patients with VTE who have completed the treatment phase of therapy?	None	…	…	…
Should reduced-dose factor Xa inhibitor (apixaban or rivaroxaban) vs full-dose factor Xa inhibitor (apixaban or rivaroxaban) be provided to patients with VTE who have been selected to receive extended-phase anticoagulant therapy?	None	…	…	…
Should aspirin vs anticoagulant therapy be provided to patients with VTE who have been selected to receive extended-phase therapy?	None	…	…	…
Should graduated compression stockings vs no graduated compression stockings be provided to patients with acute DVT to reduce the risk of postthrombotic syndrome?	…	…	…	…
All Disclosures	Educational consultancies for Bayer Global, Daiichi Sankyo, and Pfizer-BMS; speakers bureau for Bristol-Myers Squibb/ Pfizer; advisory board for Portola	Advisory board for Bayer Global, legal testimony—duration of anticoagulation; research grant from Bayer Global	Speakers bureau for Genentech; advisory board for Boehringer Ingelheim	Stock—UnitedHealth Group

PICO Question	Description of COI			
	Erica Lake, MLS, AHIP	Lisa K. Moores, MD	Susan Murin, MD	Scott M. Stevens, MD
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated distal DVT?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated subsegmental pulmonary embolism?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with incidentally diagnosed asymptomatic acute pulmonary embolism?	None	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with cerebral vein or cerebral venous sinus thrombosis?	None	None	None	None

(Continued)

TABLE 23] *(Continued)*

PICO Question	Description of COI			
	Erica Lake, MLS, AHIP	Lisa K. Moores, MD	Susan Murin, MD	Scott M. Stevens, MD
Should thrombolytic, mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute DVT?	None	None	None	None
Should systemic thrombolytic therapy vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None	None
Should an inferior vena cava filter (permanent or retrievable) be used in addition to anticoagulant therapy vs anticoagulant therapy alone in patients with acute pulmonary embolism?	None	None	None	None
Should treatment in hospital vs outpatient treatment be provided to patients with acute pulmonary embolism?	None	None	None	None
All disclosures	None	None	None	Funds for patient enrollment in research to institution from Bristol-Myers Squibb

PICO Question	Description of COI		
	Janine R. E. Vintch, MD	Philip S. Wells, MD	Scott C. Woller, MD
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated distal DVT?	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated subsegmental pulmonary embolism?	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with incidentally diagnosed asymptomatic acute pulmonary embolism?	None	None	None
Should anticoagulant therapy vs no anticoagulant therapy be given to patients with cerebral vein or cerebral venous sinus thrombosis?	None	None	None
Should thrombolytic, mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute DVT?	None	None	None

(Continued)

TABLE 23] *(Continued)*

PICO Question	Description of COI		
	Janine R. E. Vintch, MD	Philip S. Wells, MD	Scott C. Woller, MD
Should systemic thrombolytic therapy vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None
Should mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?	None	None	None
Should an inferior vena cava filter (permanent or retrievable) be used in addition to anticoagulant therapy vs anticoagulant therapy alone in patients with acute pulmonary embolism?	None	None	None
Should treatment in hospital vs outpatient treatment be provided to patients with acute pulmonary embolism?	None	None	None
Should graduated compression stockings vs no graduated compression stockings be provided to patients with acute DVT to reduce the risk of postthrombotic syndrome?	None	None	None
All disclosures	Educational advisory board for Syneos Health/Avillion; legal testimony on influenza, ARDS, pneumonia, sleep apnea, pulmonary embolism; research grant to institution from GlaxoSmithKline; royalty from McGraw-Hill Publishing	Educational advisory boards for Sanofi, Bayer Global, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo; research grant from Bristol-Myers Squibb/Pfizer	Legal testimony on postoperative DVT, assessment of thromboprophylaxis, and duration of anticoagulation; funds for patient enrollment in research to institution from Bristol-Myers Squibb

COI = conflict of interest; DOAC = direct-acting oral anticoagulant; PE = pulmonary embolism; PICO = Population, Intervention, Comparator, Outcome; VKA = vitamin K antagonist.
†Deceased.

in the smaller studies however the 2014 study demonstrated no reduction in PTS at 24 months and no effect on severe PTS.

The AT9 recommendation was mainly based on findings of two small, single-center, randomized trials in which patients and study personnel were not blinded.[222,224,227] At the time of the 1st update, a much larger multicenter, placebo-controlled trial at low risk of bias found that routine use of graduated compression stockings did not reduce PTS or have other important benefits.[225]

Comparison With Prior Versions

AT9 suggested routine use of graduated compression stockings for 2 years after DVT to reduce the risk of PTS. The 1st update panel reversed the statement and suggested that graduated compression stockings not be used routinely to prevent PTS and considered the certainty of the evidence to be moderate. The 2nd update panel opted to endorse the statement from the 1st update, with minor changes to phrasing.

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Additional information: Coauthor Clive Kearon MD, PhD, died June 3, 2020.

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