CHEST

Executive Summary

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: AC = anticoagulation; APS = antiphospholipid syndrome; ASH = American Society of Hematology; 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; CVT = cerebral vein thrombosis; DOAC = direct-acting oral anticoagulant; ESC = European Society of Cardiology; EtD = evidence-to-decision; ISSPE = isolated subsegmental pulmonary embolism; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; PICO = Population, Intervention, Comparator, Outcome; PTS = postthrombotic syndrome; SVT = superficial venous thrombosis; VKA = vitamin K antagonist

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Editor's Note: *The online supplement to this guideline [https://journal.chestnet.org/article/S0012-3692(21)01506-3/fulltext] contains an expanded introduction and methods section with a full delineation of terminology, organization of the PICO questions in the guideline, panel selection, and description of conflict of interest management. For each PICO, the online supplement contains the evidence profile with complete summary of findings, additional comments, background information, evidence-to-decision description, and comparison with prior versions of the guideline.*

CHEST has been developing and publishing guidelines for the treatment of VTE for almost 40 years. The last full edition of the guideline, *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* ("AT9") was published in 2012.[1] Questions that form the basis for recommendations are defined using the Population, Intervention, Comparator, Outcome (PICO) framework. AT9 addressed 50 PICO questions organized into 11 domains and contained 91 guidance statements. The 2016 update to the guideline, entitled Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, was published in 2016.[2] The 2016 update ("1st update") addressed 12 PICO questions from AT9, added three previously unaddressed PICOs, and contained 29 guidance statements. This 2021 publication is the "2nd update" to AT9. It addresses 14 PICOs contained in previous editions (two of these have been merged into a single PICO) and adds four previously unaddressed PICOs. Twenty-nine guidance statements are presented. The guidance statements are intended primarily for physicians who treat patients with VTE, but may inform researchers in selecting questions for future studies. Patients and policy makers may also be informed by the guideline content. This guideline is the first addressing this topic that will be regularly updated as new evidence emerges according to the Living Guidelines process of the American College of Chest Physicians.[3]

The order of presentation of the PICOs and guidance statements in the guideline is intended to follow the chronology of VTE management, and they are arranged as follows:

- Whether to treat
- Interventional and adjunctive treatments
- Initiation phase
- Treatment phase
- Extended phase
- Complications of VTE

Guidance statements for antithrombotic therapy for VTE are arranged according to the descriptions of the phase of management:

- Initiation phase (~5-21 days): The initial provision of anticoagulants following VTE diagnosis
- Treatment phase (3 months): The period after initiation that completes treatment for the acute VTE event
- Extended phase (3 months-no planned stop date): The period of anticoagulant use at full or reduced dose for the goal of secondary prevention

Precipitating factors for VTE have been characterized[4] and are described as:

- VTE provoked by a major transient risk factor (present within the 3 months before VTE diagnosis)
- VTE provoked by a minor transient risk factor (present within the 2 months before VTE diagnosis)
- VTE provoked by a persistent risk factor
- Unprovoked VTE

Oral anticoagulants include vitamin K antagonists (VKAs), direct thrombin inhibitors, and factor Xa inhibitors (collectively referred to as *direct-acting oral anticoagulants* [DOACs]). DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) will be presented in alphabetical order. The order should not be

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interpreted as the guideline panel's order of preference for the use of these agents.

The following estimated incidences from the evidence profile for each PICO were used to classify the magnitude of desirable or undesirable effects of an intervention:

- 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
- Large: More than 50 events per 1,000 subjects

To facilitate understanding of the magnitude of any outcome, the symbols ↔, ↑, and ↓ accompany each selected summary of findings to indicate whether the outcome addressed by the PICO does not cross unity (↔), is increased (↑), or is decreased (↓). Each summary reports a point estimate per 1,000 cases for the outcome and the CIs.

Certainty of evidence was based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and categorized as high, moderate, low, or very low.

PICO Topics and Guidance Statements

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

PICO Question: Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated distal DVT?:

Guidance statements:

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).

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 managed with anticoagulation, the same anticoagulation regimen as for patients with acute proximal should be used.

Selected summary of findings:

↓ Recurrent VTE at 3 months: 60 fewer events per 1,000 cases (from 77 fewer to 21 fewer)
↔ Major bleeding at 3 months: 2 fewer events per 1,000 cases (from 7 fewer to 29 more)
↔ Overall mortality at 3 months: 0 fewer events per 1,000 cases (from 0 fewer to 0 more)

Comments: Isolated distal DVT is defined as thrombus affecting deep veins of the lower extremity with most proximal extent distal to the popliteal vein. The key management decision when isolated distal DVT is diagnosed is whether to offer anticoagulation or perform serial ultrasound (weekly for 2 weeks or with worsening symptoms) and offer anticoagulation only if proximal propagation is observed. Several factors that encapsulate patient preference and risk influence this decision, further detailed in the online supplement to this guideline [https://journal.chestnet.org/article/S0012-3692(21)01506-3/fulltext].

Other guidelines:

2018 American Society of Hematology (ASH) guideline: No specific guidance.[5]

2020 National Institute for Health and Care Excellence (NICE) guideline: Recommendations for only proximal DVT.[6]

Whether to Treat Isolated Subsegmental Pulmonary Embolism

PICO Question: Should anticoagulant therapy vs no anticoagulant therapy be given to patients with isolated subsegmental pulmonary embolism?:

Guidance statement:

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).

Comments: Because isolated subsegmental PE (ISSPE) is associated with DVT, the panel endorsed excluding proximal DVT with bilateral leg ultrasound, or at another location if clinically suspected (eg, upper extremity if DVT is suspected), before choosing to withhold anticoagulation for ISSPE. Clinical surveillance involves patient education to ensure an understanding of clinical signs and symptoms worrisome for progressive thrombosis that would require return for reassessment. Considering whether ISSPE is a true positive finding, and the likelihood of progressive thrombosis, informs decision-making regarding anticoagulation, further detailed in the online supplement to this guideline [https://journal.chestnet.org/article/S0012-3692(21)01506-3/fulltext].

Other guidelines:
2019 European Society of Cardiology (ESC) guideline: Suggests further imaging to confirm PE when isolated subsegmental filling defects are seen on CT pulmonary angiography.[7]

Whether to Treat an Incidentally Diagnosed Asymptomatic Acute PE

PICO Question: Should anticoagulant therapy vs no anticoagulant therapy be given to patients with incidentally diagnosed asymptomatic acute pulmonary embolism?:

Guidance statement:

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

Comments: Asymptomatic PE is diagnosed in about 1% of outpatients and about 4% of inpatients who have contrast-enhanced chest CT scans (notably performed during a diagnostic workup in patients with cancer) and may represent false-positive imaging findings; therefore it is important to ensure a false-positive result is not likely. Observational data suggest that asymptomatic PE carries a similar prognosis to symptomatic PE (data predominantly from patients with cancer), implying a similar approach to treatment is needed.[8]

Other guidelines:
2019 ESC: Suggests anticoagulation for asymptomatic/incidental PE in patients with cancer but notes treatment of asymptomatic/incidental PE in other patient groups represents an important evidence gap.[7]

Whether to Treat Cerebral Vein Thrombosis

PICO Question: Should anticoagulant therapy vs no anticoagulant therapy be given to patients with cerebral vein or cerebral venous sinus thrombosis?:

Guidance statement:

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.[9]

Selected summary of findings:
↔ Overall mortality at 90 days: 108 fewer events per 1,000 cases (from 162 fewer to 47 more)
↔ New intracranial hemorrhage or PE at 90 days: 69 fewer events per 1,000 cases (from – fewer to 83 more)

Comments: Anticoagulation therapy (with most evidence regarding the use of low-molecular-weight heparin [LMWH]) appears safe and effective for the treatment of cerebral vein thrombosis (CVT). The guidance statement applies both to patients who have and have not experienced intracranial hemorrhage as a complication of CVT. No randomized controlled trial evidence currently evaluates the use of DOACs among patients with CVT.

Other guidelines:
2016 Anticoagulation (AC) Forum guidance statement: Includes six guidance statements related to CVT. Two statements relate to initial and treatment-phase anticoagulant therapy and are similar to this guidance statement.[10]

2014 American Heart Association/American Stroke Association guideline: Contains similar guidance and includes an additional statement on duration of anticoagulation and subsequent use of antiplatelet therapy.[11]

Thrombolytic and Mechanical Interventions in Acute DVT

PICO Question: Should thrombolytic, mechanical, or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute DVT?:

Guidance statement:

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).

Selected summary of findings:

- ↓ Postthrombotic syndrome (6 months to 5 years of follow-up): 116 fewer events per 1,000 cases (from 180 fewer to 37 fewer)
- ↓ Postthrombotic syndrome at > 5 years: 308 fewer events per 1,000 cases (from 400 fewer to 189 fewer)
- ↑ Bleeding (excluding intracranial and minor bleeding): 33 more events per 1,000 cases (from 13 more to 64 more)
- ↔ Early stroke or intracerebral bleeding: 0 fewer per 1,000 cases (from 0 fewer to 0 fewer)
- ↔ All-cause mortality (1-30 days of follow-up): 3 fewer events per 1,000 cases (from 9 fewer to 11 more)

Comments: In patients with very severe, limb-threatening DVT (such as those with phlegmasia or threatened venous gangrene) the benefits of more rapid thrombus resolution may outweigh the risk of harm. In contrast, a systematic review and meta-analysis suggested no benefit of thrombolysis for either iliofemoral or femoropopliteal DVT.[12,13] All catheter-directed methods (thrombolytic, mechanical, or pharmacomechanical) were pooled for comparison.

Other guidelines:

2016 AC Forum: Suggests individual risk-to-benefit analysis for catheter-directed therapy (CDT) and suggests against systemic thrombolysis for DVT.[14]

2020 NICE: Suggests considering CDT in patients with iliofemoral DVT who have symptoms lasting less than 14 days, good functional status, a life expectancy of 1 year or more, and low risk for bleeding.[6]

Thrombolytic Therapy in Patients With Acute PE

PICO Question: Should systemic thrombolytic therapy vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?:

Guidance statements:

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 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).

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.[9]

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: Such patients should be treated with full anticoagulation and monitored for evidence of clinical deterioration (decrease in systolic BP, increase in heart rate, worsening gas exchange, signs of inadequate perfusion, worsening right ventricular function, or increasing cardiac biomarkers). Such deterioration should prompt consideration of thrombolytic therapy in the absence of frank shock if the bleeding risk is deemed acceptable.

Selected summary of findings:

- ↓ Recurrent PE (7 days to 12 months of follow-up): 19 fewer events per 1,000 cases (from 27 fewer to 4 fewer)
- ↑ Major bleeding (7 days to 12 months of follow-up): 65 more events per 1,000 cases (from 33 more to 107 more)
- ↓ All-cause mortality (7 days to 12 months of follow-up): 20 fewer events per 1,000 cases (from 30 fewer to 6 fewer)

Comments: Agreement existed among the panelists to administer thrombolysis to most patients (in the absence of a contraindication) with acute PE and prolonged hypotension. Thrombolysis among patients with acute PE without hypotension[15] has been associated with a reduction in risk for cardiovascular collapse but

increased major (including intracranial) bleeding, with the benefits and harms finely balanced and with no convincing net benefit from thrombolytic therapy.

Other guidelines:

2016 AC Forum: Suggests an individual risk-to-benefit analysis for use of thrombolysis in patients with acute PE, and suggests that the benefit-to-risk ratio is more favorable for PE with hypotension.[14]

2019 ESC: Recommends thrombolysis for high-risk PE and indicates CDT should be considered in high-risk patients with PE in whom systemic thrombolysis is contraindicated or has failed. They recommend systemic thrombolysis in patients with intermediate- or low-risk PE who have hemodynamic deterioration, but are against the routine use of such therapy.[7]

2020 NICE: Recommends that thrombolysis be considered in patients with hemodynamic instability, but against its use in patients who are hemodynamically stable, regardless of the presence of right ventricular dysfunction.[6]

Catheter-Assisted Thrombus Removal in Patients With Acute PE

PICO Question: Should mechanical or pharmacomechanical interventions vs anticoagulant therapy alone be given to patients with acute pulmonary embolism?:

Guidance statements:

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).

Comments: No randomized trials or observational studies have compared contemporary CDT with systemic thrombolytic therapy. Evidence for the use of mechanical or pharmacomechanical interventions compared with anticoagulation alone is of low certainty, and our recommendations are weak.

Other guidelines:

2016 AC Forum: Suggests both systemic and catheter-directed or pharmacomechanical therapy are effective options for massive PE in appropriately selected patients.[14]

2019 ESC: Recommends percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[7]

2020 NICE: Addresses only systemic thrombolytic therapy for PE.[6]

Inferior Vena Cava Filter in Addition to Anticoagulation in Patients With Acute PE

PICO Question: 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?:

Guidance statements:

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).

Selected summary of findings[2]:

- ↔ All-cause mortality at 90 days: 15 more events per 1,000 cases (from 24 fewer to 96 more)
- ↔ Recurrent PE at 90 days: 15 more events per 1,000 cases (from 7 fewer to 104 more)
- ↔ Major bleeding at 90 days: 10 fewer events per 1,000 cases (from 34 fewer to 49 more)

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).

Comments: IVC filters are overused and, given the known risks of harm and significant uncertainty of benefit of IVC filters,[16] the panel endorses a conservative approach to their placement by suggesting use only in patients with acute VTE (eg, diagnosed in the preceding 1 month) with an absolute contraindication to anticoagulation (eg, active major bleeding, severe thrombocytopenia, high bleeding risk, CNS lesion).

Other guidelines:

2016 AC Forum: Suggests IVC filter placement in patients with acute PE or proximal DVT and a contraindication to anticoagulation.[14]

2019 ESC: Recommends considering an IVC filter in patients with acute PE and an absolute contraindication to anticoagulation and in patients with progressive PE despite anticoagulation. It recommends against routine use of IVC filter.[7]

2020 NICE: Suggests considering an IVC filter in patients with proximal DVT or PE when anticoagulation is contraindicated, and when new or progressive PE occurs during anticoagulation. Filter use is also suggested in the setting of a clinical trial.[6]

Setting of Initial Anticoagulation

PICO Question: Should treatment in hospital vs outpatient treatment be provided to patients with acute pulmonary embolism?:

Guidance statement:

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 outpatient treatment ("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.[9]

Selected summary of findings:

↔ Long-term all-cause mortality (at 90 days): 0 fewer events per 1,000 cases (from 4 fewer to 64 more)
↔ Major bleeding at 90 days: 0 fewer events per 1,000 cases (from 0 fewer to 0 more)
↔ Recurrent PE at 90 days: 0 fewer events per 1,000 cases (from 0 fewer to 0 more)

Comments: Home treatment is more convenient and less expensive than hospital treatment and is preferred by most patients.[17] Patients who satisfy all the following criteria are suitable for treatment of acute PE out of the hospital: (1) clinically stable with good cardiopulmonary reserve; (2) no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie, $< 50{,}000/mm^3$); (3) expected to be compliant with treatment; and (4) the patient feels well enough to be treated at home. In addition, a system to ensure outpatient follow-up and access to prompt care in the event of patients' questions or worsening of symptoms should be in place.[18]

Other guidelines:

2016 AC Forum: Suggests many patients with PE can be treated as outpatients,
and suggests evaluation with laboratory, imaging, and risk prediction models to select suitable patients.[19]

2019 ESC: Suggests that patients with low-risk PE can be treated with early discharge or at home.[7]

2020 NICE: Suggests considering outpatient treatment in patients with low-risk PE, using a validated risk-stratification tool.[6]

Choice of Treatment-Phase Anticoagulant

PICO Question: Should standard anticoagulation (LMWH transitioned to an oral VKA) vs DOAC be provided for treatment-phase therapy in patients with acute VTE?:

Guidance statement:

15. In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over 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.[9]

Selected summary of findings: Comparison: Dabigatran etexilate vs standard anticoagulation

↔ Recurrent VTE at 6 months: 2 fewer events per 1,000 cases (from 15 fewer to 20 more)
? All-cause mortality: Not estimable
↔ Major bleeding: 5 fewer events per 1,000 cases (from 9 fewer to 7 more)

Comparison: Oral Xa inhibitor vs standard anticoagulation

↔ Recurrent VTE at 6 months: 5 fewer events per 1,000 cases (from 12 fewer to 4 more)
↔ All-cause mortality: 3 more events per 1,000 cases (from 4 fewer to 14 more)
↔ Major bleeding: 1 fewer event per 1,000 cases (from 6 fewer to 7 more)

Comments: The choice of anticoagulant for the treatment phase of VTE necessitates consideration of patient-specific factors (eg, renal function, direct patient expense, payor considerations, bleeding risk, anticipated compliance), drug availability, and the patient's preferences. Guidance is driven by the comparable

efficacy and improved safety of DOACs over traditional therapy. DOACs also offer greater convenience. Certain clinical situations favor VKA (eg, extremes of weight, severe renal impairment, or presence of antiphospholipid syndrome). Cost may also drive the clinical decision.

Other guidelines:

2016 AC Forum: Suggests DOACs as an alternative to standard anticoagulation in appropriately selected patients.[19]

2018 ASH: Suggests VKA or LMWH rather than DOAC in patients requiring administration of inhibitors or inducers of P-glycoprotein or strong inhibitors or inducers of cytochrome P450 enzymes.[5]

2019 ESC: Recommends DOAC in preference to VKA in eligible patients ready to start an oral anticoagulant.[7]

2020 NICE: Recommends apixaban or rivaroxaban as initial choices, and suggests other regimens for patients not suitable for one of these two drugs.[6]

DOACs in Cancer-Associated Thrombosis

PICO Question: Should LMWH vs oral Xa inhibitor be provided for treatment-phase therapy in patients with acute venous thromboembolism in the setting of cancer ("cancer-associated thrombosis")?:

Guidance statement:

16. In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over 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 gastrointestinal malignancy, while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.

Selected summary of findings:

↓ Recurrent VTE at 6 months: 31 fewer events per 1,000 cases (from 47 fewer to 7 fewer)

↔ Major bleeding at 6 months: 10 more events per 1,000 cases (from 6 fewer to 36 more)

Comparison: Edoxaban/rivaroxaban vs LMWH

↑ Major GI bleeding (6-12 months of follow-up): 25 more events per 1,000 cases (from 5 more to 65 more)

Comparison: Apixaban vs LMWH

↔ Major GI bleeding (6-12 months of follow-up): 2 more events per 1,000 cases (from 7 fewer to 22 more)

Comments: 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.[20] Because DOACs have not been compared head-to-head among patients with cancer, the panelists remarked that apixaban or LMWH may be the preferred option in patients with luminal GI malignancies who place higher value on avoiding GI major bleeding, whereas others may elect the convenience of once-daily DOAC therapy (edoxaban or rivaroxaban).However, LMWH has the potential advantages of bypassing the GI system in patients with nausea or mucositis and may be more easily dose-adjusted in patients with thrombocytopenia due to cancer therapy.[20,21]

Other guidelines:

2016 AC Forum: Suggests LMWH for a minimum of 6 months in patients with CAT.[22]

2018 National Comprehensive Cancer Network guideline: Indicates that LMWH is the preferred agent for the first six months in patients with CAT.[21]

2019 European Society of Cardiology guideline: Recommends LMWH, edoxaban, or rivaroxaban for management of CAT.[7]

2019 International clinical practice guidelines (for the treatment and prophylaxis of VTE in patients with cancer): Recommend LMWH for the initial treatment of established VTE in CAT, or rivaroxaban or edoxaban in patients who do not have a high risk of GI or genitourinary bleeding.[23]

2020 NICE: Suggests considering a DOAC for patients with CAT, and LMWH alone or LMWH transitioned to warfarin in patients unsuitable for DOAC.[6]

DOACs in Patients With Antiphospholipid Syndrome

PICO Question: Should standard anticoagulation (heparinoid transitioned to an oral VKA inhibitor) vs DOAC be provided for treatment- and extended-phase therapy in patients with acute venous thromboembolism in the setting of antiphospholipid syndrome?:

Guidance statement:

17. In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, we suggest adjusted-dose VKA (target international

normalized ratio [INR] 2.5) over DOAC therapy during the treatment phase (weak recommendation, low-certainty evidence).

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

Selected summary of findings:

↔ Any thrombosis at 6 months: 0 fewer events per 1,000 cases (from 0 fewer to 0 more)
↔ Any thrombosis at 36 months: 63 more events per 1,000 cases (from 14 fewer to 260 more)
↔ Major bleeding at 6 months: 1 more event per 1,000 cases (from 9 fewer to 65 more)
↔ Major bleeding at 36 months: 10 fewer events per 1,000 cases (from 52 fewer to 108 more)
↔ All-cause mortality at 6 months: 2 more events per 1,000 cases (from 21 fewer to 86 more)
↔ All-cause mortality at 36 months: 21 more events per 1,000 cases (from 19 fewer to 183 more)

Comments: Panelists agreed that DOACs should be avoided in patients with antiphospholipid syndrome (APS), especially if positive for lupus anticoagulant, anti-cardiolipin, and anti-β_2-glycoprotein-I antibodies (ie, "triple-positive"), and in those with arterial thrombosis. For these patients VKA should be elected as first-line therapy.

Other guidelines:

2018 ASH: No specific guidance statement on treatment of patients with APS.[5]

2020 International Society on Thrombosis and Haemostasis Scientific and Standardization Subcommittee guidance statement: Recommends VKA over DOAC for most patients with APS.[24]

2020 16th International Congress on Antiphospholipid Antibodies Task Force report on antiphospholipid syndrome: Guidance is similar to our statement.[25]

Role of Anticoagulation in Spontaneous Superficial Vein Thrombosis

PICO Question: Should anticoagulant therapy vs no anticoagulant therapy be provided to patients with acute superficial venous thrombosis of the lower extremities?:

Guidance statements:

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).

Selected summary of findings: Comparison: Prophylactic LMWH vs placebo

↔ VTE at 3 months: 10 more events per 1,000 cases (from 28 fewer to 129 more)
↓ Extension or recurrence of SVT: 185 fewer events per 1,000 cases (from 244 fewer to 86 fewer)
? Major bleeding at 97 days: Not estimable

Comparison: Therapeutic LMWH vs placebo

↔ VTE at 3 months: 7 fewer events per 1,000 cases (from 34 fewer to 92 more)
↓ Extension or recurrence of SVT: 178 fewer events per 1,000 cases (from 241 fewer to 76 fewer)
? Major bleeding at 97 days: Not estimable

Comparison: Fondaparinux vs rivaroxaban

↔ VTE at 90 days: 9 fewer events per 1,000 cases (from 12 fewer to 28 more)
? Major bleeding at 45 days: Not estimable
↔ All-cause mortality at 90 days: 3 fewer events per 1,000 cases (from 4 fewer to 30 more)

Comments: SVT has been less well studied than DVT, likely occurs more often,[26] and usually affects the lower limbs. Although historically considered a benign disease, more recent appreciation of the seriousness of SVT has informed treatment studies. The anticoagulants fondaparinux and rivaroxaban 10 mg orally once daily for 45 days prevent progression of SVT, DVT, PE, or death among select patients with SVT.[27] Factors that favor the use of anticoagulation for the treatment of SVT include extensive SVT; involvement above the knee, particularly if close to the saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; and recent surgery.

Other guidelines:

No recent evidence-based guidelines for management of SVT were identified.

A review commissioned by the American Society of Hematology's Education Program included a management algorithm that suggested either fondaparinux or rivaroxaban in selected patients with more extensive SVT, risk factors for VTE, and no contraindications to anticoagulant therapy.[26]

Duration of Anticoagulation in Patients With Acute VTE

PICO Question: Should extended-phase anticoagulant therapy vs no extended-phase anticoagulant therapy be provided to patients with venous thromboembolism who have completed the treatment phase of therapy?:

Guidance statements:

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: On 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. While most patients in these studies did not stop anticoagulation therapy at the end of follow-up, the risk:benefit balance of continuing extended anticoagulation therapy beyond this time is uncertain. It is advised that this decision involve shared decision-making with the patient, taking into consideration her/his values and preferences.

Selected summary of findings:

↓ Recurrent VTE at 7 to 48 months of follow-up: 64 fewer events per 1,000 cases (from 80 fewer to 37 fewer)

↑ Major bleeding (7-48 months of follow-up): 6 more events per 1,000 cases (from 1 more to 14 more)

↔ All-cause mortality (7-48 months of follow-up): 4 fewer events per 1,000 cases (from 10 fewer to 5 more)

Comments: Duration of anticoagulation refers to the length of the initiation and treatment phases of anticoagulant therapy as well as the decision on whether to offer extended-phase therapy. While extended-phase therapy is defined as having no planned stop date, the longest duration of follow up to assess outcomes was about four years. 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. Patients receiving extended-phase anticoagulation should be periodically reassessed for bleeding risk, burdens of therapy, and any change in values and preferences. Categorization of risk factors is further detailed in the online supplement to this guideline [https://journal.chestnet.org/article/S0012-3692(21)01506-3/fulltext].

Other guidelines:

2016 AC Forum: Suggests 3 months of anticoagulation for patients with surgical risk factor-associated VTE, for at least 3 months in patients with medical illness or travel-associated VTE, and extended anticoagulation for

patients with unprovoked VTE. They note uncertainty regarding extended anticoagulation of longer than 2 years.[19]

2019 ESC: Recommends discontinuing anticoagulants after 3 months in patients with PE secondary to a major transient/reversible risk factor, recommends indefinite anticoagulation for patients with recurrent unprovoked PE and in patients with PE and APS, and suggests considering indefinite anticoagulation in patients with initial unprovoked PE, PE provoked by a persistent risk factor other than APS, and in patients with PE associated with a minor transient or reversible risk factor.[7]

2020 NICE: Suggests considering stopping anticoagulants after 3 months (or 3-6 months in patients with active cancer) following VTE in the setting of a provoking factor that is no longer present; and suggests continuing anticoagulation beyond 3 months (3-6 months in patients with active cancer) following an unprovoked VTE.[6]

2020 ASH: Describes transient risk factors as surgical/trauma or nonsurgical, that risk for recurrent VTE is lower following surgery/trauma compared with a nonsurgical risk factor, but that the risk is low for both groups and that patients with VTE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment (3-6 months of anticoagulation).[28]

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

PICO Question: Should reduced-dose Xa inhibitor (apixaban or rivaroxaban) vs full-dose Xa inhibitor (apixaban or rivaroxaban) be provided to patients with venous thromboembolism who have been selected to receive extended-phase anticoagulant therapy?:

Guidance statement:

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.

Selected summary of findings:

↔ Recurrent symptomatic VTE at 12 months: 2 more events per 1,000 cases (from 5 fewer to 12 more)

↔ Major or clinically relevant nonmajor bleeding at 12 months: 10 fewer events per 1,000 cases (from 18 fewer to 2 more)

? Mortality: Not estimable

Comments: When electing extended -phase antithrombotic therapy, the choice of a particular drug and dose is informed by multiple variables. We suggest choice of low-dose vs full-dose (treatment phase) anticoagulants when available, while considering patient-specific variables including BMI, renal function, adherence to dosing regimen, and cost.[29] Should cessation of anticoagulation be elected, then we suggest aspirin over no such therapy (see *Aspirin for Extended Treatment of VTE* for discussion).

Other guidelines:

2016 AC Forum: Notes that reduced-dose DOAC "may be attractive" for some patients undergoing extended therapy.[19]

2019 ESC: Recommends reducing the dose of apixaban or rivaroxaban after 6 months of full-dose therapy in patients receiving extended anticoagulation.[7]

Aspirin for Extended Treatment of VTE

PICO Question: Should aspirin vs anticoagulant therapy be provided to patients with venous thromboembolism who have been selected to receive extended-phase therapy?:

Guidance statements:

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.[9]

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.

Selected summary of findings: Comparison: Reduced-dose DOAC vs aspirin or placebo

↓ Recurrent symptomatic VTE at 12 months: 46 fewer events per 1,000 cases (from 54 fewer to 34 fewer)
↔ Major or clinically relevant nonmajor bleeding at 12 months: 4 more events per 1,000 cases (from 4 fewer to 18 more)
? Mortality: Not estimable

Comparison: Rivaroxaban vs aspirin

↓ Recurrent VTE (2-4 years of follow-up): 39 fewer events per 1,000 cases (from 47 fewer to 25 fewer)
↔ Major bleeding (2-4 years of follow-up): 4 more events per 1,000 cases (from 1 fewer to 52 more)

Comparison: Aspirin vs no aspirin (placebo)

↓ Recurrent VTE (2-4 years of follow-up): 53 fewer events per 1,000 cases (from 84 fewer to 13 fewer)
↔ Major bleeding (2-4 years of follow-up): 3 more events per 1,000 cases (from 6 fewer to 28 more)
↔ All-cause mortality (2-4 years of follow-up): 2 fewer events per 1,000 cases (from 18 fewer to 26 more)

Comments: Aspirin is not a recommended alterative to anticoagulation, based on direct and indirect comparisons demonstrating that the net benefit of extended anticoagulant therapy in patients with unprovoked VTE is substantially greater than the benefits of extended aspirin therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin and these benefits must be balanced against aspirin's risk of bleeding and inconvenience.

Other guidelines:
2016 AC Forum: Suggests aspirin should be considered an option for patients at risk for recurrent VTE who are not considered candidates for an anticoagulant, or who choose to stop anticoagulant therapy.[19]

2019 ESC: Suggests that aspirin or sulodexide (not available in the United States) may be considered for extended VTE prophylaxis.[7]

2020 NICE: Suggests considering aspirin 75 mg or 150 mg daily in people who decline extended anticoagulation treatment.[6]

Compression Stockings in Preventing Postthrombotic Syndrome

PICO Question: Should graduated compression stockings vs no graduated compression stockings be provided to patients with acute DVT to reduce the risk of PTS?:

Guidance statement:

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

Selected summary of findings:

↔ Any post-thrombotic syndrome (PTS) of the leg (6-37 months of follow-up): 139 fewer events per 1,000 cases (from 268 fewer to 76 more).
↔ Severe PTS of the leg (6-37 months of follow-up): 23 fewer events per 1,000 cases (from 58 fewer to 57 more).

Comments: Graduated compression stockings may reduce acute symptoms of DVT or chronic symptoms in those who have developed PTS; but there is no evidence demonstrating reduction in the risk for developing PTS. There is also no evidence that the use of graduated compression stockings reduces the risk for recurrent DVT.

Other guidelines:
2016 AC Forum: Suggests that graduated compression stockings do not increase the risk of recurrent VTE but do not have any beneficial effect on leg discomfort in patients with acute DVT. No statements are made regarding prevention of PTS.[19]

2020 NICE: Recommends against offering graduated compression stockings for the prevention of PTS, but notes that they can be offered to manage leg symptoms after DVT.[6]

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