JAMA Clinical Guidelines Synopsis

Antithrombotic Therapy for Venous Thromboembolism

Christopher D. Jackson, MD; Adam S. Cifu, MD; Desirée C. Burroughs-Ray, MD, MPH

GUIDELINE TITLE Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report

DEVELOPER AND FUNDING SOURCE American College of Chest Physicians

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PRIOR VERSIONS December 2012 (Antithrombotic Therapy and Prevention of Thrombosis) and February 2016 (Antithrombotic Therapy for VTE Disease)

TARGET POPULATION Adult patients with VTE

MAJOR RECOMMENDATIONS

- Patients with low-risk pulmonary embolism should receive outpatient treatment (strong recommendation, low certainty of evidence)
- Direct-acting oral anticoagulants (DOACs) should be used to treat acute VTE for the 3-month treatment phase (strong recommendation, moderate evidence)
- Oral Xa inhibitors should be used to treat acute VTE in a patient with cancer for both the initial and extended treatment phases (strong recommendation, moderate evidence)
- In patients with acute VTE, treat with full dose DOACs for 3 months (strong recommendation, moderate evidence) followed by reduced-dose DOACs for extended therapy if indicated (weak recommendation, moderate evidence)
- Extended anticoagulation therapy beyond 3 months is not routinely recommended in patients with major or minor transient risk factors (strong recommendation, moderate evidence)

Summary of the Clinical Problem

Venous thromboembolism (VTE) includes superficial and deep vein thrombosis of the leg or pelvis and pulmonary embolism (PE).[1] VTE affects an estimated 600 000 people in the US, with approximately 60 000 to 100 000 people dying from VTE and PE annually.[2] Despite its prevalence, 25% to 40% of all VTE events are idiopathic, making diagnosis and prevention difficult.[1]

Characteristics of the Guideline Source

The guidelines oversight committee of the American College of Chest Physicians appointed the editor for the guideline update.[3] The editor was responsible for nominating panelists approved by the committee based on their qualifications and conflict of interest disclosures (**Table**). The panelists included general internists, thrombosis specialists, pulmonologists, hematologists, methodologists, and medical librarians. The committee assessed financial and intellectual conflicts of interest and classified them as primary or secondary. Panelists with primary conflicts were required to abstain from voting but could participate in discussions. After being approved by all panel members, the manuscript was reviewed externally. The final manuscript was reviewed and approved by the Chest guidelines oversight committee and the Board of Regents.

Evidence Base

The panel performed a systematic review to identify articles that addressed the questions of interest. The analysis was limited to English-language clinical trials, randomized controlled trials, and systematic reviews. Each recommendation was rated as either strong or weak. Strong recommendations are those that practitioners should follow in most patients. Weak recommendations require practitioners to leverage their clinical experience, patients' preferences, and local resources to determine the best management course. The strength of evidence rating reflects the confidence members of the guideline panel had in the supporting data. Factors considered in the strength of evidence rating include study design, risk of bias, imprecision, and applicability of study results. Panelists would rarely, upon discussion and vote, upgrade or downgrade the guidance (eg, from "suggest" to "recommend" or vice versa) if high value was thought to exist with adherence to the statement.

The guidelines recommend that patients with low-risk PE receive treatment in the outpatient setting. Previous studies defined low-risk PE by a Pulmonary Embolism Severity Index (PESI) score of less than 85 or a simplified PESI score of 0. The PESI score is a clinical prediction rule that classifies the risk for mortality of patients with a PE. PESI scores of 85 or less correlate to a 30-day mortality rate of 3.5% or less.[4] In a recent clinical trial of 1980 patients with PE without hemodynamic compromise, similar rates of 30-day recurrent VTE, major bleeding, and all-cause death were noted in patients classified as low risk by the Hestia or simplified PESI score.[5] For this recommendation, the panelists upgraded the guidance in favor of outpatient treatment for eligible patients with PE despite that the "evidence to decision" framework warranted a weak recommendation. The panelists placed a high value on avoiding potential harm associated with hospitalization.

Table. Guideline Rating

Standard	Rating
Establish transparency	Good
Management of conflict of interest in the guideline group	Good
Guideline development group composition	Good
Clinical practice guideline-systematic review intersection	Fair
Establishing evidence foundations and rating strength for each of the guideline recommendations	Fair
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

In the initial treatment phase of acute VTE, the guideline recommends therapy with direct-acting oral anticoagulants (DOACs) over vitamin K antagonist therapy given that DOACs reduce the risk for recurrent VTE similarly (risk ratio [RR], 0.51 [95% CI, 0.15-1.67] for dabigatran and RR, 0.91 [95% CI, 0.56-1.48] for oral factor Xa inhibitors) with a lower risk for major bleeding. For patients with acute VTE and cancer, the guideline suggests oral factor Xa inhibitors over low-molecular-weight heparin for initial and extended treatment. This recommendation is based on 4 trials showing significant reductions in recurrent VTE events (RR, 0.62 [95% CI, 0.43-0.91]) without a statistically significant increase in major bleeding events (RR, 1.31 [95% CI, 0.83-2.08]). Treatment with oral factor Xa inhibitors should continue for 3 months, followed by an evaluation for extended therapy.

The decision to extend anticoagulation therapy for VTE beyond 3 months is nuanced. The duration of extended anticoagulant therapy is not well defined in the guidelines, with trial participants receiving anticoagulation for 2 to 4 years. The guideline does not recommend the routine use of extended therapy in patients with major (eg, trauma, surgery requiring general anesthesia for >30 minutes) and minor (eg, prolonged car or air travel, pregnancy) transient risk factors. The panel determined that harms could outweigh benefits in this patient population. Conversely, patients with VTE provoked by ongoing risk factors (eg, cancer, antiphospholipid syndrome) likely benefit from extended anticoagulation. Additionally, patients with VTE and no identified risk factors probably benefit from extended anticoagulation therapy (defined as anticoagulation with no plan to stop date, periodically revisiting anticoagulation duration) based on a reduction of VTE events (RR, 0.43 [95% CI, 0.28-0.67]), albeit with an increase in major bleeding events (RR, 1.98 [95% CI, 1.18-3.32]).

Benefits and Harms

Avoiding unnecessary hospitalization in patients with low-risk acute PE is a benefit of these guidelines. Advocating for the use of factor Xa inhibitors for most patients with VTE, except in the case of antiphospholipid syndrome (for which vitamin K antagonist therapy is preferred), will lead to greater ease of treatment. The guidelines reflect the current uncertainty regarding duration of anticoagulation.

Discussion

The Chest guidelines on VTE are similar to the 2012 and 2016 recommendations from the American College of Chest Physicians.[3,6,7] Both older guidelines suggest anticoagulation therapy for at least 3 months in patients receiving treatment for VTE. The type of VTE event does not affect this treatment duration. For oral anticoagulation, DOACs are preferred given their ease of administration, efficacy and effectiveness in preventing VTE, and favorable adverse effect profile. The use of DOACs helps facilitate the treatment of stable patients with VTE at home if there is no evidence of right heart strain and adequate resources to navigate VTE treatment outside the hospital setting.

Areas in Need of Future Study or Ongoing Research

Further research is needed to determine whether treating incidental PEs reduces mortality in affected patients. Similarly, the benefits and risks of treating isolated subsegmental PEs merit further investigation.[8,9] The guidelines mention catheter-assisted thrombus removal as a treatment modality, but trials highlighting its effectiveness are lacking. Larger and longer trials to identify subgroups of patients who would benefit from longer duration or permanent anticoagulation would be welcome.

ARTICLE INFORMATION

Author Affiliations: Division of General Internal Medicine, Department of Medicine, University of Tennessee Health Science Center, Memphis (Jackson, Burroughs-Ray); Section of General Internal Medicine, Department of Medicine, University of Chicago, Chicago, Illinois (Cifu); Division of Pediatric Hospital Medicine, Department of Pediatrics, University of Tennessee Health Science Center, Memphis (Burroughs-Ray).

Corresponding Author: Christopher D. Jackson, MD, Division of General Internal Medicine, Department of Medicine, University of Tennessee Health Science Center, 956 Court Ave, Memphis, TN 38163 (cjacks67@uthsc.edu).

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REFERENCES

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):3-14. doi:10.1007/s11239-015-1311-6

2. Maughan BC, Frueh L, McDonagh MS, Casciere B, Kline JA. Outpatient treatment of low-risk pulmonary embolism in the era of direct oral anticoagulants: a systematic review. *Acad Emerg Med*. 2021;28(2):226-239. doi:10.1111/acem.14108

3. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease. *Chest*. 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055

4. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172(8):1041-1046. doi:10.1164/rccm.200506-862OC

5. Roy PM, Penaloza A, Hugli O, et al; HOME-PE Study Group. Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. *Eur Heart J*. 2021;42(33):3146-3157. doi:10.1093/eurheartj/ehab373

6. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026

7. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e419S-e496S. doi:10.1378/chest.11-2301

8. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. *Blood*. 2013;122(7):1144-1149. doi:10.1182/blood-2013-04-497545

9. Ikesaka R, Carrier M. Clinical significance and management of subsegmental pulmonary embolism. *J Thromb Thrombolysis*. 2015;39(3):311-314. doi:10.1007/s11239-015-1169-7