Antithrombotic Therapy for Venous Thromboembolism

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

Characteristics of the Guideline Source
The guidelines oversight committee of the American College of Chest Physicians appointed the editor for the guideline update. 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 PE. PESI scores of 85 or less correlate to a 30-day mortality rate of 3.5% or less. 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. 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.
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 anticoagulation therapy is not well defined in the guidelines, with trial participants receiving anticoagulation for 2 to 4 years. The guidelines do 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.

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. 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
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REFERENCES