JAMA Clinical Guidelines Synopsis

Prevention and Management of Venous Thromboembolism

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GUIDELINE TITLE 2018 Guidelines for Management of Venous Thromboembolism

DEVELOPERS American Society of Hematology (ASH) and McMaster University GRADE Centre

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FUNDING SOURCE ASH

TARGET POPULATION Hospitalized and nonhospitalized medical patients, pregnant women, and children

MAJOR RECOMMENDATIONS

- In all acutely ill medical patients, venous thromboembolism (VTE) prophylaxis is recommended during hospitalization but not after discharge (strong recommendation; moderate certainty).
- For VTE prophylaxis, low-molecular-weight heparin (LMWH) or fondaparinux is preferred over unfractionated heparin (UFH) (conditional recommendation; low certainty for LMWH in non–critically ill patients; moderate certainty for LMWH in critically ill patients; very low certainty for fondaparinux) and over a direct oral anticoagulant (DOAC) (strong recommendation; moderate certainty).
- A strategy that begins with D-dimer for excluding pulmonary embolism (PE) in a population with low prevalence/pretest probability (≤5%) is recommended, followed by ventilation perfusion ($\dot{V}\dot{Q}$) scan or computed tomography pulmonary angiography (CTPA) for patients requiring additional testing (strong recommendation; moderate to high certainty).
- For patients at low to moderate risk of recurrent VTE who require interruption of vitamin K antagonist therapy for invasive procedures, the guideline recommends against periprocedural bridging with LMWH or UFH in favor of interruption alone (strong recommendation; moderate certainty).
- For pregnant women with acute VTE, antithrombotic therapy is recommended (strong recommendation; high certainty) with LMWH over UFH (strong recommendation; moderate certainty).

Summary of the Clinical Problem

Up to 50% of all VTE events occur during or shortly after hospitalization.[1] The morbidity and mortality of VTE is high: about 10% of hospital deaths are associated with PE and nearly one-third of all VTE patients experience a recurrence within 10 years of the initial event.[1]

Characteristics of the Guideline Source

Under the guidance of the McMaster University GRADE Centre, the ASH convened more than 100 experts (eg, hematologists, clinicians from other specialties, and patient representatives) in 10 panels to synthesize the current evidence base, assess certainty in the evidence, and formulate recommendations.[2-5] Panelists disclosed financial and nonfinancial interests, and conflicts of interest were managed through panel composition, disclosure, and recusal. The GRADE approach was used to assess evidence and make recommendations.[6] More than 200 recommendations, subject to public comment, are included as part of the initial 6 chapters peer reviewed and published in *Blood Advances* (**Table**).

Audio

Evidence Base

For VTE prophylaxis in acutely ill medical patients, LMWH or fondaparinux is preferred over UFH or a DOAC. The data for LMWH over UFH is strongest in critically ill medical patients, with 3 randomized clinical trials (RCTs) showing a moderate reduction in mortality (24 fewer deaths per 1000) and no difference in major bleeding.[7] Inpatient LMWH vs DOACs was studied in 3 RCTs showing no meaningful difference in VTE-related mortality or new VTE. The guideline recommends against extending pharmacological prophylaxis with DOACs after discharge given lack of reduction in mortality or symptomatic deep vein thrombosis (DVT) and only a very small reduction in PE (1 fewer per 1000 treated). Inpatient and extended-prophylaxis DOACs are also associated with increased risk of major bleeding.[2]

The guideline recommendations on diagnosis of VTE emphasize the importance of categorizing patients based on likelihood of VTE using validated clinical decision rules prior to testing. High-sensitivity D-dimer is recommended to exclude DVT in patients with low (≤10%) pretest probability. For intermediate or high (>25%) pretest probability, primary imaging using proximal lower extremity or whole-limb ultrasound is recommended, followed by a 1-week ultrasound if the initial study is negative in patient populations with increased prevalence. The guidelines base these recommendations on 45 studies including 15 718 patients.[3]

Table. Guideline Rating

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

Box. Venous Thromboembolism (VTE) Recurrence Risk Stratification in the Perioperative Setting

High risk
VTE within past 3 months
Protein C or S or antithrombin deficiency
Antiphospholipid antibody syndrome
Multiple thrombophilic abnormalities
Moderate risk
VTE within past 3-12 months
Heterozygous factor V Leiden
Prothrombin 20210 mutation
Recurrent VTE
Active cancer
Low risk
VTE >12 months prior without other risk factors

Pulmonary embolism can be excluded using a high-sensitivity D-dimer assay in patients with a low probability of disease (<5%). Ventilation perfusion scans are preferred over CTPA as the subsequent test to limit radiation exposure in patients likely to have a diagnostic scan and in centers where V̇Q̇ scans can be performed reliably. In patients with a high probability of PE (>50%), CTPA is recommended as the first test. For patients with an intermediate probability of PE (about 20%), D-dimer can be used to exclude PE, followed by V̇Q̇ scan or CTPA if D-dimer results are positive. In all cases in which V̇Q̇ scanning is considered, a baseline chest radiograph should be performed to ensure a diagnostic V̇Q̇ scan and to identify alternative diagnoses. These diagnostic recommendations were based on 75 studies including 44 834 patients.[3]

For invasive procedures, the guideline recommends against periprocedural bridging with LMWH or UFH in favor of interruption alone for patients at low to moderate risk of recurrent VTE. Risk stratification is shown in the **Box**. Studies used as the basis for this recommendation found no deaths and very low rates of recurrent VTE during 30-day follow-up in either group, and bleeding was increased in a clinically relevant manner among those receiving bridging.[4]

For pregnant women with acute VTE, the guideline recommends anticoagulation with LMWH over UFH based primarily on a systematic review and meta-analysis published in 2013.[8] These data suggest overall major bleeding rates in the antepartum period to be low (1%-2%) and similar to nonpregnant anticoagulated VTE patients.[5] In breastfeeding women with VTE, the guideline recommends against DOACs and favors UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options with no or very limited excretion in breast milk.

Benefits and Harms

Avoiding unnecessary testing by choosing initial studies based on pretest probability and prevalence of disease is a benefit of these guidelines. CTPA (and V̇Q̇) would be used less in low-risk patients, minimizing radiation exposure. Furthermore, an evidence-based approach to initial and extended anticoagulation management should result in lower bleeding risks.

Discussion

A major difference between the ASH VTE guidelines and others is consistent use of systematic reviews (both previously published and newly conducted). Forthcoming chapters of this guideline will address DVT and PE treatment (including thrombolysis and nonpharmacologic [ie, catheter-based or surgical] therapies for intermediate- or high-risk patients), thrombophilia, cancer-related VTE, and prophylaxis in surgical patients. Prevention and management of VTE in cancer patients is likely nuanced, with tumor type, chemotherapy, and abnormal hemostasis being important variables. The guidelines may not be fully generalizable to all acutely ill medical patients.

Areas in Need of Future Study or Ongoing Research

Research and validation of clinical decision rules for patients with suspected recurrent VTE are needed. Likewise, data supporting the choice of initial diagnostic tests for patients with suspected recurrent VTE with intermediate probability of disease are lacking. The clinical relevance and appropriate management of distal leg vein thrombosis detected by ultrasound is currently uncertain. Furthermore, sufficiently powered RCTs comparing LMWH/UFH bridging vs anticoagulation interruption in patients at high risk of recurrent VTE are needed. A need for validated, rapid point-of-care tests of DOAC effect is also a research priority.

Related guidelines

Antithrombotic therapy for VTE disease (American College of Chest Physicians evidence-based clinical practice guidelines)

Antithrombotic therapy for VTE disease (CHEST Guideline and Expert Panel report)

ARTICLE INFORMATION

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REFERENCES

1. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12(8):464-474. doi:10.1038/nrcardio.2015.83

2. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198-3225. doi:10.1182/bloodadvances.2018022954

3. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256. doi:10.1182/bloodadvances.2018024828

4. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257-3291. doi:10.1182/bloodadvances.2018024893

5. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359. doi:10.1182/bloodadvances.2018024802

6. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. *BMJ*. 2016;353:i2089. doi:10.1136/bmj.i2089

7. Alhazzani W, Lim W, Jaeschke RZ; et al. Heparin thromboprophylaxis in medical-surgical critically ill patients. *Crit Care Med*. 2013;41(9):2088-2098. doi:10.1097/CCM.0b013e31828cf104

8. Romualdi E, Dentali F, Rancan E, et al. Anticoagulant therapy for venous thromboembolism during pregnancy. *J Thromb Haemost*. 2013;11(2):270-281. doi:10.1111/jth.12085