



Guideline Summary NGC-10400

Guideline Title

Venous thromboembolism (VTE).

Bibliographic Source(s)

University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2014 May. 29 p. [48 references]


Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2009 Feb. 13 p. [10 references]

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [November 6, 2013 – Low Molecular Weight Heparins](#) : The U.S. Food and Drug Administration (FDA) is recommending that health care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labels of anticoagulant drugs known as low molecular weight heparins, including Lovenox and generic enoxaparin products and similar products.

Scope

Disease/Condition(s)

Venous thromboembolism (VTE), comprising:

- Acute deep venous thrombosis (DVT) of the upper and lower extremity
- Pulmonary embolism (PE)

Guideline Category

Diagnosis
Evaluation
Management
Treatment

Clinical Specialty

Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Pharmacology

Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To improve the recognition of venous thromboembolism (VTE) and selection of appropriate testing
- To improve selection of appropriate therapy
- To shorten resolution time for clinical symptoms
- To reduce bleeding and other complications
- To reduce recurrence of VTE
- To reduce incidence of pulmonary embolism (PE)
- To reduce mortality
- To avoid preventable emergency department visits and hospital admissions

Target Population

Outpatient adults with suspected acute deep venous thrombosis (DVT) of the upper and lower extremity, pulmonary embolism (PE), or both (venous thromboembolism [VTE])

Interventions and Practices Considered

Diagnosis

1. Clinical likelihood estimation
2. Venous color duplex Doppler ultrasound imaging
3. D-dimer testing
4. Computed tomography (CT)

Treatment/Management

1. Heparin anticoagulation
 - Low molecular weight heparin (LMWH)
 - Unfractionated heparin (UFH)
 - Minimum time period of treatment
 - Nonheparin anticoagulant agent (e.g., argatroban) if heparin is contraindicated
2. Vitamin K antagonist (warfarin)
3. Direct factor Xa inhibitors (rivaroxaban, apixaban)
4. Aggressive therapy (emergent thrombolytic therapy or thrombectomy)
5. Consideration of duration of therapy

Major Outcomes Considered

- Duration of clinical symptoms
- Length of hospital stay
- Recurrence rate of thrombosis (pulmonary embolism [PE] or deep vein thrombosis [DVT])
- Incidence of PE
- Post-thrombotic syndrome
- Mortality and complication rates
- Incidence of bleeding complications

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The initial prospective literature searches for this project were performed on MEDLINE in 1996, 1997, 2002, and 2008. The current update is based on a supplemental literature search performed on MEDLINE in May 2013. Literature published since January 2008 was searched. The team also reviewed the overlapping literature search results published in the American College of Chest Physician evidence-based clinical practice guidelines "Diagnosis of deep venous thrombosis (DVT)" and "Antithrombotic therapy for VTE disease" published in 2012.

The specified population was adults. Major key words were: pulmonary embolism and deep venous thrombosis thrombophlebitis (includes venous thromboembolism, thromboembolism, and venous thrombosis), guidelines, controlled trials, meta-analyses. Additional search terms for diagnosis were: primary risk factors (hereditary predisposition for clotting, estrogen [women], tobacco, etc.), acquired risk factors (malignancy, antiphospholipid antibody syndrome, etc.), duplex venous scan, pulmonary angiography, V/Q scan, arterial blood gasses (O₂ saturation), computed tomography, CT angiography, CT venography, magnetic resonance imaging, risk scores for DVT, risk scores for PE, D-dimer, pulmonary hypertension – embolism, and pregnancy and VTE diagnosis. Additional search terms for treatment were: low molecular weight heparin, heparin, warfarin, oral factor Xa inhibitors (rivaroxaban, apixaban, dabigatran, direct thrombin inhibitors (argatroban, bivalirudin), fondaparinux, idraparinux, factor 10 testing, international normalized ratio, prothrombin time, vena cava filter, temporary filter, emergency room treatment, indications for angiographic embolism removal, indications for ECMO, indications for thrombolytic, indications for iliofemoral DVT thrombolysis, pregnancy and VTE treatment, nonpharmacologic modalities of DVT treatment (e.g., sequential compression device, compression stockings/hose, physical therapy), DVT and PE prophylaxis after treatment (secondary prevention), treatment of late complications: pulmonary hypertension and post-thrombotic syndrome (edema). Detailed search terms and strategy are available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

- A. Randomized controlled trials
- B. Controlled trials, no randomization
- C. Observational studies
- D. Opinion of expert panel

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Conclusions were based on prospective randomized controlled trials (RCTs) if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

- I. Generally should be performed
- II. May be reasonable to perform
- III. Generally should not be performed

Cost Analysis

Low molecular weight heparin (LMWH) is less costly in overall treatment expense though its acquisition cost is higher. Shorter, or even no, hospital stays account for some of that advantage. However, even in the inpatient setting the costs of intravenous (IV) administration and monitoring make unfractionated heparin (UFH) costlier than LMWH.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Cardiology, Emergency

divisions of the University of Michigan Medical School to which the content is most relevant: Cardiology, Emergency Medicine, Family Medicine, General Medicine, Nuclear Medicine, Pulmonary & Critical Care Medicine, Radiology, Surgery, and Vascular Surgery. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

Recommendations

Major Recommendations

Note from the University of Michigan Health System (UMHS) and the National Guideline Clearinghouse (NGC): The following guidance was current as of May 2014. Because UMHS occasionally releases minor revisions to its guidance based on new information, users may wish to consult the [original guideline document](#) for the most current version.

Note from NGC: The following key points summarize the content of the guideline. Refer to the original guideline document for additional information.

The strength of recommendation (I-III) and levels of evidence (A-D) are defined at the end of the "Major Recommendations" field.

Initiate treatment immediately. Patients without contraindications to anticoagulation should begin treatment at time of diagnosis [IA]. If pulmonary embolism (PE) is clinically likely, initiation of anticoagulation should not await testing; if only deep vein thrombosis (DVT) is suspected and testing will be prompt, initiation may await testing. Therapeutic levels of anticoagulation should be achieved as quickly as possible. If warfarin is used for anticoagulation, initiate it on treatment day 1 simultaneous to initiation of low molecular weight heparin. Other oral agents may not require bridging treatment with heparin.

Diagnosis

Deep Venous Thrombosis (Lower Extremity DVT)

Clinical likelihood estimation. Symptoms and signs alone are not adequately sensitive or specific for diagnosis or exclusion of DVT but clinical likelihood estimation based on symptoms and signs is a necessary step in the testing strategy [IA].

Venous color duplex Doppler ultrasound imaging. This imaging is the standard for diagnosis [IA].

Pulmonary Embolism

D-dimer testing must be interpreted in the context of pretest probability [IC]. D-dimer testing alone is not adequately sensitive or specific to diagnose or exclude PE [IIIC]. See Figure 1 in the original guideline document.

Diagnostic testing determined by clinical likelihood estimation. The diagnostic approach differs depending on prior probability (see Figure 1, Tables 5, 6, 7, 8, and Appendix A in the original guideline document). Low probability patients with negative D-dimer require no further testing [IA]. Others should generally undergo computed tomography (CT) scanning [IA]. High or intermediate probability patients with negative CT or low probability patients with CT positive for sub- or segmental PE require further investigation (see text in the original guideline document) [IA].

Treatment

Heparin

Low molecular weight heparin (LMWH). LMWH is preferred for initial treatment over unfractionated heparin (UFH) or fondaparinux due to better safety and outcomes [IA].

Outpatient use of LMWH for DVT. LMWH is appropriate for most patients with DVT to use at home [IIA]. Some require initial brief hospital admission and stabilization. Clinically stable patients not at elevated risk due to comorbidities can be managed entirely as outpatients using LMWH.

Unfractionated heparin. UFH is no longer first line therapy. If UFH is used, it should be initiated and dosed in a structured manner (see Appendix B in the original guideline document) [IIA].

Minimum time period. When warfarin is chosen as an oral agent, continue heparin (LMWH or UFH) until either international normalized ratio (INR) is optimally >2.0 or for at least five days to minimize risk of extension of thrombosis or occurrence/recurrence of embolism [IB].

If heparin contraindicated. When heparin is contraindicated (bleeding risk or drug sensitivity), consider a nonheparin anticoagulant agent (e.g., argatroban) [IIB]. If anticoagulation is contraindicated, place inferior vena cava filter to prevent pulmonary embolization [IIB].

Vitamin K antagonist: warfarin. Patients should begin warfarin on day 1 of heparin, and INRs should optimally be >2.0 before discontinuation of heparin [IA,B]. Start warfarin at the anticipated therapeutic dose [IC].

If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [IA], preferably LMWH.

Direct factor Xa inhibitors: rivaroxaban, apixaban. For selected patients (see text in the original guideline document) begin rivaroxaban or apixaban as immediate monotherapy. See Table 12 in the original guideline document [IB].

Aggressive therapy. Patients with "massive" proximal DVT producing severe limb swelling and pain, or patients with "massive" PE producing shock or systemic hypoperfusion, may be candidates for emergent thrombolytic therapy or (in the case of DVT) thrombectomy. Such patients should be discussed with a consultant immediately [IID].

Duration of therapy. Most patients with VTE should be anticoagulated for 3 months [IB].

Definitions:

Levels of Evidence

- A. Randomized controlled trials
- B. Controlled trials, no randomization

- C. Observational studies
- D. Opinion of expert panel

Strength of Recommendation

- I. Generally should be performed
- II. May be reasonable to perform
- III. Generally should not be performed

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Algorithm for the diagnosis of pulmonary embolism
- Algorithm for the use of a V/Q scan in PE diagnosis

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

Conclusions were based on prospective randomized controlled trials (RCTs) if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis, treatment, and management of acute deep venous thrombosis (DVT) of the upper and lower extremity, pulmonary embolism (PE), or both venous thromboembolism (VTE)

Potential Harms

- Complications of anticoagulation include major bleeding, heparin-induced thrombocytopenia (HIT) and warfarin-induced skin necrosis.
- Patients taking warfarin should be aware of the effect of both diet and drug interactions on their anticoagulation status. Information on dietary sources of vitamin K that can reduce the effect of warfarin should be provided as part of patient education, as should warning about over the counter (OTC) vitamin supplementation. Since the list of medications that interact with warfarin is lengthy, anticoagulated patients should be advised to consult with their physician and/or a pharmacist before taking any prescription or OTC medications, and be given a written list of potential interactions (such as a package insert or patient education sheet).
- Careful monitoring of unfractionated heparin (UFH) therapy must be performed at regular intervals to ensure that this agent is effective and safe.
- D-dimer levels increase normally during pregnancy, thus using the standard threshold values for "abnormal" results in a high false positive rate.

Contraindications

Contraindications

- Contraindications to anticoagulation
 - Fresh surgical wound
 - Active gastrointestinal (GI) or other bleeding (not occult blood)
 - Recent hemorrhage cerebrovascular accident (CVA)
 - Multiple/major trauma
 - Recent neurosurgery
 - Inability or unwillingness to comply with oral anticoagulation
 - Pregnancy and impending delivery date
- Use of warfarin is contraindicated during pregnancy and can cause birth defects.
- Bleeding risk or drug sensitivity are contraindications to heparin.
- Contraindications to computed tomography angiography (CTA) include renal disease, severe contrast allergy and radiation dose concern.
- Contraindications to outpatient treatment are detailed in Table 9 in the original guideline document.

Qualifying Statements

Qualifying Statements

These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1998 Jun (revised 2014 May)

Guideline Developer(s)

University of Michigan Health System - Academic Institution

Source(s) of Funding

University of Michigan Health System

Guideline Committee

Venous Thromboembolism Guideline Team

Composition of Group That Authored the Guideline

Team Leader: Grant M Greenberg, MD, MA, MHSA, Family Medicine

Team Members: Brian J Brophy, MD, General Medicine; Kirk A Frey, MD, PhD, Nuclear Medicine; James B Froehlich, MD, MPH, Director, Anticoagulation Services; R Van Harrison, PhD, Medical Education; Steven Kronick, MD, Emergency Medicine; Melissa A Miller, MD, MS, Pulmonary & Critical Care Medicine; Marc J Moote, MS, PA-C, Surgery; David M Williams, MD, Radiology; Thomas W Wakefield, MD, Vascular Surgery

Ambulatory Care Guidelines Oversight: Grant M. Greenberg, MD, MA, MHSA; R Van Harrison, PhD

Financial Disclosures/Conflicts of Interest

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers

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Team Member	Relationship	Company
Brian Brophy, MD	None	
Kirk Frey, MD, PhD	Consultant	MIM Software, Lilly, AVID Radiopharmaceuticals, Bayer-Schering, Siemens and Piramal Imaging
	Grant	GE Healthcare
	Stock	General Electric, Novo-Nordisk, Bristol-Myers-Squibb, Merck, Medtronic
James Froelich, MD	Consultant	Pfizer, Merck, Janssen, Boehringer-Ingelheim, Sanofi-Aventis
Grant Greenberg, MD, MA, MHSA	None	
Van Harrison, PhD	None	
Melissa Miller, MD, MS	None	
Marc Moote, PA-C		
Thomas Wakefield, MD	None	
David Williams, MD	Consultant	Boston Scientific, Cook

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This guideline updates a previous version: University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2009 Feb. 13 p. [10 references]

Guideline Availability

Electronic copies: Available from the [University of Michigan Health System Web site](#).

Availability of Companion Documents

Continuing Medical Education (CME) information is available from the [University of Michigan Health System Web site](#).

Patient Resources

None available

NGC Status

This summary was completed by ECRI on May 20, 1999. The information was verified by the guideline developer on June 17, 1999. This NGC summary was updated on November 8, 2004. The updated information was verified by the guideline developer on December 7, 2004. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on July 13, 2009. The updated information was verified by the guideline developer on July 21, 2009. This summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This summary was updated by ECRI Institute on March 7, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins. This summary was updated by ECRI Institute on September 11, 2014.

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