

Management of Venous Thromboembolism: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians

Vincenza Snow, MD; Amir Qaseem, MD, PhD, MHA; Patricia Barry, MD, MPH; E. Rodney Hornbake, MD; Jonathan E. Rodnick, MD; Timothy Tobolic, MD; Belinda Ireland, MD, MS; Jodi B. Segal, MD; Eric B. Bass, MD, MPH; Kevin B. Weiss, MD, MPH; Lee Green, MD, MPH; Douglas K. Owens, MD, MS; and the Joint American College of Physicians/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism*

Venous thromboembolism is a common condition affecting 7.1 persons per 10 000 person-years among community residents. Incidence rates for venous thromboembolism are higher in men and African Americans and increase substantially with age. It is critical to treat deep venous thrombosis at an early stage to avoid development of further complications, such as pulmonary embolism or recurrent deep venous thrombosis. The target audience for this

guideline is all clinicians caring for patients who have been given a diagnosis of deep venous thrombosis or pulmonary embolism. The target patient population is patients receiving a diagnosis of pulmonary embolism or lower-extremity deep venous thrombosis.

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For author affiliations, see end of text.

RECOMMENDATIONS

Recommendation 1: Low-molecular-weight heparin (LMWH) rather than unfractionated heparin should be used whenever possible for the initial inpatient treatment of deep venous thrombosis (DVT). Either unfractionated heparin or LMWH is appropriate for the initial treatment of pulmonary embolism.

Consistent evidence demonstrates that LMWH is superior to unfractionated heparin for the initial treatment of DVT, particularly for reducing mortality and reducing the risk for major bleeding during initial therapy. Additional trials are needed to more rigorously examine the efficacy of LMWH for the initial treatment of pulmonary embolism, but systematic reviews of existing trials indicate that LMWH is at least as effective as unfractionated heparin for these patients as well. In addition, trials of unfractionated heparin in pulmonary embolism show that many patients are subtherapeutic or supratherapeutic while receiving unfractionated heparin, whereas LMWH is quickly and consistently therapeutic, an important consideration in the treatment of VTE.

Recommendation 2: Outpatient treatment of DVT, and possibly pulmonary embolism, with LMWH is safe and cost-effective for carefully selected patients and should be considered if the required support services are in place.

In trials that compared inpatient and outpatient treatment, the rates of recurrent DVT, major bleeding, and death during follow-up differed only slightly. These studies were conducted among highly selected groups of patients

and in clinical systems with the required support services in place. Several studies allowed a brief inpatient admission for stabilization of the patients before randomization to the outpatient group. While some studies enrolled patients with concomitant pulmonary embolism, most excluded such patients. Inclusion criteria were strict: Most studies excluded patients with previous VTE, thrombophilic conditions, or significant comorbid illnesses; pregnant patients; and those unlikely to adhere to outpatient therapy. Therefore, this recommendation cannot be generalized (1).

Recommendation 3: Compression stockings should be used routinely to prevent postthrombotic syndrome, beginning within 1 month of diagnosis of proximal DVT and continuing for a minimum of 1 year after diagnosis.

The evidence demonstrated a marked reduction in the incidence and severity of postthrombotic syndrome among patients wearing compression stockings, either over-the-counter stockings or custom-fit stockings, if use was initiated within 1 month diagnosis of proximal DVT. Most diagnoses of postthrombotic syndrome occurred early, within the first 2 years after DVT.

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*Clinical Efficacy and Assessment Subcommittee of the American College of Physicians: Douglas K. Owens, MD, MS (*Chair*); Mark Aronson, MD; Donald E. Casey Jr., MD, MPH, MBA; J. Thomas Cross Jr., MD, MPH; Nancy C. Dolan, MD; Nick Fitterman, MD; E. Rodney Hornbake, MD; Paul Shekelle, MD, PhD; Katherine D. Sherif, MD; and Kevin Weiss, MD, MPH (*Immediate Past Chair*). Commission on Science of the American Academy of Family Physicians: Eric M. Wall, MD, MPH (*Chair*); Kevin A. Peterson, MD, MPH; James M. Gill, MD; Robert C. Marshall, MD, MPH; Jonathan E. Rodnick, MD; Kenneth G. Schellhase, MD, MPH; Steven W. Strode, MD, MEd, MPH; Kurtis S. Elward, MD, MPH; James W. Mold, MD, MPH; Jonathan L. Temte, MD, PhD; Frederick M. Chen, MD, MPH; Thomas F. Koinis, MD; Donya A. Powers, MD; Karl M. Kochendorfer, MD; Peter John Oppelt; Herbert F. Young, MD, MA; and Bellinda K. Schoof, MHA. Approved by the American College of Physicians Board of Regents in April 2006. Approved by the American Academy of Family Physicians Board of Directors on 28 March 2006.

Recommendation 4: There is insufficient evidence to make specific recommendations for types of anticoagulation management of VTE in pregnant women.

During pregnancy, women have a 5-fold increased risk for VTE compared with nonpregnant women. Clinicians should avoid vitamin K antagonists in pregnant women because these drugs cross the placenta and are associated with embryopathy between 6 and 12 weeks' gestation, as well as fetal bleeding (including intracranial hemorrhage) at delivery. Neither LMWH nor unfractionated heparin crosses the placenta, and neither is associated with embryopathy or fetal bleeding.

Recommendation 5: Anticoagulation should be maintained for 3 to 6 months for VTE secondary to transient risk factors and for more than 12 months for recurrent VTE. While the appropriate duration of anticoagulation for idiopathic or recurrent VTE is not definitively known, there is evidence of substantial benefit for extended-duration therapy.

For VTE secondary to transient risk factors, 3 or 6 months of treatment was associated with similar risks for recurrent VTE. In the single study that exclusively enrolled patients presenting with a second episode of VTE, extended-duration (>12 months or indefinite) anticoagulant therapy was associated with fewer recurrences than was termination after 6 months of therapy. For patients with idiopathic VTE (including those with recurrent VTE), extended-duration therapy decreased the relative risk for recurrence by 64% to 95%. Length of therapy in the trials varied widely, from greater than 3 months to 12 months to up to 4 years. The results for extended-duration therapy reflect follow-up only to 4 years; the risk–benefit ratio is not known for longer durations. Clinicians should weigh the benefits, harms, and patient preferences in deciding on the duration of anticoagulation.

Recommendation 6: LMWH is safe and efficacious for the long-term treatment of VTE in selected patients (and may be preferable for patients with cancer).

Evidence from high-quality randomized trials supports the use of LMWH as comparable to oral anticoagulation for VTE in selected patients. Low-molecular-weight heparin may be a useful treatment for patients in whom control of the international normalized ratio (INR) is difficult and may be more efficacious than oral anticoagulants in patients with cancer.

BACKGROUND

Deep venous thrombosis in the lower extremities is the most frequent manifestation of VTE, and the most life-threatening manifestation is pulmonary embolism. An important complication of DVT is postthrombotic syndrome, which may result in lifelong limb pain and edema (2). Venous thromboembolism recurs in about 20% of patients after 5 years of observation, but this rate varies greatly depending on the presence of risk factors for recurrence (2, 3).

The intent of this guideline is to provide evidence-based recommendations for management of VTE. The target audience is all clinicians caring for patients who have received a diagnosis of DVT or pulmonary embolism. The target patient population is patients who have been given a diagnosis of pulmonary embolism or lower-extremity DVT.

METHODS

The American Academy of Family Physicians (AAFP) nominated this topic to the Agency for Healthcare Research and Quality Evidence-Based Practice Centers (EPC) program, and the American College of Physicians (ACP) supported the nomination. Recommendations are based on evidence from only high-quality randomized trials unless otherwise stated. This is the second of 2 joint guidelines by the ACP and the AAFP covering the diagnosis and management of VTE. The intent of this guideline is to provide evidence-based recommendations for management of VTE. Diagnosis of VTE is the other guideline and is covered in a paper by Qaseem and colleagues (4). The guideline is based on a systematic review of the evidence, as detailed in a comprehensive evidence report published in 2003 (5); that review has been updated in the accompanying background paper in this issue (30) by members of the Johns Hopkins University Evidence-based Practice Center who prepared the original report. Those papers contain substantial additional detail about the evidence for each recommendation in this guideline. The AAFP and the ACP formulated the following questions relevant to the management of VTE. The EPC authors reviewed the evidence that was available to answer each question. This evidence is summarized below.

EVIDENCE SUMMARY

Is Heparin or LMWH Safer and More Efficacious for Initial Treatment of VTE? Is It Cost-Effective or Cost-Saving to Use LMWH rather than Unfractionated Heparin for the Initial Treatment of VTE?

The EPC authors found 16 systematic reviews of randomized trials that reviewed rates of recurrent venous thromboembolism, major bleeding, or death (5–13). Of the 11 reviews that pooled the trial results, none demonstrated that unfractionated heparin was superior to LMWH in preventing recurrent DVT. Patients treated with LMWH had significantly fewer episodes of bleeding than those treated with unfractionated heparin. Nine of 10 reviews showed that LMWH significantly reduced mortality during the 3 to 6 months of follow-up compared with unfractionated heparin (14). Only 4 systematic reviews reported summary results separately for patients with pulmonary embolism, concluding that LMWH was as effective as unfractionated heparin in these patients (9, 11, 14, 15). In addition, heparin-induced thrombocytopenia is a possibility with both therapies, although LMWH is less likely to cause antibody formation for this condition.

In summary, the evidence suggests that LMWH is superior to unfractionated heparin for treating DVT of the lower extremities, particularly for reducing mortality and the risk for major bleeding during initial therapy. It is at least as safe and effective as unfractionated heparin for patients with pulmonary embolism. For the initial treatment of VTE, LMWH is either cost-saving or cost-effective compared with unfractionated heparin.

Is Outpatient Treatment of VTE Safe and Effective Compared with Inpatient Treatment?

Twelve studies compared the outcomes of patients with VTE treated with LMWH administered at home to the outcomes of those treated with unfractionated heparin in the hospital (9, 10, 16–24). Three of these were randomized trials (16–18); the other 9 were cohort studies. An additional 5 studies, including 2 randomized trials (25, 26) compared outcomes and costs for patients receiving LMWH at home to those for patients receiving LWMH in the hospital (25–29).

Seven of the studies allowed a brief inpatient admission for stabilization of the patients before randomization to the outpatient group. Four of these studies enrolled patients with concomitant pulmonary embolism (21, 24, 27, 29). Inclusion criteria were strict: Most studies excluded patients with previous VTE, thrombophilic conditions, or significant comorbid illnesses; pregnant patients; and patients unlikely to adhere to outpatient therapy. Very few studies reported on the adequacy of anticoagulation in the unfractionated heparin groups or after transition from heparin to warfarin. All the studies were carried out in settings with well-developed patient education and home care support infrastructures.

The rates of recurrent DVT in the different treatment groups differed only slightly (30). Rates of pulmonary embolism (27), major bleeding, and death during follow-up did not differ between treatment groups; however, because these complications occurred at low rates, study power may have been inadequate to detect differences. Fewer inpatient days accrued in the LMWH treatment groups. Ten of these 17 studies reported on treatment costs (9, 10, 16, 20–22, 24–26, 28), and 9 found the outpatient strategy cost-saving compared with inpatient therapy. For more in-depth analysis of the cost-effectiveness of initial outpatient therapy, please see the Appendix (available at www.annals.org) of the background paper (30).

In summary, there is consistent evidence that outpatient treatment of VTE with LMWH is cost-saving and is at least as safe as inpatient treatment among highly selected patients in settings where the required support services are in place.

Are Compression Stockings Efficacious at Reducing the Incidence of Postthrombotic Syndrome?

There is no standardized definition of postthrombotic syndrome, but most descriptions include chronic postural-dependent edema and pain or localized discomfort in a

patient with previous venous thrombosis. Three randomized, controlled trials have examined the efficacy of compression stockings for prevention of postthrombotic syndrome after DVT, but only 2 examined their use within the first month after diagnosis (31, 32). Follow-up lasted nearly 5 years in these trials. Both trials demonstrated greater than 50% relative risk reduction in the incidence of postthrombotic syndrome among patients wearing compression stockings, whether over-the-counter stockings or more expensive, custom-fit stockings.

The evidence suggests that the use of compression stockings starting from 1 month of diagnosis or earlier and lasting 2 years after DVT diagnosis reduces the incidence and severity of postthrombotic syndrome.

What Are the Optimal Therapies for Pregnant Women with VTE?

During pregnancy, women have a 5-fold increased risk for VTE compared with nonpregnant women. The absolute risk for symptomatic VTE during pregnancy is between 0.5 and 3.0 per 1000 persons based on studies using radiographic documentation (33). The EPC identified 19 studies that evaluated treatment of VTE during pregnancy, but after they excluded studies that evaluated prophylaxis only, very small studies, and those without clinical outcomes, only 11 studies—all observational—remained for review (34–44).

There is not adequate evidence for definitive recommendations for management of VTE in pregnancy. Clinicians should avoid vitamin K antagonists in pregnant women because these drugs cross the placenta and are associated with embryopathy between 6 and 12 weeks' gestation, as well as with fetal bleeding (including intracranial hemorrhage) at delivery. Neither LMWH nor unfractionated heparin crosses the placenta, and neither is associated with embryopathy or fetal bleeding.

What Is the Optimal Duration of Vitamin K Antagonist Therapy for VTE Treatment, and What Is the Optimal INR for Extended-Duration Therapy?

The EPC authors restricted their review to 10 trials, all published since 1995, that used objective radiologic documentation of VTE and measured therapeutic intensity by INR (45–54). Patients with cancer or those judged to be at high risk for bleeding were excluded from all but 1 study (45). Anticoagulation was generally managed by specialized anticoagulation clinics. The rates of recurrent DVT in these trials varied tremendously depending on whether the enrolled patients had had idiopathic DVT (48, 49, 51, 53), DVT in the setting of a transient risk factor (54), a permanent risk factor for recurrent DVT, or a history of multiple previous thromboses (47).

In a pooled analysis of the 4 trials of VTE that compared 3 or fewer months to 4 to 12 months of therapy (46, 49, 50, 52), there was a trend toward fewer recurrences with longer treatment, although the confidence interval included 1.0. The results were largely driven by a single study

that randomly assigned patients to 6 weeks or 6 months of therapy (46). In the only study that exclusively enrolled patients presenting with a second episode of VTE, long-term (indefinite-duration), conventional-intensity therapy (INR, 2.0 to 2.85) was associated with markedly fewer recurrences (relative risk of placebo compared with warfarin, 8.0) than was termination after 6 months of therapy (47). However, there was a trend toward more major bleeding events for the patients receiving long-term treatment. A trial of indefinite-duration, low-dose anticoagulation after 6 months of full-dose anticoagulation for idiopathic VTE (48) was terminated at 4 years because clear evidence of benefit made it unethical to continue randomly assigning patients to placebo (absolute risk reduction for recurrent VTE, 4.6 per 100 patient-years; absolute risk for harm, 1 per 100 patient-years).

Seven studies (46–48, 50, 51, 53, 54) enrolled patients with pulmonary embolism (52), but only 1 focused exclusively on patients with pulmonary embolism. In that study, 6 to 12 months of therapy (6 months for patients with transient risk factors or 12 months for those with an idiopathic event) and 3 to 6 months of abbreviated therapy (3 months for patients with transient risk factors or 6 months for those with an idiopathic event) were associated with similar risks for recurrent VTE (3.1 episodes of VTE per 100 patient-years [95% CI, 1.7 to 5.2] vs. 4.1 episodes of VTE per 100 patient-years [CI, 2.4 to 6.5]) (52).

Four studies addressed the intensity of anticoagulation (47, 48, 51, 53). Two studies evaluated low-intensity anticoagulation (INR, 1.5 to 2.0) after conventional-intensity therapy (INR, 2.0 to 3.0) (51, 53), and 3 evaluated the efficacy of continuous conventional-intensity therapy (47, 48, 53). Long-term, conventional-intensity therapy was more effective than long-term, low-intensity therapy, with an incremental benefit of 1.2 per 100 patient-years, and the rates of major bleeding were similar in the 2 groups (53). Approximately 19% of patients discontinued long-term anticoagulation because of complications, preference, or an inability to adhere.

The evidence best supports conventional-intensity therapy (INR, 2.0 to 3.0) for 3 to 6 months among patients with VTE secondary to transient risk factors and for at least 12 months among patients with a second episode of VTE and extended-duration conventional-intensity oral anticoagulation among patients with idiopathic events. The results for extended-duration therapy reflect follow-up only to 4 years; the risk–benefit ratio of continuous, conventional anticoagulation may change with longer treatment.

What Is the Evidence to Support Use of LMWH in Place of a Vitamin K Antagonist for Treatment of VTE?

The EPC authors identified 9 well-designed randomized, controlled trials (55–63) and 1 large, prospective cohort study (64) that compared the safety and efficacy of LMWH with those of oral vitamin K antagonists for the

full course of treatment of VTE. All studies were open-label, eligibility criteria were somewhat restrictive (thereby limiting generalizability), and most studies lasted 3 months. The percentage of time that the INR was in a therapeutic range was not particularly high and probably mirrors clinical practice. The rates of recurrence of VTE did not substantially differ, and the bleeding rates in the LMWH group did not exceed those in the oral anticoagulant group in any trial.

High-quality evidence supports the use of LMWH as similar to oral anticoagulation for VTE in selected patients. Low-molecular-weight heparin is an option for patients in whom INR control is difficult, and it may be more efficacious than oral anticoagulants in patients with cancer (30).

What Are the Incidences of Pulmonary Embolism and DVT Recurrences after Placement of Vena Cava Filters?

A single, randomized trial addressed this question (65). After 2 years of follow-up, filter placement with anticoagulation was associated with a slight reduction in symptomatic pulmonary embolism compared with anticoagulation alone. However, filters were associated with a significant increase in recurrent DVT compared with anticoagulation alone (20.8% in the filter group vs. 11.6% in the no-filter group; $P = 0.02$). This study provides no information about the effectiveness of filters for patients who do not receive anticoagulation, for whom filter placement is typically considered.

An observational cohort study used administrative data to assess patients with VTE who did and did not receive vena cava filters during a 5-year period (66). After adjustment for risk factors associated with recurrent VTE, filter placement did not reduce pulmonary embolism but was associated with a 2-fold increase in the relative hazard of subsequent DVT among patients with initial pulmonary embolism. The time to recurrent pulmonary embolism was similar in filter recipients and nonrecipients.

Overall, there is insufficient evidence to make recommendations in this area.

Does Catheter-Directed Thrombolysis for Treatment of DVT Reduce Recurrence Rates and Reduce the Incidence of Postthrombotic Syndrome Relative to Standard Anticoagulation?

Catheter-directed thrombolysis involves administration of thrombolytics directly through the side ports of a catheter traversing the thrombus. Only 1 small randomized trial has compared catheter-directed thrombolysis with conventional, sequenced heparin and warfarin in patients with acute iliofemoral DVT (67). Six months after treatment, the patency rate was significantly higher in the group that received catheter-directed thrombolysis, and the prevalence of venous reflux was lower. Most other studies of catheter-directed thrombolysis are observational studies or case series (68–77). While these studies suggest that catheter-directed thrombolysis may be efficacious in well-cho-

sen patients, the evidence is insufficient to make recommendations.

From the American College of Physicians, Philadelphia, Pennsylvania; Merck Institute of Aging and Health, Gloucester Point, Virginia; University of California, San Francisco, San Francisco, California; Byron Family Medicine, Byron Center, Mississippi; American Academy of Family Physicians, Leawood, Kansas; Johns Hopkins University School of Medicine, Baltimore, Maryland; Hines Veterans Affairs Hospital and Northwestern University, Chicago, Illinois; University of Michigan, Ann Arbor, Michigan; and Veterans Affairs Palo Alto Health Care System and Stanford University, Stanford, California.

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Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Drs. Snow and Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Barry: 1584 York River Drive, Gloucester Point, VA 23062.
Dr. Hornbake: 7 Shelter Rock Road, PO Box 218, Hadlyme, CT 06439.
Dr. Rodnick: University of California, San Francisco, Box 0886, San Francisco, CA 94143.
Dr. Tobolic: Byron Center Medicine, PO Box 307, 7751 Byron Center Avenue, Byron Center, MI 49315.
Dr. Ireland: BJC HealthCare, 600 South Taylor, Suite 122, St. Louis, MO 63110.

Drs. Segal and Bass: Johns Hopkins University, 1830 East Monument Street, 8th Floor, Baltimore, MD 21205.

Dr. Weiss: Hines Veterans Affairs Hospital, PO Box 5000, Hines, IL 60141.

Dr. Green: University of Michigan, 1018 Fuller Street, Campus #0708, Ann Arbor, MI 48109.

Dr. Owens: Stanford University, 117 Encina Commons, Stanford, CA 94305.