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

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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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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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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 LWMH 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.

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References

1. **Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al.** A prediction rule to identify low-risk patients with pulmonary embolism. Arch Intern Med. 2006;166:169-75. [PMID: 16432084]

2. **Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd.** Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160:761-8. [PMID: 10737275]

3. **Hansson PO, Sörbo J, Eriksson H.** Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med. 2000;160: 769-74. [PMID: 10737276]

4. **Qaseem A, Snow V, Barry P, Hornbake R, Rodnick JE, Tobolic T, et al.** Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. Ann Fam Med. 2007. [In press].

5. **Segal JB, Eng J, Jenckes MW, Tamariz LJ, Bolger DT, Krishnan JA, et al.** Diagnosis and treatment of deep venous thrombosis and pulmonary embolism. Evid Rep Technol Assess (Summ). 2003:1-6. [PMID: 12674745]

6. **Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al.** Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12. [PMID: 8721797]

7. **Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, et al.** Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69:548-56. [PMID: 14971837]

8. **Brewer D.** Should low-molecular-weight heparins replace unfractionated heparin as the agent of choice for adults with deep venous thrombosis? J Fam Pract. 1998;47:185-92. [PMID: 9752370]

9. **Dolovich M.** Rationale for spacer use in children. Pediatr Pulmonol Suppl. 1997;16:184-5. [PMID: 9443266]

10. **Gould MK, Dembitzer AD, Sanders GD, Garber AM.** Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med. 1999; 130:789-99. [PMID: 10366368]

11. **Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AW.** Low molecular weight heparin: a critical analysis of clinical trials. Pharmacol Rev. 1994;46: 89-109. [PMID: 8190751]

12. **Hettiarachchi RJ, Prins MH, Lensing AW, Buller HR.** Low molecular weight heparin versus unfractionated heparin in the initial treatment of venous thromboembolism. Curr Opin Pulm Med. 1998;4:220-5. [PMID: 10813237]

13. **Hirsh J, Siragusa S, Cosmi B, Ginsberg JS.** Low molecular weight heparins (LMWH) in the treatment of patients with acute venous thromboembolism. Thromb Haemost. 1995;74:360-3. [PMID: 8578485]

14. **Howard PA.** Dalteparin: a low-molecular-weight heparin. Ann Pharmacother. 1997;31:192-203. [PMID: 9034422]

15. **Raschke R, Hirsh J, Guidry JR.** Suboptimal monitoring and dosing of unfractionated heparin in comparative studies with low-molecular-weight heparin. Ann Intern Med. 2003;138:720-3. [PMID: 12729426]

16. **Rocha E, Martínez-González MA, Montes R, Panizo C.** Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis? A meta-analysis. Haematologica. 2000;85:935-42. [PMID: 10980632]

17. **van Den Belt AG, Prins MH, Lensing AW, Castro AA, Clark OA, Atallah AN, et al.** Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2000:CD001100. [PMID: 10796593]

18. **van der Heijden JF, Prins MH, Büller HR.** For the initial treatment of venous thromboembolism: are all low-molecular-weight heparin compounds the same? Thromb Res. 2000;100:V121-30. [PMID: 11053625]

19. **Belcaro G, Nicolaides AN, Cesarone MR, Laurora G, De Sanctis MT, Incandela L, et al.** Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. Angiology. 1999;50:781-7. [PMID: 10535716]

20. **Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, et al.** Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med. 1996;334:682-7. [PMID: 8594426]

21. **Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al.** A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med. 1996;334:677-81. [PMID: 8594425]

22. **Pearson SD, Blair R, Halpert A, Eddy E, Mckean S.** An outpatient program to treat deep venous thrombosis with low-molecular-weight heparin. Eff Clin Pract. 1999;2:210-7. [PMID: 10623053]

23. **Huse DM, Cummins G, Taylor DC, Russell MW.** Outpatient treatment of venous thromboembolism with low-molecular-weight heparin: an economic evaluation. Am J Manag Care. 2002;8:S10-6. [PMID: 11822346]

24. **Grau E, Tenias JM, Real E, Medrano J, Ferrer R, Pastor E, et al.** Home treatment of deep venous thrombosis with low molecular weight heparin: Long-term incidence of recurrent venous thromboembolism. Am J Hematol. 2001;67: 10-4. [PMID: 11279651]

25. **Vinson DR, Berman DA.** Outpatient treatment of deep venous thrombosis: a clinical care pathway managed by the emergency department. Ann Emerg Med. 2001;37:251-8. [PMID: 11223760]

26. **Smith BJ, Weekley JS, Pilotto L, Howe T, Beven R.** Cost comparison of at-home treatment of deep venous thrombosis with low molecular weight heparin to inpatient treatment with unfractionated heparin. Intern Med J. 2002;32:29-34. [PMID: 11783670]

27. **O'Brien JA, Caro JJ.** Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. Pharmacoeconomics. 2002; 20:603-15. [PMID: 12141888]

28. **Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G.** Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. Chest. 2002;122:108-14. [PMID: 12114345]

29. **Rymes NL, Lester W, Connor C, Chakrabarti S, Fegan CD.** Outpatient management of DVT using low molecular weight heparin and a hospital outreach service. Clin Lab Haematol. 2002;24:165-70. [PMID: 12067281]

30. **Segal JB, Streiff MB, Hoffman LV, Thornton K, Bass EB.** Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med. 2007;146:211-22.

31. **Grunwald MR, Hofmann LV.** Comparison of urokinase, alteplase, and re-

teplase for catheter-directed thrombolysis of deep venous thrombosis. J Vasc Interv Radiol. 2004;15:347-52. [PMID: 15064337]
32. **Ouriel K, Katzen B, Mewissen M, Flick P, Clair DG, Benenati J, et al.** Reteplase in the treatment of peripheral arterial and venous occlusions: a pilot study. J Vasc Interv Radiol. 2000;11:849-54. [PMID: 10928520]
33. **López-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G, et al.** Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. J Vasc Surg. 2001;33:77-90. [PMID: 11137927]
34. **Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al.** Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162:1729-35. [PMID: 12153376]
35. **Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, et al.** Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost. 1994;72:191-7. [PMID: 7831650]
36. **Veiga F, Escribá A, Maluenda MP, López Rubio M, Margalet I, Lezana A, et al.** Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thromb Haemost. 2000;84:559-64. [PMID: 11057850]
37. **Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S, et al.** Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thromb Haemost. 1999;81:26-31. [PMID: 9974369]
38. **Monreal M, Roncales FJ, Ruiz J, Muchart J, Fraile M, Costa J, et al.** Secondary prevention of venous thromboembolism: A role for low-molecular-weight heparin. Haemostasis. 1998;28:236-43. [PMID: 10420072]
39. ACOG Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin. Thrombembolism in pregnancy. Int J Gynaecol Obstet. 2001;75:203-12. [PMID: 11724031]
40. **Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J.** Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. Am J Obstet Gynecol. 2004;190:495-501. [PMID: 14981396]
41. **Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al.** Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. BJOG. 2001;108:1134-40. [PMID: 11762651]
42. **Aburahma AF, Mullins DA.** Endovascular caval interruption in pregnant patients with deep vein thrombosis of the lower extremity. J Vasc Surg. 2001;33:375-8. [PMID: 11174792]
43. **Aburahma AF, Boland JP.** Management of deep vein thrombosis of the lower extremity in pregnancy: a challenging dilemma. Am Surg. 1999;65:164-7. [PMID: 9926752]
44. **Aburahma AF, Bastug DF, Tiley EH 3rd, Killmer SM, Boland JP.** Management of deep vein thrombosis of the lower extremity in pregnancy. W V Med J. 1993;89:445-7. [PMID: 8266682]
45. **Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al.** Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349:759-62. [PMID: 9074574]
46. **Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, et al.** Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med. 2001;161:2105-9. [PMID: 11570939]
47. **Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al.** Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med. 2004;141:249-56. [PMID: 15313740]
48. **Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, et al.** A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med. 1998;338:409-15. [PMID: 9459643]
49. **White RH, Zhou H, Kim J, Romano PS.** A population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. Arch Intern Med. 2000;160:2033-41. [PMID: 10888977]
50. **Hann CL, Streiff MB.** The role of vena caval filters in the management of venous thromboembolism. Blood Rev. 2005;19:179-202. [PMID: 15784297]
51. **Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al.** Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost. 1995;74:606-11. [PMID: 8584992]
52. **Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, et al.** A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N Engl J Med. 1995;332:1661-5. [PMID: 7760866]
53. **Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, et al.** The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997;336:393-8. [PMID: 9010144]
54. **Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al.** A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901-7. [PMID: 10089183]
55. Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345:165-9. [PMID: 11463010]
56. Investigators of the "Durée Optimale du Traitement AntiVitamines K" (DOTAVK) Study. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation. 2001;103:2453-60. [PMID: 11369685]
57. PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348:1425-34. [PMID: 12601075]
58. Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003;139:19-25. [PMID: 12834314]
59. Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:631-9. [PMID: 12917299]
60. SOFAST Investigators. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. J Thromb Haemost. 2004;2:743-9. [PMID: 15099280]
61. **Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV.** Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World J Surg. 1996;20:521-6; discussion 526-7. [PMID: 8661630]
62. **Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, et al.** Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. J Vasc Surg. 1999;30:283-92. [PMID: 10436448]
63. Bemiparin Investigators. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost. 2003;89:674-80. [PMID: 12669122]
64. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53. [PMID: 12853587]
65. **Razavi MK, Wong H, Kee ST, Sze DY, Semba CP, Dake MD.** Initial clinical results of tenecteplase (TNK) in catheter-directed thrombolytic therapy. J Endovasc Ther. 2002;9:593-8. [PMID: 12431142]
66. **Sugimoto K, Hofmann LV, Razavi MK, Kee ST, Sze DY, Dake MD, et al.** The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. J Vasc Surg. 2003;37:512-7. [PMID: 12618684]
67. **Rodger MA, Gagné-Rodger C, Howley HE, Carrier M, Coyle D, Wells PS.** The outpatient treatment of deep vein thrombosis delivers cost savings to patients and their families, compared to inpatient therapy. Thromb Res. 2003;112:13-8. [PMID: 15013267]
68. **Boccalon H, Elias A, Chalé JJ, Cadène A, Gabriel S.** Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Arch Intern Med. 2000;160:1769-73. [PMID: 10871969]
69. **Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS.** Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost. 2000;83:209-11. [PMID: 10739374]

70. **Lapidus L, Börretzen J, Fahlén M, Thomsen HG, Hasselblom S, Larson L, et al.** Home treatment of deep vein thrombosis. An out-patient treatment model with once-daily injection of low-molecular-weight heparin (tinzaparin) in 555 patients. Pathophysiol Haemost Thromb. 2002;32:59-66. [PMID: 12214150]
71. **Ageno W, Steidl L, Marchesi C, Dentali F, Mera V, Squizzato A, et al.** Selecting patients for home treatment of deep vein thrombosis: the problem of cancer. Haematologica. 2002;87:286-91. [PMID: 11869941]
72. **Elsharawy M, Elzayat E.** Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. Eur J Vasc Endovasc Surg. 2002;24:209-14. [PMID: 12217281]
73. **Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH.** Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology. 1999;211:39-49. [PMID: 10189452]
74. **Comerota AJ, Throm RC, Mathias SD, Haughton S, Mewissen M.** Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg. 2000;32:130-7. [PMID: 10876214]
75. **Bjarnason H, Kruse JR, Asinger DA, Nazarian GK, Dietz CA Jr, Caldwell MD, et al.** Iliofemoral deep venous thrombosis: safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. J Vasc Interv Radiol. 1997;8:405-18. [PMID: 9152914]
76. **Raju S, Fountain T, McPherson SH.** Catheter-directed thrombolysis for deep venous thrombosis. J Miss State Med Assoc. 1998;39:81-4. [PMID: 9538591]
77. **Castaneda F, Li R, Young K, Swischuk JL, Smouse B, Brady T.** Catheter-directed thrombolysis in deep venous thrombosis with use of reteplase: immediate results and complications from a pilot study. J Vasc Interv Radiol. 2002;13:577-80. [PMID: 12050297]

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