DEEP VENOUS THROMBOSIS
Supporting information

This guideline has been prepared with reference to the following:

NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. 2023. NICE. London

https://www.nice.org.uk/guidance/ng158

Stevens SM, Woller SC, Kreuziger LB et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160:e545-e608

https://linkinghub.elsevier.com/retrieve/pii/S0012-3692(21)01506-3

NICE. Percutaneous mechanical thrombectomy for acute deep vein thrombosis of the leg. 2019. NICE. London

https://www.nice.org.uk/guidance/ipg651

NICE. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2019. NICE. London

https://www.nice.org.uk/guidance/ng89

Recognition and assessment

Do most episodes of PE follow popliteal/iliofemoral DVT?
Lower limb DVT is “responsible for over 90% of pulmonary emboli” (Kearon, 2003).
In a series of 78 patients who had evidence of PE on pulmonary arteriograms but no findings in the legs, venography (or radionuclide venography) showed that 24 patients (31%) had asymptomatic DVT of the superficial femoral or popliteal vein (Ferris, 1992).
An autopsy series (Havig, 1977) showed that two-thirds of emboli described as “contributing to death” originated in the proximal iliofemoral veins.
Bilateral DVT resulted in the worst outcomes in a study of 1913 patients (Seinturier, 2005), with survival at 2 years of 65% for bilateral proximal disease, compared to 80% for unilateral distal disease.

Ferris EJ. Deep venous thrombosis and pulmonary embolism: correlative evaluation and therapeutic implications. Am J Roentgenol 1992;159:1149-55
http://www.ajronline.org/doi/pdf/10.2214/ajr.159.6.1442374

Havig O. Deep vein thrombosis and pulmonary embolism: an autopsy study with multiple regression analysis of possible risk factors. Acta Chir Scand Suppl 1977;478:1-120

Kearon C. Natural history of venous thromboembolism. Circulation 2003;107:I22-30
http://circ.ahajournals.org/cgi/pmidlookup?view=long&pmid=12814982

Seinturier C, Bosson JL, Colonna M, et al. Site and clinical outcome of deep vein thrombosis of the lower limbs: an epidemiologic study. J Thromb Haemost 2005;3:1362-7
http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2005.01393.x/full

Evidence Level: V

Calf DVT rarely leads to PE?
A 2017 systematic review identified 21 papers which assessed PE frequency in patients with calf DVT, which included 8 RCTs and 13 prospective cohort studies (Wu, 2017). The incidence of PE from isolated calf DVT in this review was 0% to 6.2%.

Wu AR, Garry J, Labropoulos N et al. Incidence of pulmonary embolism in patients with isolated calf deep vein thrombosis. J Vasc Surg Venous Lymphat Disord. 2017;5:274-9

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Evidence Level: I

What is the probability of a doppler leg scan being positive for a DVT when V/Q probability of PE is intermediate/low?
A subgroup analysis of a prospective cohort study (Wells, 1998) followed 702 patients with suspected PE whose V/Q scans were classed as "non-high-probability". These were divided into those with a low pretest probability (n=454) and with a moderate pretest probability (n=248). 4 of the "low" group (0.8%) and 19 of the "moderate" group (7.6%) had abnormal results on ultrasonography.
Other prospective studies involving smaller numbers of patients have given ranges of 21-26% of "low" and 30-55% of "moderate" pretest probabilities having demonstrable thrombosis on lower limb ultrasound (Baxter, 1997; Bradley, 1995).

Baxter GM. The role of ultrasound in deep venous thrombosis. Clin Radiol 1997;52:1-3

Bradley MJ, Alexander L. The role of venous colour flow Doppler to aid the non-diagnostic lung scintigram for pulmonary embolism. Clin Radiol 1995;50:232-4

Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998;129:997-1005

Evidence Level: III

If second Doppler ultrasound scan is negative but pre-test probability was high, contrast venography should be considered?
Contrast venography has been described as the "gold standard" for the diagnosis of DVT (Hanley, 2012) but is now rarely used in routine DVT assessment, except in complex cases.
Venography "is able to diagnose a higher frequency of DVT and smaller thrombi (presumably at an early stage)" (Cohen, 2006).
Ultrasonography is considered to be the best non-invasive method and has been evaluated against venography in many studies, showing an average sensitivity of 97% for proximal DVT (Tovey, 2003; Line, 1997).

Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-9
http://www.bmj.com/content/332/7537/325

Line BR, Peters TL, Keenan J. Diagnostic test comparisons in patients with deep venous thrombosis. J Nucl Med 1997;38:89-92
http://jnm.snmjournals.org/content/38/1/89.long

Hanley M, Donahue J, Rybicki F, et al. ACR Appropriateness Criteria: Suspected lower extremity deep vein thrombosis: Expert Panel on Cardiovascular Imaging, American College of Radiology, 2013
http://www.guideline.gov/content.aspx?id=47686

Tovey C, Wyatt S. Diagnosis, investigation, and management of deep vein thrombosis. BMJ 2003;326:1180-4
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1126050/

Evidence Level: V

Immediate treatment

Should ambulation be encouraged following a DVT?
A meta-analysis of 5 studies in a total of 3048 patients (Aissaoui, 2009) found that early ambulation was not associated with a higher incidence of a new PE (RR 1.03; 95% CI 0.65-1.63; p=0.90). Furthermore, early ambulation was associated with a trend toward a lower incidence of new PE and new or progression of DVT than bed rest (RR 0.79; 95% CI 0.55-1.14; p=0.21) and lower incidence of new PE and overall mortality (RR 0.79; 95% CI 0.402-1.56; p=0.50).
A subsequent 2015 meta-analysis (Liu, 2015) which included 13 experimental and observational studies (3269 patients) similarly concluded that compared to bed rest, early ambulation was not associated with a higher risk of PE, progression of DVT or DVT related deaths (risk difference -0.03; 95% CI -0.05 to -0.02). Early ambulation was also associated with better outcomes with regard to the

remission of acute pain in those patients who suffered initial moderate or severe pain (standard mean difference: 0.42 95% CI 0.09 to 0.74).

Aissaoui N, Martins E, Mouly S, et al. A meta-analysis of bed rest versus early ambulation in the management of pulmonary embolism, deep vein thrombosis, or both. Int J Cardiol 2009;137:37-41

Liu Z, Tao X, Chen Y et al. Bed Rest versus Early Ambulation with Standard Anticoagulation in The Management of Deep Vein Thrombosis: A Meta-Analysis. PLOS. 2015.10.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0121388

Evidence Level: I

Is low molecular weight heparin (LMWH) superior to unfractionated heparin (UFH) in reducing the risk of PE from known DVT?
An updated Cochrane review of 23 trials involving 9587 patients (Erkens, 2010) found that major haemorrhage occurred in 1.1% of patients treated with LMWH, vs 1.9% treated with UFH. In 19 trials, of patients given LMWH 4.3% died, vs 5.8% on UFH. The authors concluded that LMWH was more effective than UFH for the initial treatment of DVT.

Erkens PMG, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2010;9
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001100.pub2/full

Evidence Level:

If unfractionated heparin (UFH) is used, the APTT ratio should be maintained between 1.5 and 2.5 times the control value?
A prospective study in 234 patients (Basu, 1972) found no recurrence of DVT in those whose APTT ratio was kept at 1.5 – 2.5 times the control level. 5 patients (3%) who did suffer a recurrence all had values far lower than those with no recurrence, despite receiving similar amounts of heparin.
A randomised trial in 96 patients on oral anticoagulants (Hull, 1982) compared 47 patients kept in a target range of 2.0 – 2.5 with 49 at 3.0 – 4.5. There was a similar incidence of recurrence (1/47 = 2.1% vs 1/49 = 2.0%) but a significant reduction in haemorrhages (2/47 = 4.3% vs 11/49 = 22.4%) during a 12-week period.

Basu D, Gallus A, Hirsh J, et al. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972;287:324-7

Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982;307:1676-81

Evidence Level: II

Long term use of Rivaroxaban (new anticoagulant) compared to Dalteparin?
The XAMOS Global non-interventional study (Turpie 2013) evaluated Rivaroxaban for prophylaxis of VT after major hip and knee surgery, following over 17, 000 patients after major orthopaedic surgery in approx. 200 centres. Results show that the drug was associated with fewer thrombotic events than with standard care. However, increased bleeding in patients in the Rivaroxaban group was noted.
The Einstein-DVT trial (2010) randomised 3,449 patients (Rivaroxaban-n=1731, enoxaparain-n=1,718) and concluded that Rivaroxaban was an effective single drug that could be used in initial treatment and secondary prevention of VTE. This study found that for DVT treatment the single-drug regimen of Rivaroxaban had an overall greater clinical benefit than the standard therapy of enoxaparin plus a Vitamin K Antagonist (recurrent DVT occurring in 14 vs 28 patients for comparison group) but Rivaroxaban was not superior to standard therapy for the primary efficacy or safety endpoints. Pulmonary Embolisms did not differ between the comparison groups.
The Einstein-Ext trial (2010) compared Rivaroxaban (20mg once daily; n=602) with placebo once daily (n=594) in patients with confirmed symptomatic DVT or pulmonary embolism that had been treated with a vitamin K antagonist (Warfarin or Acunecoumarol) or Rivaroxaban up to moment of randomisation. The study found that after 6-12 months of treatment, Rivaroxaban significantly reduced the risk of recurrent VTE (1.3%, n=8 vs 7.1%, n=42 in placebo group) at the cost of a moderate increase in bleeding complications.

EINSTEIN Investigators et al. Oral rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010; 363: 2499-510
http://www.nejm.org/doi/full/10.1056/NEJMoa1007903#t=articleTop

Turpie et al. A non-interventional comparison of rivaroxaban with standard of care for thrombophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. Thromb Haemost. 2010;111:94-102

Evidence Level: II

Subsequent management (non-pregnant patients)

Class 3 compression hose reduces swelling after DVT when the patient is mobilised?
A systematic review of 4 trials in a total of 493 patients (Giannoukas, 2006) found that post-thrombotic syndrome developed in 24% (61 of 254) of the compression groups vs 46% (110 of 239) of the control groups (p = 0.0001).
A systematic review of 14 RCTs in a total of 3264 patients (Sajid, 2006) found that 36 of 1568 (2.3%) randomised to knee-length stockings developed DVT, vs 79 of 1696 (5%) of those given thigh-length stockings. Although the study population included both hospitalised patients and passengers on long-haul flights, a benefit in favour of knee-length stockings still emerged from the combined data (weighted OR 1.01; 95% CI 0.35-2.90).
A randomised trial in 69 patients (Roumen-Klappe, 2009) found that “Immediate multilayer compression bandaging in the acute phase of DVT is effective in reducing edema and complaints in the first week, but has no effect on thrombus regression, valve incompetence and the development of clinical PTS after 1 year.”
A Cochrane systematic review of 20 RCTs (Sachdeva, 2018) found that, in the treatment group (graduated compression stockings) of 1445 units, 134 developed DVT (9%) in comparison to the control group of 1408 units where 290 (21%) developed DVT. The OR was 0.35 (95% CI 0.28 to 0.43).

Giannoukas AD, Labropoulos N, Michaels JA. Compression with or without early ambulation in the prevention of post-thrombotic syndrome: a systematic review. Eur J Vasc Endovasc Surg 2006;32:217-21
http://www.sciencedirect.com/science/article/pii/S1078588406000864

Roumen-Klappe EM, den Heijer M, van Rossum J, et al. Multilayer compression bandaging in the acute phase of deep-vein thrombosis has no effect on the development of the post-thrombotic syndrome. J ThrombThrombolysis 2009;27:400-5
http://link.springer.com/article/10.1007/s11239-008-0229-7/fulltext.html

Sachdeva A, Dalton M, Amaragiri SV, et al. Graduated compression stockings for prevention of deep vein thrombosis. Cochrane Database of Systematic Reviews 2018, Art. No.: CD001484
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001484.pub4/full

Sajid MS, Tai NR, Goli G, et al. Knee versus thigh length graduated compression stockings for prevention of deep venous thrombosis: a systematic review. Eur J Vasc Endovasc Surg 2006;32:730-6
http://www.sciencedirect.com/science/article/pii/S1078588406003601

Evidence Level: I

Should compression stockings be used to prevent Post-Thrombotic Syndrome after a DVT?
A 2024 systematic review found that early initiation and consistent use of compression stockings in patients with acute proximal DVT significantly reduced the incidence of mild-moderate Post-Thrombotic Syndrome (OR: 0.48; 95% CI: 0.36 to 0.63) as well as severe Post-Thrombotic Syndrome (OR: 0.44; 95% CI: 0.28-0.58) [Nielsen, 2024]. This meta-analysis incorporated four studies comprising a total of 1467 patients. Another 2024 systematic review concluded that compression stockings reduce the frequency and severity of Post-Thrombotic Syndrome (Thieme, 2024).
However, the largest placebo-stocking controlled trial of 804 patients (‘SOX’ study) [Kahn, 2014] failed to show any interventional effect. In this study, Post-Thrombotic Syndrome developed in 14.2% of the active compression stocking group vs 12.7% in the placebo group (Hazard Ratio 1.13, 95% CI 0.73 to 1.76, p = 0.58). However, one reason for the lack of efficacy could be due to the substantially lower compliance rate in this study compared to other RCTs (Wang, 2023).

Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: A randomised placebo-controlled trial. Lancet. 2014;383:880–888

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Nielsen JD, Hermann TS, Fredskilde PCA at al. Graduated elastic compression stockings in the prevention of post-thrombotic syndrome: A systematic review and meta-analysis. Phlebology. 2024;39:229-37

Thieme D, Linnemann B, Mühlberg K et al. Compression Therapy in Acute Deep Venous Thrombosis of the Lower Limb and for the Prevention of Post-Thrombotic Syndrome—a Review Based on a Structured Literature Search. Dtsch Arztebl Int. 2024;121:188-94
https://pmc.ncbi.nlm.nih.gov/articles/PMC11079798/

Wang J, Smeath E, Lim HY et al. Current challenges in the prevention and management of post-thrombotic syndrome-towards improved prevention. Int J Hematol. 2023;118:547-67
https://pmc.ncbi.nlm.nih.gov/articles/PMC10615940/

Evidence Level: I

Should compression stockings be used to prevent DVT recurrence after initial DVT?
A 2016 systematic review of RCTs (2160 patients) found that compression stockings did not prevent the recurrence of deep vein thrombosis (OR 0.93 [95% CI 0.66 to 1·31]). However, the authors highlight that the level of evidence was low and heterogeneity was high (Subbiah, 2016). A 2023 systematic review similarly found no evidence that compression stockings reduced the rate of recurrent DVTs (Meng, 2023).

Meng J, Liu W, Wu Y et al. Is it necessary to wear compression stockings and how long should they be worn for preventing post thrombotic syndrome? A meta-analysis of randomized controlled trials. Thromb Res. 2023:225: 79-86
https://www.sciencedirect.com/science/article/pii/S0049384823000907?via%3Dihub

Subbiah R, Aggarwal V, Zhao H et al. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. Lancet Haematol. 2016;3:e293-300

Evidence Level: I

When should warfarin be started following DVT?
A study in 266 patients (Gallus, 1986) found that 139 patients started on warfarin within 3 days (average 1 day) of IV heparin treatment had reduced hospital stays (9.1 +/- 3.5 days vs 13.0 +/- 3.0 days, average reduction 3.9 days or 30%), compared to 127 patients started on warfarin after 7 days of iv heparin.
A small retrospective review of 26 patients (Westblom, 1985) concluded that US practice (at that time) of starting heparin on average 8 days following IV heparin resulted in longer hospital stay (average 16.8 +/- 5.1 days).
A later randomised trial in 119 patients (Mohiuddin, 1992) also concluded that early (within 48 hours) introduction of warfarin was safe, effective, and resulted in shorter hospital stay.

Gallus A, Jackaman J, Tillett J, et al. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. Lancet 1986;ii:1293-6

Mohiuddin SM, Hilleman DE, Destache CJ, et al. Efficacy and safety of early versus late initiation of warfarin during heparin therapy in acute thromboembolism. Am Heart J 1992;123:729-32

Westblom TU, Marienfeld RD. Prolonged hospitalization because of inappropriate delay of warfarin therapy in deep venous thrombosis. South Med J 1985;78:1164-7

Evidence Level: II

If patient is an injection drug user, consider continuing therapeutic dalteparin treatment, rather than converting to warfarin?
This question has been addressed by a “best evidence” topic report (Russell, 2004). The authors concluded that: “Low molecular weight heparin seems to be a safe method of anticoagulation and may be considered as an alternative to warfarin in the anticoagulation of IDUs because it does not require ongoing monitoring. However, the evidence is very limited. Local guidelines should be followed.”

Russell M, Dawson D. Best evidence topic report. Low molecular weight heparin for intravenous drug users with deep vein thrombosis. Emerg Med J 2004;21:711

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http://emj.bmj.com/cgi/pmidlookup?view=long&pmid=15496703

Evidence Level: V

Discharge policy

For how long should warfarin be continued after a first DVT?
For six weeks if DVT occurred postoperatively in an otherwise healthy patient; for three months after a first DVT without a clear underlying cause; and indefinitely for recurrent DVT and in patients with co-existent active malignant disease?
A randomised, double-blind trial in 162 patients (Kearon, 1999) compared continued warfarin therapy with placebo in thromboembolism patients already treated with heparin and 3 months of warfarin. The trial was halted after 17 of 83 patients in the placebo group had suffered recurrences, compared to 1 of 79 patients in the warfarin group. The authors concluded that patients with a first episode of idiopathic DVT should be treated for longer than 3 months, but the optimum period remained unknown. The risk of major bleeding, although increased, was considered to be small compared to the benefits of continued anticoagulant therapy (except for those patients at high risk of bleeding, who were excluded from this study).
A randomised trial in 267 patients (Agnelli, 2001) found that the benefits of extending the period of anticoagulation to 1 year were not maintained after discontinuation of the therapy. A later multicentre trial by the same team (Agnelli, 2003) concluded that patients with PE had a substantial risk of recurrence after discontinuation of warfarin, regardless of the duration of treatment.
A randomised, multicentre trial in 897 patients followed up for 2 years (Schulman, 1995) compared 6 weeks with 6 months of warfarin therapy. There were 123 recurrences of DVT, with 80 in the 6 week group and 43 in the 6 month group. There were no differences in mortality or major haemorrhage. Subgroup analysis showed that the reduced risk of recurrence approached 50% in nearly every group when treatment continued for 6 months. Patients with only temporary risk factors for DVT (i.e. surgery) suffered no excess recurrence if treated for 6 weeks. The latter finding was also confirmed in a randomised trial in 736 patients (Pinede, 2001), although this study demonstrated an equivalence between 3 and 6 months of treatment for proximal DVT or PE.
A meta-analysis of 33 RCTs (Linkins, 2003) found that, in patients receiving anticoagulant therapy for > 3 months, the case-fatality rate of major bleeding was 9.1% (95% CI 2.5%-21.7%).
A multicentre, prospective, randomised study in 46 UK hospitals (Campbell, 2007) compared patients taking anticoagulants for 3 months (n=369) with those taking them for 6 months (n=380). Fatal and non-fatal DVT or PE occurred in 31 (8%) of the 3 month group and 29 (8%) of the 6 month group. There were no fatal haemorrhages in either group, but there were 8 cases of major haemorrhage in the 6 month group vs none in the 3 month group. The authors concluded that the longer duration of treatment offered no advantage, whilst posing an increased risk of haemorrhage.
A randomised trial in 538 consecutive outpatients with a first episode of DVT (Prandoni, 2009) compared fixed-duration to flexible-duration treatment. Overall, 46 (17.2%) of 268 patients allocated to fixed-duration anticoagulation and 32 (11.9%) of 270 patients allocated to flexible-duration anticoagulation developed recurrent VTE (adjusted hazard ratio [HR], 0.64 [95% CI, 0.39 to 0.99]). For patients with unprovoked DVT, the adjusted HR was 0.61 (CI, 0.36 to 1.02) and 0.81 (CI, 0.32 to 2.06) for those with secondary DVT. Major bleeding occurred in 2 (0.7%) patients in the fixed-duration group and 4 (1.5%) patients in the flexible-duration group (P = 0.67). The authors concluded that tailoring the duration of anticoagulation on the basis of ultrasonography findings reduced the rate of recurrent VTE in adults with proximal DVT.
A review of the available evidence on this question (East, 2010) concluded that: “Short durations of anticoagulation are only appropriate for calf DVTs in patients with reversible risk factors. Patients with nonreversible risk factors, such as malignancy and certain inherited thrombophilias with a strong family history of venous thromboembolism will require lifelong anticoagulation. Those with proximal DVT due to reversible risk factors require 3 to 6 months of anticoagulation. Patients with idiopathic DVT require reassessment of risk-to-benefit ratio of hemorrhage from oral vitamin K antagonist therapy compared to reducing risk of recurrence and frequently require prolonged oral anticoagulant therapy”.

Agnelli G, Prandoni P, Santamaria MG, et al. 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

Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003;139:19-25

Campbell IA, Bentley DP, Prescott RJ, et al. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. BMJ 2007;334:674-80
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1839169/

East AT, Wakefield TW. What is the optimal duration of treatment for DVT? An update on evidence-based medicine of treatment for DVT. Semin Vasc Surg 2010;23:182-91

Kearon C, Gent M, Hirsh J, 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

Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003;139:893-900
http://m.hem-aids.ru/system/files/attachments/1443/gemostaz_gemostaz_0152.pdf

Pinede L, Ninet J, Duhaut P, et al. 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
http://circ.ahajournals.org/content/103/20/2453.long

Prandoni P, Prins MH, Lensing AW, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med 2009;150:577-85
http://www.caphri.nl/data/files/alg/id101/577.full.pdf

Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995;332:1661-5

Evidence Level: I

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