Antithrombotic Therapy for Venous Thromboembolic Disease*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Clive Kearon, MB, PhD; Susan R. Kahn, MD; Giancarlo Agnelli, MD; Samuel Goldhaber, MD, FCCP; Gary E. Raskob, PhD; and Anthony J. Comerota, MD

This chapter about treatment for venous thromboembolic disease is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs. Grade 2 suggests that individual patient values may lead to different choices (for a full understanding of the grading, see "Grades of Recommendation" chapter). Among the key recommendations in this chapter are the following: for patients with objectively confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), we recommend anticoagulant therapy with subcutaneous (SC) low-molecular-weight heparin (LMWH), monitored IV, or SC unfractionated heparin (UFH), unmonitored weight-based SC UFH, or SC fondaparinux (all Grade 1A). For patients with a high clinical suspicion of DVT or PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C). For patients with confirmed PE, we recommend early evaluation of the risks to benefits of thrombolytic therapy (Grade 1C); for those with hemodynamic compromise, we recommend short-course thrombolytic therapy (Grade 1B); and for those with nonmassive PE, we recommend against the use of thrombolytic therapy (Grade 1B). In acute DVT or PE, we recommend initial treatment with LMWH, UFH or fondaparinux for at least 5 days rather than a shorter period (Grade 1C); and initiation of vitamin K antagonists (VKAs) together with LMWH, UFH, or fondaparinux on the first treatment day, and discontinuation of these heparin preparations when the international normalized ratio (INR) is ≥ 2.0 for at least 24 h (Grade 1A). For patients with DVT or PE secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A). For patients with unprovoked DVT or PE, we recommend treatment with a VKA for at least 3 months (Grade 1A), and that all patients are then evaluated for the risks to benefits of indefinite therapy (Grade 1C). We recommend indefinite anticoagulant therapy for patients with a first unprovoked proximal DVT or PE and a low risk of bleeding when this is consistent with the patient's preference (Grade 1A), and for most patients with a second unprovoked DVT (Grade 1A). We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A). We recommend at least 3 months of treatment with LMWH for patients with VTE and cancer (Grade 1A), followed by treatment with LMWH or VKA as long as the cancer is active (Grade 1C). For prevention of postthrombotic syndrome (PTS) after proximal DVT, we recommend use of an elastic compression stocking (Grade 1A). For DVT of the upper extremity, we recommend similar treatment as for DVT of the leg (Grade 1C). Selected patients with lower-extremity (Grade 2B) and upper-extremity (Grade 2C). DVT may be considered for thrombus removal, generally using catheter-based thrombolytic techniques. For extensive superficial vein thrombosis, we recommend treatment with prophylactic or intermediate doses of LMWH or intermediate doses of UFH for 4 weeks (Grade 1B).

(CHEST 2008; 133:454S–545S)

Key words: cancer; chronic thromboembolic pulmonary hypertension; deep vein thrombosis; fondaparinux; low-molecular-weight heparin; plasminogen activator; pulmonary embolism; thrombectomy; thrombolytic therapy; thrombophlebitis; unfractionated heparin; vena caval filter; venous thromboembolism; vitamin K antagonist

Abbreviations: APTT = activated partial thromboplastin time; CDT = catheter-directed thrombolysis; CI = confidence interval; CTPH = chronic thromboembolic pulmonary hypertension; DVT = deep venous thrombosis; INR = international normalized ratio; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; MPFF = micronized purified flavonoid fraction; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; PE = pulmonary embolism; PTS = postthrombotic (phlebitic) syndrome; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; rt-PA = recombinant tissue plasminogen activator; SC = subcutaneous; SVC = superior vena cava; SVT = superficial venous thrombosis; tPA = tissue plasminogen activator; UEDVT = upper-extremity deep vein thrombosis; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Summary of Recommendations

1.1 Initial Anticoagulation of Acute DVT of the Leg

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH (Grade 1A)**, IV UFH** (Grade 1A)**, monitored SC UFH** (Grade 1A)**, fixed-dose SC UFH** (Grade 1A)**, or SC fondaparinux** (Grade 1A) **rather than no such short-term treatment.**

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C)**.**

1.1.3. In patients with acute DVT, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for 24 h (Grade 1C)**.**

1.1.4. In patients with acute DVT, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A)**.**

1.2 IV UFH for the Initial Treatment of DVT

1.2.1. In patients with acute DVT, if IV UFH is chosen, we recommend that after an initial IV bolus (80 U/kg or 5,000 U), it be administered by continuous infusion (initially at a dose of 18 U/kg/h or 1,300 U/h) with dose adjustment to achieve and maintain an activated partial thromboplastin time (APTT) prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C)**.**

1.3 SC UFH Compared With IV Heparin for the Initial Treatment of DVT

1.3.1. In patients with acute DVT, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of about 250 U/kg bid, with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (see also Section 1.5) [Grade 1C]**.**

1.3.2. In patients with acute DVT, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/Kg followed by 250 U/kg bid rather than non–weight-based dosing (see also Section 1.5) [Grade 1C]**.**

1.4 LMWH for the Initial Treatment of DVT

1.4.1. In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible (Grade 1C)**, or as an inpatient if necessary** (Grade 1A)**, rather than treatment with IV UFH.**

1.4.2. In patients with acute DVT treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A)**.**

1.4.3. In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C)**.**

1.9 Catheter-Directed Thrombolysis for Acute DVT

1.9.1. In selected patients with extensive acute proximal DVT (*eg*, iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year) who have a low risk of bleeding, we suggest that catheter-directed thrombolysis (CDT) may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B)**.**

1.9.2. After successful CDT in patients with acute DVT, we suggest correction of underlying venous lesions using balloon angioplasty and stents (Grade 2C)**.**

1.9.3. We suggest pharmacomechanical thrombolysis (*eg*, with inclusion of thrombus fragmentation and/or aspiration) in preference to CDT alone to shorten treatment time if appropriate expertise and resources are available (Grade 2C)**.**

1.9.4. After successful CDT in patients with acute DVT, we recommend the same intensity and duration of anticoagulant therapy as for comparable patients who do not undergo CDT (Grade 1C)**.**

*From McMaster University Clinic (Dr. Kearon), Henderson General Hospital, Hamilton, ON, Canada; Thrombosis Clinic and Centre for Clinical Epidemiology and Community Studies (Dr. Kahn), Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada; University of Perugia (Dr. Agnelli), Perugia, Italy; Brigham and Women's Hospital (Dr. Goldhaber), Boston, MA; College of Public Health, University of Oklahoma Health Science Center (Dr. Raskob), Oklahoma City, OK; and Jobst Vascular Center (Dr. Comerota), Toledo, OH.

Manuscript accepted December 20, 2007.

Correspondence to: Clive Kearon, MB, PhD, Hamilton Health Sciences, Henderson Division, 711 Concession St, Hamilton, ON, L8V 1C3, Canada; e-mail: kearonc@mcmaster.ca

DOI: 10.1378/chest.08-0658

1.10 Systemic Thrombolytic Therapy for Acute DVT

1.10.1. In selected patients with extensive proximal DVT (*eg*, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year) who have a low risk of bleeding, we suggest that systemic thrombolytic therapy may be used to reduce acute symptoms and postthrombotic morbidity if CDT is not available (Grade 2C).

1.11 Percutaneous Venous Thrombectomy

1.11.1. In patients with acute DVT, we suggest that they should not be treated with percutaneous mechanical thrombectomy alone (Grade 2C).

1.12 Operative Venous Thrombectomy for Acute DVT

1.12.1. In selected patients with acute iliofemoral DVT (*eg*, symptoms for < 7 days, good functional status, and life expectancy of ≥ 1 year), we suggest that operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B). **If such patients do not have a high risk of bleeding, we suggest that catheter-directed thrombolysis is usually preferable to operative venous thrombectomy** (Grade 2C).

1.12.2. In patients who undergo operative venous thrombectomy, we recommend the same intensity and duration of anticoagulant therapy afterwards as for comparable patients who do not undergo venous thrombectomy (Grade 1C).

1.13 Vena Caval Filters for the Initial Treatment of DVT

1.13.1. For patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (Grade 1A).

1.13.2. For patients with acute proximal DVT, if anticoagulant therapy is not possible because of the risk of bleeding, we recommend placement of an inferior vena cava (IVC) filter (Grade 1C).

1.13.3. For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).

1.14 Immobilization for the Treatment of Acute DVT

1.14.1. In patients with acute DVT, we recommend early ambulation in preference to initial bed rest when this is feasible (Grade 1A).

2.1 Duration of Anticoagulant Therapy

2.1.1. For patients with DVT secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A).

2.1.2. For patients with unprovoked DVT, we recommend treatment with a VKA for at least 3 months (Grade 1A). **We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-benefit ratio of long-term therapy** (Grade 1C). **For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment** (Grade 1A).

Values and preferences: This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A). **For patients with a first isolated distal DVT that is unprovoked, we suggest that 3 months of anticoagulant therapy is sufficient rather than indefinite therapy** (Grade 2B).

2.1.3. For patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). **For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4)** [Grade 1C].

2.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C).

2.2 Intensity of Anticoagulant Effect

2.2.1. In patients with DVT, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 to 3.0) for all treatment durations (Grade 1A). **For patients with unprovoked DVT who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of con-**

ventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment (Grade 1A). **We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared to an INR range of 2.0 to 3.0** (Grade 1A).

2.6 Treatment of Asymptomatic DVT of the Leg

2.6.1. In patients who are unexpectedly found to have asymptomatic DVT, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 1C).

3.1 Elastic Stockings and Compression Bandages To Prevent PTS

3.1.1. For a patient who has had a symptomatic proximal DVT, we recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A). **Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum of 2 years, and longer if patients have symptoms of PTS. (Note: feasibility, both short and long term, refers to ability of patients and their caregivers to apply and remove stockings.)** *Values and preferences:* This recommendation attaches a relatively high value to long-term prevention of the PTS and a low value to the burden (*eg*, inconvenience or discomfort) associated with wearing stockings.

3.2 Physical Treatment of PTS Without Venous Leg Ulcers

3.2.1. For patients with severe edema of the leg due to PTS, we suggest a course of intermittent pneumatic compression (IPC) [Grade 2B].
3.2.2. For patients with mild edema of the leg due to PTS, we suggest the use of elastic compression stockings (Grade 2C).

3.3 Physical Treatment of Venous Leg Ulcers

3.3.1. In patients with venous ulcers resistant to healing with wound care and compression, we suggest the addition of IPC (Grade 2B).

3.4 Hyperbaric Oxygen and the Management of Patients With Venous Ulcers

3.4.1. For patients with venous ulcers, we suggest that hyperbaric oxygen not be used (Grade 2B).

3.5.1. Pentoxifylline

3.5.1. In patients with venous leg ulcers, we suggest pentoxifylline, 400 mg po tid, in addition to local care and compression and/or IPC (Grade 2B).

3.5.2. Micronized Purified Flavonoid Fraction or Sulodexide for the Treatment of Venous Leg Ulcers

3.5.2. In patients with persistent venous ulcers, we suggest that rutosides, in the form of micronized purified flavonoid fraction administered orally, or sulodexide administered intramuscularly and then orally, be added to local care and compression (Grade 2B).

4.1 IV or SC UFH, SC LMWH, SC Fondaparinux, and VKA for the Initial Treatment of PE

4.1.1. For patients with objectively confirmed PE, we recommend short-term treatment with SC LMWH (Grade 1A), **IV UFH** (Grade 1A), **monitored SC UFH** (Grade 1A), **fixed-dose SC UFH** (Grade 1A), **or SC fondaparinux** (Grade 1A) **rather than no such acute treatment. Patients with acute PE should also be routinely assessed for treatment with thrombolytic therapy (see Section 4.3 for related discussion and recommendations).**
4.1.2. For patients in whom there is a high clinical suspicion of PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C).
4.1.3. In patients with acute PE, we recommend initial treatment with LMWH, UFH or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for at least 24 h (Grade 1C).
4.1.4. In patients with acute PE, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A).
4.1.5. In patients with acute PE, if IV UFH is chosen, we recommend that after an initial IV bolus (80 U/kg or 5,000 U), it be administered by continuous infusion (initially at dose of 18 U/kg/h or 1,300 U/h) with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C).
4.1.6. In patients with acute PE, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of approximately 250 U/kg bid, with dose adjustment to

achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (Grade 1C).

4.1.7. In patients with acute PE, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/Kg followed by a twice-daily dose of 250 U/kg rather than non–weight-based dosing (Grade 1C).

4.1.8. In patients with acute nonmassive PE, we recommend initial treatment with LMWH over IV UFH (Grade 1A). **In patients with massive PE, in other situations where there is concern about SC absorption, or in patients for whom thrombolytic therapy is being considered or planned, we suggest IV UFH over SC LMWH, SC fondaparinux, or SC UFH** (Grade 2C).

4.1.9. In patients with acute PE treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A).

4.1.10. In patients with acute PE and severe renal failure, we suggest UFH over LMWH (Grade 2C).

4.3 Systemically and Locally Administered Thrombolytic Therapy for PE

4.3.1. All PE patients should undergo rapid risk stratification (Grade 1C). **For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk** (Grade 1B). **Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy** (Grade 2B). **The decision to use thrombolytic therapy depends on the clinician's assessment of PE severity, prognosis, and risk of bleeding. For the majority of patients with PE, we recommend against using thrombolytic therapy** (Grade 1B).

4.3.2. In patients with acute PE, when a thrombolytic agent is used, we recommend that treatment be administered via a peripheral vein rather than placing a pulmonary artery catheter to administer treatment (Grade 1B).

4.3.3. In patients with acute PE, with administration of thrombolytic therapy, we recommend use of regimens with short infusion times (*eg*, a 2-h infusion) over those with prolonged infusion times (*eg*, a 24-h infusion) [Grade 1B].

4.4 Catheter Extraction or Fragmentation for the Initial Treatment of PE

4.4.1. For most patients with PE, we recommend against use of interventional catheterization techniques (Grade 1C). **In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest use of interventional catheterization techniques if appropriate expertise is available** (Grade 2C).

4.5 Pulmonary Embolectomy for the Initial Treatment of PE

4.5.1. In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest that pulmonary embolectomy may be used if appropriate expertise is available (Grade 2C).

4.6 Vena Caval Filters for the Initial Treatment of PE

4.6.1. For most patients with PE, we recommend against the routine use of a vena caval filter in addition to anticoagulants (Grade 1A).

4.6.2. In patients with acute PE, if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an IVC filter (Grade 1C).

4.6.3. For patients with acute PE who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).

5.0 Long-term Treatment of Acute PE

5.1.1. For patients with PE secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A).

5.1.2. For patients with unprovoked PE, we recommend treatment with a VKA for at least 3 months (Grade 1A). **We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked PE should be evaluated for the risk-benefit ratio of long-term therapy** (Grade 1C). **For patients with a first unprovoked episode of VTE that is a PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant**

monitoring is achievable, we recommend long-term treatment (Grade 1A).

Values and preferences: This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A).

5.1.3. For patients with PE and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). **For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved** (Grade 1C).

5.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C).

5.1.5. In patients with PE, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A). **For patients with unprovoked PE who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of conventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (INR range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment** (Grade 1A). **We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared with an INR range of 2.0 to 3.0** (Grade 1A).

5.1.6. In patients who are unexpectedly found to have asymptomatic PE, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 1C).

6.1 Pulmonary Thromboendarterectomy, VKA, and Vena Caval Filter for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

6.1.1. In selected patients with chronic thromboembolic pulmonary hypertension (CTPH), such as those with central disease under the care of an experienced surgical/medical team, we recommend pulmonary thromboendarterectomy (Grade 1C).

6.1.2. For all patients with CTPH, we recommend life-long treatment with a VKA targeted to an INR of 2.0 to 3.0 (Grade 1C).

6.1.3. For patients with CTPH undergoing pulmonary thromboendarterectomy, we suggest the placement of a permanent vena caval filter before or at the time of the procedure (Grade 2C).

6.1.4. For patients with inoperable CTPH, we suggest referral to a center with expertise in pulmonary hypertension so that patients can be evaluated for alternative treatments, such as vasodilator therapy or balloon pulmonary angioplasty (Grade 2C).

7.1 Treatment of Infusion Thrombophlebitis

7.1.1. For patients with symptomatic infusion thrombophlebitis as a complication of IV infusion, we suggest oral diclofenac or another nonsteroidal antiinflammatory drug (Grade 2B), **topical diclofenac gel** (Grade 2B), **or heparin gel** (Grade 2B) **until resolution of symptoms or for up to 2 weeks. We recommend against the use of systemic anticoagulation** (Grade 1C).

7.2 Treatment of SVT

7.2.1. For patients with spontaneous superficial vein thrombosis, we suggest prophylactic or intermediate doses of LMWH (Grade 2B) **or intermediate doses of UFH** (Grade 2B) **for at least 4 weeks. We suggest that as an alternative to 4 weeks of LMWH or UFH, VKA (target INR, 2.5; range, 2.0 to 3.0) can be overlapped with 5 days of UFH and LMWH and continued for 4 weeks** (Grade 2C). **We suggest that oral nonsteriodal antiinflammatory drugs should not be used in addition to anticoagulation** (Grade 2B). **We recommend medical treatment with anticoagulants over surgical treatment** (Grade 1B).

Remark: It is likely that less extensive superficial vein thrombosis (*ie*, where the affected venous segment is short in length or further from the saphenofemoral junction) does not require treatment with anticoagulants. It is reasonable to use oral or topical nonsteriodal antiinflammatory drugs for symptom control in such cases.

8.1. IV UFH or LMWH for the Initial Treatment of Upper-Extremity DVT

8.1.1. For patients with acute upper-extremity DVT (UEDVT), we recommend initial treatment with therapeutic doses of LMWH, UFH, or fondaparinux as described for leg DVT (see Section 1) [Grade 1C].

8.2 Thrombolytic Therapy for the Initial Treatment of UEDVT

8.2.1. For most patients with acute UEDVT, we recommend against the routine use of systemic or catheter-directed thrombolytic therapy (Grade 1C).

8.2.2. In selected patients with acute UEDVT (*eg*, in those with a low risk of bleeding and severe symptoms of recent onset), we suggest that CDT may be used for initial treatment if appropriate expertise and resources are available (Grade 2C).

8.3 Catheter Extraction, Surgical Thrombectomy, Transluminal Angioplasty, Stent Placement, Staged Approach of Lysis Followed by Interventional or Surgical Procedure, Superior Vena Cava Filter Insertion for the Initial Treatment of UEDVT

8.3.1. For most patients with acute UEDVT, we recommend against the routine use of catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, or superior vena cava (SVC) filter placement (Grade 1C).

8.3.2. In selected patients with acute UEDVT (*eg*, those with primary UEDVT and failure of anticoagulant or thrombolytic treatment who have severe persistent symptoms), we suggest that catheter extraction, surgical thrombectomy, transluminal angioplasty, or a staged approach of lysis followed by a vascular interventional or surgical procedure may be used if appropriate expertise and resources are available (all Grade 2C).

8.3.3. In selected patients with acute UEDVT (*eg*, those for whom anticoagulant treatment is contraindicated and there is clear evidence of DVT progression or clinically significant PE), we suggest placement of an SVC filter (Grade 2C).

8.4 Anticoagulants for the Long-term Treatment of UEDVT

8.4.1. For patients with acute UEDVT, we recommend treatment with a VKA for ≥ 3 months (Grade 1C).

Remark: A similar process as for lower-extremity DVT (see Section 2) should be used to determine the optimal duration of anti-coagulation.

8.4.2. For most patients with UEDVT in association with an indwelling central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C).

8.4.3. For patients who have UEDVT in association with an indwelling central venous catheter that is removed, we do not recommend that the duration of long-term anticoagulant treatment be shortened to < 3 months (Grade 2C).

8.5 Prevention of PTS of the Arm

8.5.1. For patients at risk for PTS after UEDVT, we do not suggest routine use of elastic compression or venoactive medications (Grade 2C).

8.6 Treatment of PTS of the Arm

8.6.1. In patients with UEDVT who have persistent edema and pain, we suggest elastic bandages or elastic compression sleeves to reduce symptoms of PTS of the upper extremity (Grade 2C).

This section will describe the role of antithrombotic agents as well as devices or surgical techniques that are used in the treatment of patients with acute venous thromboembolism (VTE), a disease that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). In addition, the treatment of patients with acute upper-extremity DVT (UEDVT), superficial vein thrombosis (SVT), and the two most important long-term complications of VTE, postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTPH), are discussed. In this chapter, consistent with most previous reports, patients with VTE are dichotomized into those with symptoms of PE (with or without concomitant symptoms of DVT), and those who present only with symptoms of DVT. Table 1 describes the eligibility criteria for the studies considered in each section of the recommendations that follow.

1.0 Initial Treatment of Acute DVT of the Leg

1.1. Initial Anticoagulation of Acute DVT of the Leg

Anticoagulation is the main therapy for acute DVT of the leg. The main objectives of anticoagulant therapy in the initial treatment of this disease are to prevent thrombus extension and early and late recurrences of VTE. The evidence for the need for anticoagulation in patients with DVT is based on studies performed > 40 years ago. The first and only trial[1] that compared anticoagulant therapy with no anticoagulant therapy in patients with symptomatic DVT or PE was published in 1960 (Barritt and Jordan; Table 15). This trial of patients with acute PE showed that 1.5 days of heparin and 14 days of vitamin K antagonist (VKA) therapy markedly reduced recurrent PE and mortality. Subsequent uncontrolled studies[2–4] support that mortality is reduced when heparin is used to treat VTE and reported a high mortality when patients did not receive anticoagulant therapy. Comparatively recently, the requirement for an initial course of heparin in addition to

Table 1—*Question Definition and Eligibility Criteria (Section: Introduction)*

Section	Population	Intervention or Exposure	Outcome	Methodology
1.1	Initial treatment of acute DVT of the leg	IV UFH or LMWH, fondaparinux, and VKA (direct comparison of any of these treatments or their combinations with a shorter or no treatment)	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.2	Initial treatment of acute DVT of the leg	IV UFH; comparison of different regimens of IV UFH	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.3	Initial treatment of acute DVT of the leg	SC UFH vs IV UFH	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.4	Initial treatment of acute DVT of the leg	LMWH vs IV UFH, SC UFH, and comparison of different regimens of SC LMWH	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.5	Initial treatment of acute DVT of the leg	SC UFH vs SC LMWH	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.7	Initial treatment of acute DVT of the leg	New antithrombotic agents	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.6	Initial treatment of acute DVT of the leg	Fondaparinux vs UFH or LMWH	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
1.9	Initial treatment of acute DVT of the leg	CDT vs placebo or systemically administered thrombolysis	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
1.10	Initial treatment of acute DVT of the leg	Systemically administered thrombolysis vs anticoagulant therapy alone	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
1.11	Initial treatment of acute DVT of the leg	Percutaneous venous thrombectomy vs other endovascular techniques or anticoagulant therapy alone	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
1.12	Initial treatment of acute DVT of the leg	Operative venous thrombectomy vs any other mode of treatment	Recurrent DVT and PE, total mortality, QOL, and PTS	RCTs and cohort studies
1.13	Initial treatment of acute DVT of the leg	Vena caval filter insertion vs no venal caval filter	Recurrent DVT and PE, total mortality, QOL, and PTS	RCTs and cohort studies
1.14	Initial treatment of acute DVT of the leg	Immobilization vs active mobilization	Recurrent DVT and PE, total mortality, QOL, and PTS	RCTs and cohort studies
2.1	Long-term treatment of acute DVT of the leg	Comparison of different durations of VKA therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
2.2	Long-term treatment of acute DVT of the leg	Comparison of intensities of VKA therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
2.3	Long-term treatment of acute DVT of the leg	SC UFH vs VKA	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
2.4	Long-term treatment of acute DVT of the leg	LMWH vs VKA	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
2.5	Long-term treatment of acute DVT of the leg	New antithrombotic agents (*eg*, ximelagatran, idraparinux) vs no treatment or other anticoagulants	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
2.6	Treatment of asymptomatic DVT	Treatment with any anticoagulant therapy vs no treatment	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
3.1	Prophylaxis for PTS	Compression stockings vs no stockings	Symptomatic PTS	RCTs
3.2	Treatment of PTS	Physical measures vs no intervention in patients without leg ulcers	Symptomatic relief, QOL and ulceration	RCTs and cohort studies
3.3	Treatment of PTS	Physical measures vs no intervention in patients with leg ulcers	Symptomatic relief, ulcer healing, QOL, and ulceration	RCTs and cohort studies
3.4	Treatment of PTS	Hyperbaric oxygen vs no hyperbaric oxygen in patients with leg ulcers	Symptomatic relief, ulcer healing, QOL, and ulceration	RCTs and cohort studies

Table 1—*Continued*

Section	Population	Intervention or Exposure	Outcome	Methodology
3.5TC	Treatment of PTS	Drug therapies vs control in patients with leg ulcers	Symptomatic relief, QOL, and ulceration	RCTs and cohort studies
4.1	Initial treatment of acute PE	IV UFH, LMWH, fondaparinux, and/or VKA vs no anticoagulation; comparisons among these agents, and of different regimens of the same agent	Recurrent DVT and PE, major bleeding, total mortality, QOL, and CTPH	RCTs
4.2	Initial treatment of acute PE	New antithrombotic agent (*eg*, ximelagatran, idraparinux) compared to no treatment or conventional therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and CTPH	RCTs and cohort studies
4.3	Initial treatment of acute PE	Systemically and locally administered thrombolytic therapy compared to anticoagulant therapy alone, or comparisons of different thrombolytic agents or different regimens of the same agent	Recurrent DVT and PE, total mortality, QOL, and CTPH	RCTs and cohort studies
4.4	Initial treatment of acute PE	Catheter extraction or fragmentation vs no such therapy	Recurrent DVT and PE, total mortality, QOL, and CTPH	RCTs and cohort studies
4.5	Initial treatment of acute PE	Pulmonary embolectomy vs no such surgery	Recurrent DVT and PE, total mortality, QOL, and CTPH	RCTs and cohort studies
4.6	Initial treatment of acute PE	Vena caval filter insertion vs no vena caval filter	Recurrent DVT and PE, total mortality, QOL, and CTPH	RCTs and cohort studies
5.1	Long-term treatment of acute PE	Comparison of different durations of VKA therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
5.2	Long-term treatment of acute PE	LMWH vs VKA therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
5.3	Long-term treatment of acute PE	New antithrombotic agents (*eg*, ximelagatran, idraparinux) compared to no treatment or conventional therapy	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs
5.4	Treatment of asymptomatic PE	Treatment with any anticoagulant therapy vs no treatment	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
6.1	CTPH	Pulmonary thrombo endarterectomy, vasodilators and/or vena caval filter vs not using these interventions	Mortality, recurrent DVT and PE, and QOL	RCTs and cohort studies
7.1	Treatment of infusion thrombophlebitis	VKA, UFH, LMWH, NSAIDs, aspirin, vs no such treatment, each other, or different durations or regimens of the same agent	Extension of thrombus, symptomatic relief, symptomatic DVT and PE, major bleeding	RCTs and cohort studies
7.2	Treatment of SVT	VKA, UFH, LMWH, NSAIDs, aspirin, vs no such treatment, each other, or different durations or regimens of the same agent	Extension of thrombus, symptomatic relief, symptomatic DVT and PE, major bleeding	RCTs and cohort studies
8.1	Initial treatment of acute UEDVT	IV UFH or LMWH compared to placebo or each other	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies
8.2	Initial treatment of acute UEDVT	Thrombolytic therapy compared to no thrombolytic therapy	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies
8.3	Initial treatment of acute UEDVT	Catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, SVC filter insertion, compared with no interventions	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies
8.4	Long-term treatment of acute UEDVT	VKA, UFH, LMWH or fondaparinux; comparisons of different durations or different agents	Recurrent DVT and PE, major bleeding, total mortality, QOL, and PTS	RCTs and cohort studies
8.5	Prevention of PTS of the arm	Compression glove or elastic bandages vs no compression therapy	Symptomatic PTS	RCTs and cohort studies
8.6	Treatment of PTS of the arm	Compression glove or elastic bandages vs no compression therapy	Symptomatic relief, QOL	RCTs and cohort studies

VKA, as compared to starting treatment with VKA therapy alone, was established in a randomized controlled study[5] that reported a threefold-higher rate of recurrent VTE in patients who received VKA only. Patients with DVT should be treated with anticoagulants as soon as the diagnosis is confirmed by objective testing. If the clinical suspicion is high, or if there is a delay before diagnostic testing can be performed, treatment should be started before such testing. Five options are available for the initial treatment of DVT: (1) low-molecular-weight heparin (LMWH), administered subcutaneous (SC), without monitoring; (2) IV unfractionated heparin (UFH), with monitoring; (3) SC UFH, with monitoring (4); weight-based SC UFH, without monitoring; and (5) SC fondaparinux, without monitoring.

In relationship to the duration of initial heparin therapy, two randomized clinical trial (RCTs)[6,7] in patients with proximal DVT reported that IV UFH administered for 5 to 7 days is as effective as UFH administered for 10 to 14 days, providing that it is followed by adequate long-term anticoagulant therapy. The efficacy of this therapeutic approach is supported by subsequent studies that showed acceptable rates of recurrent VTE during 3 months of VKA therapy after 5 to7 days of heparin. Shortening the duration of initial heparin therapy from approximately 10 to 5 days is expected to have the added advantage of reducing the risk of heparin-induced thrombocytopenia. The currently recommended approach is to start both heparin and VKA at the time of diagnosis, and to discontinue heparin after 5 days provided the international normalized ratio (INR) is ≥ 2.0 for at least 24 h.

Warfarin is generally started at a dose of 2.5 to 10 mg. Two trials[9,10] performed in hospitalized patients showed that starting warfarin at a dose of 5 mg, compared to 10 mg, is associated with less excessive anticoagulation (see also chapter by Ansell et al[8] in this supplement). A similar study[11] in outpatients failed to demonstrate an advantage to starting warfarin at a dose of 5 mg compared with 10 mg. Observational studies[8,12] have shown that lower VKA maintenance doses are required in older patients, women, and those with impaired nutrition and vitamin K deficiency. Taken together, these data suggest that warfarin can usually be started at a dose of 10 mg in younger (*eg*, < 60 years), otherwise healthy outpatients, and at a dose of 5 mg in older patients and in those who are hospitalized. Subsequent doses should be adjusted to maintain the INR at a target of 2.5 (range 2.0 to 3.0) [see Section 2.2].

Recommendations

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH (Grade 1A)**, IV UFH** (Grade 1A)**, monitored SC UFH** (Grade 1A)**, fixed-dose SC UFH** (Grade 1A)**, or SC fondaparinux** (Grade 1A) **rather than no such short-term treatment.**

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C)**.**

1.1.3. In patients with acute DVT, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is $\geq$ 2.0 for 24 h (Grade 1C)**.**

1.1.4. In patients with acute DVT, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A)**.**

1.2. IV UFH for the Initial Treatment of DVT

Heparin was initially administered by intermittent IV boluses, but this practice was replaced by continuous IV infusion, which was shown to be associated with a lower risk of bleeding.[13] Initially, continuous IV infusions of UFH were administered at a starting dose of 1,000 U/h. A prospective observational study[14] showed that adjustment of the initial infusion rate of 1,000 U/h to achieve an activated partial thromboplastin time (APTT) ratio > 1.5 improved efficacy. Such adjustment also resulted in patients receiving a mean UFH dose of adpproximately 1,300 U/h, rather than the initial infusion dose of 1,000U/h, and the higher initial infusion rate was adopted in clinical practice.[15] Adjustment of initial heparin dose in proportion to body weight has also been shown to be of value.[8,16,17] When patients are treated with an initial heparin infusion of at least 1,250 U/h (corresponding to 30,000 U/d), or 18U/kg/h, it is uncertain if adjustment of heparin dose in response to the APTT or heparin levels improves efficacy or safety.[18–21] However, as all studies that have used continuous IV UFH for treatment of thrombosis have adjusted UFH dose in response to coagulation monitoring, this practice is standard and uniformly recommended. Single randomized trials support the following: (1) use of a weight-adjusted initial infusion dose of UFH in preference to starting with an infusion dose of 1,000 U/h[17]; and (2) that it is not necessary to increase UFH infusion dose $> 1,667$ U/h (corresponding to 40,000 U/d) if the anti-factor Xa heparin level is at least 0.35 U/mL even if the APTT ratio is below the therapeutic range.[22]

The starting dose of IV UFH for the treatment of DVT is either of the following: (1) a bolus dose of 5,000 U, followed by a continuous infusion of at least 30,000 U for the first 24 h; or (2) a weight-adjusted regimen of

a 80 U/kg bolus, followed by 18 U/kg/h. With both of these regimens, the infused dose of UFH should be adjusted using a standard nomogram to rapidly reach, and maintain, the APTT at levels that correspond to therapeutic heparin levels.[8,15,17] As noted in the preceding section, the requirement for an initial course of heparin was confirmed in a randomized controlled study[5] that reported a threefold-higher rate of recurrent VTE in patients who received VKA only.

Recommendation

1.2.1. In patients with acute DVT, if IV UFH is chosen, we recommend that after an initial IV bolus (80 U/kg or 5,000 U), it be administered by continuous infusion (initially at a dose of 18 U/kg/h or 1,300 U/h), with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C)**.**

1.3 SC UFH Compared With IV Heparin for the Initial Treatment of DVT

UFH can be administered SC twice daily as an alternative to continuous IV infusion for the initial treatment of DVT. The relative value of IV and SC administration of UFH has been evaluated in eight clinical studies that included a total of 972 patients, and were reviewed in a metaanalysis.[23] SC UFH administered twice daily appeared to be more effective (relative risk [RR] of extension or recurrence of VTE, 0.62; 95% confidence interval [CI], 0.39 to 0.98), and at least as safe (RR of major bleeding, 0.79; 95% CI, 0.42 to 1.48) as IV UFH, provided an adequate starting dose of SC UFH was administered. The usual regimen in these studies included an initial IV bolus of approximately 5,000 U followed by an SC dose of approximately 17,500 U bid on the first day, with subsequent adjustment to achieve a 1.5 to 2.5 prolongation of the APTT drawn 6 h after the morning dose. More recently, SC UFH, with[24] and without[25] dose adjustment in response to APTT measurements, has been compared with LMWH (see Section 1.5).

Recommendations

1.3.1. In patients with acute DVT, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of approximately 250 U/kg bid, with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (see also Section 1.5) [Grade 1C]**.**

1.3.2. In patients with acute DVT, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/Kg followed by a twice-daily dose of 250 U/kg rather than non–weight-based dosing (see also Section 1.5) [Grade 1C]**.**

1.4 LMWH for the Initial Treatment of DVT

LMWHs have more predictable pharmacokinetics and greater bioavailability than UFH.[8] Due to these pharmacologic features, body weight-adjusted doses of LMWH can be administered SC once or twice daily without laboratory monitoring in the majority of patients. However, in certain clinical situations, such as severe renal failure[26] or pregnancy (see chapter by Bates and colleagues in this supplement[27]), LMWH dose adjustment may be required using anti-Xa heparin levels. The usual time to perform the anti-Xa assay is 4 h after an injection, when heparin levels are expected to be at their highest. A target range of 0.6 to 1.0 IU/mL is suggested for twice-daily administration, and a target range of 1.0 to 2.0 IU/mL is suggested for once-daily administration, although neither recommendation is firmly founded.[8]

A large number of well-designed studies[28–44] have compared the efficacy and safety of body weight-adjusted LMWH, administered SC without monitoring, with IV UFH administered with monitoring and subsequent dose adjustment. The results of these studies have been combined in a number of recent metaanalyses.[45–47] The most recent such analysis included 17 studies[28–44,48] in which UFH was administered IV (3,614 patients) and 3 older studies[48–50] in which UFH was administered SC (206 patients).[47] LMWH was associated with fewer thrombotic complications (3.6% vs 5.4%; odds ratio [OR], 0.68; 95% CI, 0.55 to 0.84), less major bleeding (1.2% vs 2.0%; OR, 0.57; 95% CI, 0.39 to 0.83), and fewer deaths (4.5% vs 6.0%; OR, 0.76; 95% CI, 0.62 to 0.92).[47] The mortality advantage with LMWH compared to UFH appeared to be confined to those with (OR, 0.53; 95% CI, 0.33 to 0.85) rather than without (OR, 0.97; 95% CI, 0.61 to 1.56) cancer.[47]

Direct Comparisons Among LMWH Regimens for Initial Treatment of VTE

Once-daily and twice-daily administration of the same LMWH have been directly compared in six studies[28,39,51–54] (the same total daily dose of LMWH has not always been compared within studies). A metaanalysis[55] of five of these studies[39,51–54] that had unconfounded comparisons between once- and twice-daily administration found no difference in recurrent

VTE (3 months: OR, 0.85; 95% CI, 0.48 to 1.49), major bleeding (at 10 days: OR, 1.2; 95% CI, 0.4 to 3.2), or mortality (3 months: OR, 1.05; 95% CI, 0.53 to 2.09). Outpatient and inpatient administration of LMWH (three preparations were used) were compared in a single study[56] of 201 patients: one recurrent VTE and two major bleeds occurred in the inpatient group, and two recurrent VTEs and two major bleeds occurred in the outpatient group.

Dalteparin and tinzaparin, each administered once daily, have been compared for outpatient treatment of VTE in a study[57] of 497 patients. There was no apparent difference in recurrent VTE at 3 months (4.5% vs 5.9%; RR, 0.91; 95% CI, 0.38 to 2.2), major bleeding at 7 days (0.4% vs 1.2%; RR, 0.34; 95% CI, 0.04 to 3.26), or death at 3 months (4.8% vs 5.5%; RR, 0.0.87; 95% CI, 0.41 to 1.84). Indirect comparisons across studies also support that there is similar efficacy and safety with the following: (1) once- and twice-daily administration, (2) outpatient and inpatient administration, and (3) use of different preparations of LMWH.[45–47]

Recommendations

1.4.1. In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible (Grade 1C)**, or as an inpatient if necessary** (Grade 1A)**, rather than treatment with IV UFH.**
1.4.2. In patients with acute DVT treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A)**.**
1.4.3. In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C)**.**

1.5 SC UFH Compared With SC LMWH for the Initial Treatment of DVT

Four randomized trials[24,25,50,58] that included a total of 1,645 patients have compared SC UFH with SC LMWH (Table 2). Two of these trials[50,58] were small (total of 217 patients) and were performed > 15 years ago, and two were large studies[24,25] (total of 1,428 patients) and were recently performed. In the Galilei study,[24] UFH was administered as an initial IV bolus followed by twice-daily SC injections of 12,500, 15,000, or 17,500 U initially, depending on the patient's weight; subsequent UFH dosing was adjusted in response to APTT measurements. There was no difference in recurrent VTE, major bleeding, or deaths during follow-up (Table 2). The upper 95% CI on the difference indicated that, compared with LMWH, monitored SC UFH was unlikely to be associated with an absolute increase of recurrent VTE of > 3.1% or major bleeding of > 1.7% at 3 months[24] (judged Grade 1B evidence for noninferiority). In the FIDO study, [25] UFH was administered at an initial SC dose of 333 U/kg (no IV bolus), followed by a fixed SC dose of 250 U/kg bid; subsequent UFH dosing was kept constant, without coagulation monitoring. There was no difference in recurrent VTE, major bleeding, or death during follow-up (Table 2). The upper 95% CI on the difference indicated that, compared with LMWH, unmonitored, fixed-dose, SC UFH was unlikely to be associated with an absolute increase of recurrent VTE of > 3.3% or major bleeding of > 0.8% at 3 months[25] (judged Grade 1B evidence for noninferiority).

1.6 Fondaparinux Compared With LMWH for the Initial Treatment of DVT

The synthetic pentasaccharide fondaparinux has been evaluated for short-term treatment of DVT and PE (see Section 4.1) in the Matisse studies.[59,60] In the Matisse DVT trial,[59] 2,205 patients were treated with a once-daily SC dose of fondaparinux (7.5 mg if 50 to 100 kg; 5.0 mg if < 50 kg; 10 mg if > 100 kg) or twice-daily SC LMWH (enoxaparin 1 mg/kg) for at least 5 days using a blinded design. With fondaparinux vs LMWH, there was no difference in recurrent VTE at 3 months (3.9% vs 4.1%; difference, – 0.15%; 95% CI, – 1.8 to 1.5%]), major bleeding during treatment (1.1% vs 1.2%; difference, – 0.1%; 95% CI, – 1.0 to 0.8%), or death at 3 months (3.8% vs 3.0%; difference, 0.8%; 95% CI, – 0.8 to 2.3%)[59] (judged Grade 1A for noninferiority).

1.7 New Antithrombotic Agents for the Short-term Treatment of DVT

A comparison of 6 months of ximelagatran[61] (since withdrawn because of hepatic toxicity) with standard therapy in patients with DVT, and a comparison of 3 months or 6 months of idraparinux[62] with standard therapy, are described in Section 2.5.

1.8 Treatment Strategies of Thrombus Removal for Acute DVT

Treatments that actively remove thrombus in patients with acute DVT have the potential to reduce acute symptoms and the risk for PTS. Thrombus removal directly reverses venous obstruction and can restore function in valves that were immobilized by thrombus. Indirectly, early removal of thrombus obstruction can prevent late development of venous valvular incompetence secondary to venous dilatation in distal venous segments that were never involved with thrombosis.[63–71] Randomized trials,[72,73] patient registries,[74,75] and studies of other designs[76–81] support that successful thrombus removal, using a variety of techniques, can improve patient outcomes (see following).[79,81–83] It is also possible that thrombus removal

Table 2—*Comparison of SC LMWH and SC UFH for Short-term Treatment of VTE: Clinical Description and Results (Section 1.5)

Author/yr (Acronym)	Interventions	Patients Analyzed†	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Lopaciuk et al[50]/ 1992	UFH at 5,000 U IV followed by 250 U/kg SC bid initially and adjusted to APTT for 10 d	72/75	1/72 (1.4)	1/72 (1.4)	3/72 (4.2)	Population: femoral DVT in 81% and popliteal or more distal DVT in 19%
	Fraxiparine at 97 IU/kg SC bid for 10 d	74/74	0/74 RR, 3.1 (95% CI, 0.1–7.5)	0/74; RR, 3.1 (95% CI, 0.1–7.5)	0/74 RR, 7.2 (95% CI, 0.4–137)	Primary outcome was repeat venography
Faivre et al[58]/ 1988	UFH at 5,000 U IV followed by 250 U/kg SC bid and adjusted to APTT for 10 d	29/35	1/35	3/35	1/35	Population: DVT (proportion of proximal and distal not reported)
	CY222 at 2,000 IU IV followed by 150 IU/kg SC bid for 10 d	30/33	1/33 RR, 0.9 (95% CI, 0.1–14.5)	0/33 RR, 6.6 (95% CI, 0.3–123)	0/33 RR, 2.8 (95% CI, 0.1–67)	Primary outcome was repeat venography
Prandoni et al[24]/ 2004 (Galilei)	UFH IV (< 50 kg, 4,000 U; 50 to 70 kg, 5,000 U; > 70 kg, 6,000 U) followed by SC bid doses (initially: < 50 kg, 12,500 U; 50 to 70 kg, 15,000 U; > 70 kg, 17,500 U) adjusted to APTT for approximately 5 d	360/360	15/360 (4.2)	5/360 (1.4)	12/360 (3.3)	Population: proximal DVT in 65%, distal DVT in 18%, PE in 17%
	Nadroparin at 85 IU/kg SC bid for approximately 6.5 d	360/360	14/360 (3.9) RR, 1.1 (95% CI, 0.5–2.2)	7/360 (1.9) RR, 0.7 (95% CI, 0.2–2.2)	12/360 (3.3) RR, 1.0; 95% CI, 0.5–2.2)	
Kearon et al[25]/ 2006 (FIDO)	UFH at 333 U/kg SC followed by 250 U/kg SC bid (no adjustment) for 6.3 d	345/355	13/345 (3.8)	6/348 (1.7)	18/348 (5.2)	Population: proximal DVT in 77%, asymptomatic or distal DVT in 4%, PE in 19%
	Dalteparin (n = 261) or enoxaparin (n = 91) at 100 IU/kg SC bid for 7.1 d	352/353	12/352 (3.4) RR, 1.1 (95% CI, 0.5–2.3)	12/352 (3.4) RR, 0.5 (95% CI, 0.2–1.3)	22/352 (6.3) RR, 0.8 (95% CI, 0.4–1.5)	70% of patients were treated entirely as an outpatient (76% of DVT and 39% of PE)
						Postrandomization exclusions in 10 UFH patients and 1 LMWH patient

*Data are presented as No. of patients/total patients (%) unless otherwise indicated. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Follow-up was for 3 mo except for the study by Faivre et al,[58] for which it was 10 days.

and relief of venous obstruction may reduce the risk of recurrent VTE. Patients with iliofemoral DVT are the subset of patients with the largest thrombus burden and highest risk for postthrombotic morbidity, with up to 75% having chronic painful edema and 40% having venous claudication when treated with anticoagulant therapy alone.[84–87]

1.9 Catheter-Directed Thrombolysis for Acute DVT

The rationale for catheter-directed thrombolysis (CDT), which was established in patients with acute arterial occlusion,[88] is that rapid lysis is achieved with lower doses of thrombolytic therapy, resulting in fewer serious bleeding complications. A single-center trial[72]

randomized 35 patients with acute iliofemoral DVT to catheter-directed, pulse-spray, intrathrombus streptokinase or to anticoagulation alone. Six-month patency was improved in the thrombolysis group (72% vs 12%, $p < 0.001$), as was preservation of normal venous valve function (89% vs 59%, $p < 0.04$); postthrombotic symptoms were not evaluated. In the 19 studies[72,75,76,78,81,89–102] of heterogeneous designs listed in Table 3, significant lysis was observed in 79% of the 945 limbs treated with CDT. In an evaluation of 98 patients with iliofemoral DVT treated with CDT (n = 68) or anticoagulation (n = 30), quality of life (QOL) was better in patients treated with CDT and correlated with the degree of lysis.[79]

In the National Venous Registry, patients treated with short-term thrombosis (< 10 days) had better outcomes than those with older clot and correction of underlying venous lesions after successful thrombolysis, usually with intravascular stenting, appeared to be beneficial.[75] Although bleeding complications are the major concern with lytic therapy, reports published during the past 6 have shown bleeding complication rates less than half (*ie*, average of 4.8%; Table 4) the rates in earlier reports, which is likely due to more appropriate patient selection and experience with the technique. Data are not available for comparing one plasminogen activator to another or a particular catheter or catheter-based technique to others, and there are inadequate data to assess the benefit or risk of inferior vena cava (IVC) filters in this setting (recommended by manufacturer with some endovascular devices and techniques whereas not with others).

The addition of mechanical thrombus fragmentation, with or without aspiration, during CDT is commonly used as part of the procedure (collectively referred to as *pharmacomechanical thrombolysis*). While randomized comparisons of CDT alone vs pharmacomechanical thrombolysis are not available, retrospective analyses[95,96] suggest they are associated with similar rates of successful thrombolysis (70 to 80%) and of major bleeding (5 to 8%); however, pharmacomechanical thrombolysis is associated with shorter treatment times, shorter ICU and hospital stays, and reduced costs. No randomized trial has compared CDT with systemic thrombolysis (see following); however, a single-center, retrospective study[81] suggests that CDT achieves better lysis (50% vs 31%) and preservation of valve function (44% vs 13%).

Recommendations

1.9.1. In selected patients with extensive acute proximal DVT (*eg*, iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy ≥ 1 year) who have a low risk of bleeding, we suggest that CDT may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B).

1.9.2. After successful CDT in patients with acute DVT, we suggest correction of underlying venous lesions using balloon angioplasty and stents (Grade 2C).

1.9.3. We suggest pharmacomechanical thrombolysis (*eg*, with inclusion of thrombus fragmentation and/or aspiration) in preference to CDT alone to shorten treatment time if appropriate expertise and resources are available (Grade 2C).

1.9.4. After successful CDT in patients with acute DVT, we recommend the same intensity and duration of anticoagulant therapy as for comparable patients who do not undergo CDT (Grade 1C).

1.10 Systemic Thrombolytic Therapy for Acute DVT

In 15 trials[81,103–120] that randomized a total of 811 patients with acute DVT to systemic thrombolytic therapy or to anticoagulant therapy alone, as assessed by early repeat phlebography, systemic thrombolytic therapy achieved a higher frequency of complete or significant lysis (54% vs 4%) or partial lysis (18% vs 14%) [Table 4]. Three of the randomized trials reported postthrombotic symptoms after follow-up of 1.0 year,[115] 1.6 years,[107] and 6.5 years[103] (Table 4). A Cochrane analysis[121] that included two of these studies[103,115] and a total of 101 patients suggests that thrombolytic therapy reduced postthrombotic morbidity (RR, 0.7; 95% CI, 0.5 to 0.9) and leg ulceration (RR, 0.5; 95% CI, 0.1 to 2.4).

In the same Cochrane analysis,[121] which included a total of 12 studies and 701 patients (number of included studies and patients differed with the outcome assessed), the following estimates were obtained with thrombolytic therapy (various agents, mostly administered systemically) vs anticoagulation alone: early PE: RR, 1.2 (95% CI, 0.3 to 4.4; 382 patients in 5 trials); late recurrent DVT: RR, 1.4 (95% CI, 0.4 to 5.4; 35 patients in 1 trial); and early significant or major bleeding: RR, 1.7 (95% CI, 1.04 to 2.9; 668 patients in 10 trials); intracranial bleeding: RR, 1.7 (95% CI, 0.2 to 14; 701 patients in 5 trials). There have been no direct comparisons of different thrombolytic agents; however, prolonged infusions of streptokinase that were used predominantly in the earlier studies appear to be associated with higher bleeding rates than other regimens (Table 4).

Table 3—*Catheter-Directed Thrombolysis for Acute DVT: Clinical Description and Results (Section 1.9)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Semba and Dake[98]/ 1994	Prospective registry	21 patients (27 limbs) with iliofemoral DVT ≤ 14 d (n = 20) or > 14 d (n = 7) duration	4.9 million U of urokinase (mean) infused over 30 h (mean), followed by heparin and then warfarin for 8–12 wk Adjunctive therapy: limbs w/ residual stenoses > 50% received angioplasty (n = 2) or stenting (n = 14)	Clot lysis, complications	3 mo	Significant lysis: 18/25 (72%) [25/27 limbs treated with CDT; 2 could not be crossed with guide wire] Partial lysis: 5/25 (20%) No lysis: 2/25 (8%) Complications: one small hematoma at puncture site, no intervention/transfusion
Semba and Dake[99]/ 1996	Case series	32 patients (41 limbs) with iliofemoral DVT ≤ 14 d (n = 25) or > 14 d (n = 16) duration	3.5 million U of urokinase (mean) infused over 30 h (mean), followed by warfarin with INR 2.0–3.0 for ≥ 6 mo Adjunctive therapy: limbs with residual stenoses of > 50% received angioplasty (n = 2) or angio/stenting (n = 20)	Clot lysis, complications	6 mo	Significant lysis: 21/32 (66%) [32 limbs treated with CDT; 4 could not be crossed with guidewire, 5 treated with angioplasty and stent alone] Partial lysis: 9/32 (28%) No lysis: 2/32 (6%) Complications: 0
Verhaeghe et al[102]/ 1997	Prospective study	24 patients with iliofemoral DVT ≤ 14 d (n = 16) or > 14 d (n = 8) duration	3 mg/h rt-PA (mean, 86 mg) infused with 1,000 U/h of IV heparin, followed by heparin, adjusted to APTT Adjunctive therapy: hydrodynamic thrombectomy (n = 3) and stents (n = 9)	Clot lysis, bleeding	13 mo (mean)	Significant lysis: 19/24 (79%) Partial lysis: 5/24 (21%) Bleeding: 6/24 (25%) Patency at 3 mo, 84% Patency at 1 yr, 78%
Bjarnason et al[76]/ 1997	Prospective registry	77 patients (87 limbs) with iliofemoral DVT ≤ 14 d (n = 69) or > 14 d (n = 18) duration	2,000–2,500 U/kg/h urokinase infused for 75 h (mean), with 5,000 IU bolus heparin plus infusion adjusted to APTT Adjunctive therapy: angioplasty (52 limbs), stent (38 limbs), AVF (15 limbs), surgical thrombectomy (13 limbs), mechanical thrombectomy (4 limbs), surgical bypass (3 limbs)	Clot lysis, PE, bleeding	1 yr	Early results: Significant lysis: 69/87 (79%) Iliac (63%) Femoral (40%) No lysis: 18/87 (21%) PE: n = 1 (1%) Bleeding: Major: 5/77 (6%) Minor: 11/77 (14%) Patency at 1 yr: Iliac (63%) Femoral (40%)
Mewissen et al[75]/ 1999 (National multicenter registry)	Prospective multicenter registry	287 patients (312 infusions) with lower-limb DVT ≤ 10 d (n = 188) or > 10 d (n = 99) duration	7.8 million U of urokinase (mean) infused for 53.4 h (mean) in 297 limbs In 6 limbs, only systemic infusion (no CDT) Adjunctive therapy: stents (104 limbs), systemic infusion (54 limbs)	Clot lysis, PE, bleeding, death	1 yr	Early results: 50–100% lysis: 258/312 (83%) < 50% lysis: 54/312 (17%) PE: 6/473 (1%) [calculated from total No. of patients in Venous Registry] Bleeding: 54/473 (11%) [calculated from total No. of patients in Venous Registry] Death: 2/473 (< 1%) [Calculated from total No. of patients in Venous Registry]; Patency at 1 yr Iliac (64%) Femoral (47%)
Comerota and Kagan[78]/2000	Retrospective study	54 patients (54 limbs) with iliofemoral DVT, average duration of leg symptoms of 5.2 d	250,000–500,000 U of urokinase bolus followed by 250,000–300,000 U/h of continuous infusion for 30 h (mean) in 47 patients; all patients received heparin infusion at 500–1,000 U/h or 4- to 8-mg bolus of rt-PA followed by 2–4 mg/h in 7 patients, with heparin as noted above Adjunctive therapy: surgical thrombectomy (n = 5)	Clot lysis, complications	ND	Early results: Significant lysis: 45/54 (83%) Iliac (78%) Complications: Major bleed: 4/54 (7%) Hematoma, puncture site: 8 (15%) Hematoma, inguinal: 1 (2%)

Table 3—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Horne et al[92]/2000	Prospective, study	10 patients (10 limbs) with lower-extremity DVT ≤ 14 d duration	rt-PA dose of 0.6 mg/kg to a maximum of 50 mg/kg per leg infused via daily pulse-spray catheter for up to 4 d of treatment; heparin was adjusted to a prothrombin time of 1.5–2.5 × baseline	Clot lysis, PE, bleeding	2–6 mo	Significant lysis: 9/10 (90%) Partial lysis: 1/10 (10%) PE: 2/10 (20%) Bleeding: 1/10 (10%)
Kasirajan et al[94]/2001	Retrospective registry	Nine patients with < 90% thrombus extraction following percutaneous mechanical thrombectomy for iliofemoral/IVC DVT	Urokinase, rt-PA, or rPA for mean of 20 h	Complete, partial, no lysis	9 mo (mean)	Complete lysis: 7/9 (78%) Partial lysis: 1/9 (11%) No lysis: 1/9 (11%)
AbuRahma et al[89]/2001	Prospective study	51 patients (51 limbs) with iliofemoral DVT given choice between conventional therapy (heparin plus warfarin) or lysis plus angio/stent (if needed); lysis offered only to patients with DVT ≤ 14 d duration and no contraindications	Anticoagulation: 33 patients administered 1,000–2,000 U/h of heparin infusion for 5–7 d CDT: 18 patients administered loading dose of 4,500 U of urokinase followed by 4,500 U/kg/h for 24–48 h, or 4-to 8-mg bolus of rt-PA followed by 2 to 4/mg/h infusion Adjunctive therapy: patients with residual stenosis > 50% received stents (n = 10)	Clot lysis, PE, bleeding	Anticoagulation for 6 mo CDT for 6 mo	Anticoagulation: 30-d significant lysis: 1/33 (3%) 6-mo patency: 8/33 (24%) Bleeding: 2/33 (6%) PE: 2/33 (6%) CDT: 30-d significant lysis: 15/18 (83%) 6-mo patency: 15/18 (83%) Bleeding: 2/18 (11%)
Vedantham et al[101]/2002	Retrospective study	20 patients (28 limbs) with symptomatic lower-extremity DVT	Intrathrombus delivery of either of the following: (1) urokinase, mean 166,000 U/h (7 limbs) (2) tPA mean 1.74 mg/h (7 limbs) (3) rPA mean 0.89 U/h (14 limbs) Adjunctive therapy: mechanical thrombectomy by catheter (28 procedures); iliac stents (15 patients)	Procedural success (< 30% residual stenosis), major bleeding	After procedure	Procedural success: 23/28 (82%) Major bleeding: 14%
Elsharawy and Elzayat[72]/2002	RCT, single center	35 patients with DVT < 10 d duration randomized to CDT or anticoagulation alone	CDT: 18 patients received approximately 1 million U of streptokinase pulse spray for 1 h, followed by 100,000 U/h of streptokinase infusion until complete lysis, no change in 12 h, or complication; adjunctive therapy: angioplasty/stent (n = 1) Anticoagulation: 17 patients received 5,000 U of heparin bolus, followed by heparin adjusted to APTT	Clot lysis, PE, bleeding	1 week and 6 mo	CDT at 1 wk Complete lysis: 11/18 (61%) No lysis: 0 (0%) PE: 0 Bleeding: 0 Anticoagulation at 1 wk: Complete lysis: 0/17 (0%) No lysis: 17/17 (100%) PE: 1/17 (6%) Bleeding: 0 CDT at 6 mo: Complete lysis: 13/18 (72%) No lysis: 0 (0%) Anticoagulation at 6 mo: Significant lysis: 2/17 (12%) No lysis: 7/17 (41%)
Castaneda et al[90]/2002	Prospective study	15 patients with acute or chronic DVT of lower extremity (n = 14) or IVC (n = 1)	16.5 U/h (median) of rt-PA infused over 29 h (median) with heparin doses of 300–400 U/h Adjunctive therapy: stenting (n = 4); angioplasty/stent (n = 6)	Clot lysis, PE, bleeding	After procedure	Significant lysis: 15/15 (100%) PE: 0 Bleeding: 0

Table 3—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Grunwald and Hofmann[91]/2005	Retrospective study	74 patients (82 limbs) with DVT of upper (n = 23) or lower (n = 59) extremity, with duration of ≤ 14 d (n = 74) or > 14 d (n = 8)	Urokinase: 11.3 U/h of urokinase for 40.6 h (38 limbs) with therapeutic heparin dosing tPA: 0.57 mg/h tPA for 30.8 h (32 limbs) with subtherapeutic heparin rt-PA: 0.74 U/h rt-PA for 24.3 h (12 limbs) with subtherapeutic heparin Adjunctive therapy: mechanical thrombolysis, angioplasty, stenting; urokinase (n = 30), tPA (n = 24), rt-PA (n = 12)	Clot lysis, PE, bleeding	After procedure	Urokinase: Significant lysis:27/38 71%) PE: 0 Bleeding: 2/38 (5%) tPA: Significant lysis: 21/32 (66%) PE: 0 Bleeding: 1/32 (3%) rt-PA: Significant lysis: 6/12 (50%) PE: 0 Bleeding: 1/12 (8%)
Laiho et al[81]/2004	Retrospective study	32 patients with iliofemoral DVT ≤ 14 d in duration received either catheter-directed (n =16) or systemic (n =16) thrombolysis	CDT treatment: 73 mg (mean) rt-PA for 33 h (mean) via catheter delivery, with LMWH and oral anticoagulants	Clot lysis, PE, bleeding, valvular competence	2–3 yr	CDT treatment Significant lysis: 8/16 (50%) PE: 2/16 (13%) Bleeding: 2/16 (13%) Valvular competence: 7/16 (44%) Any deep vein incompetence: 44%
Sillesen et al[100]/2005	Retrospective study	45 patients with iliofemoral DVT ≤ 14 d in duration	1 mg rt-PA starting dose plus 1,000–5,000 U of UFH followed by continuous infusion of 1 mg rt-PA and 1,000 U of UFH per hour (n = 9) 10 mg rt-PA pulse spray plus 1,000–5,000 U of UFH for initial 15–30 min, followed by continuous infusion of 1 mg rt-PA and 1,000 U UFH per hour (n = 36) Adjunctive therapy: angioplasty/stenting (n = 30)	Clot lysis, PE, bleeding, death	24 mo (median)	Significant lysis: 42/45 (93%) PE: 1/45 (2%) Minor bleeding: 4 (8%)
Jackson et al[93]/2005	Retrospective study	28 patients with lower-extremity DVT of ≤ 14 d (n = 20) or > 14 d in duration (n = 4) or recurrent DVT (n = 4)	60,000–180,000 U/h urokinase infused over 24–48 h (n = 2) 1–2 mg/h tPA for 24–48 h (n = 16) 1–2 U/h rt-PA for 24–48 h (n = 9) Mechanical thrombectomy only (n = 1) Adjunctive therapy: mechanical thrombectomy (n = 20), stenting (n = 12)	Clot lysis, PE, bleeding, death	15.5 mo	Lysis > 90%: 6/28 (21%) Lysis 80–89%: 2/28 (7%) Lysis 60–79%: 2/28 (7%) Lysis < 60%: 11/28 (39%) PE: 0 Minor bleeding: 2/28 (7%) Immediate patency: 92% Long-term patency: 80%
Ogawa et al[97]/2005	Prospective, study	24 patients with lower-extremity DVT	CDT: 240,000 U of urokinase infused for 1 h, followed by 2 d of 1-h infusion of 120,000 U of urokinase bid, with IV UFH to reach APTT time ratio from 1.5–2.0 within 24 h (n = 10) CDT plus IPC/IVC: thrombolysis performed as in CDT-only group; temporary IVC filter placed in infrarenal IVC and removed after CDT; IPC with foot-calf cycle begun after urokinase infusion and continued 24 h/d until CDT stopped (n = 14)	Clot lysis, PE, bleeding	CDT group: 22 mo; CDT plus IPC group: 14 mo	CDT: 100% lysis: 0/10 (50–99%) lysis: 2/10 (20%) < 50% lysis: 8/10 (80%) PE: 0 Bleeding: 0 CDT plus IPC/IVC 100% lysis: 5/14 (36%) 50–99% lysis: 6/14 (43%) < 50% lysis: 3/14 (21%) PE: 0 Bleeding: 0

Table 3—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Kim et al[95]/2006	Retrospective study	37 patients (45 limbs) with acute (< 14 d) iliofemoral DVT	CDT: 6.70 ± 5.9 million U of urokinase (mean) infused for mean of 56.5 ± 27.4 h in 26 limbs (23 patients) CDT plus pharmacomechanical: lytic treatment performed as described in CDT group plus AngioJet thrombectomy device	Clot lysis, bleeding, PE, treatment duration, cost, recurrent DVT	32 mo	Complete lysis: CDT: 21/26 (81%) CDT plus PMT: 16/21 (84%) Major bleeding: CDT: 2/26 (7%) CDT plus PMT: 1/21 (5%) PE: CDT: 1/26 (4%) CDT plus PMT: 1/21 (5%) Treatment duration: CDT: 57 h CDT plus PMT: 30 h Cost (drug plus device): CDT: $10,127 CDT plus PMT: $5,128 Recurrent DVT: CDT: 4/16 (25%) CDT plus PMT: 2/13 (15%)
Lin et al[96]/2006	Retrospective study	93 patients (98 procedures) with symptomatic DVT	CDT: 46 procedures using tPA, rt-PA, or urokinase PMT: 52 procedures using AngioJet rheolytic thrombectomy system with tPA, rt-PA, or urokinase	Clot lysis, No. of 1 yr venograms, immediate clinical improvement, bleeding, ICU/hospital stay, 1-yr primary patency, cost		Complete/partial lysis: CDT: 32/46 (70%)/14/46 (30%) CDT plus PMT: 39/52 (75%)/13/52 (25%) No. of venograms: CDT: 2.5 CDT plus PMT: 0.4 ($p < 0.001$) Immediate clinical improvement: CDT: 33/46 (72%) CDT plus PMT: 42/52 (81%) Bleeding: CDT: 2/49 (4%) CDT plus PMT: 3/46 (7%) ICU stay: CDT: 2.4 d CDT plus PMT: 0.6 d Hospital stay: CDT: 8.4 d CDT plus PMT: 2.4 d 1-yr primary patency: CDT: 64% CDT plus PMT: 68% Cost: CDT: $85,301 CDT plus PMT: $47,742

*ND = not determined. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 4—*Systemic Thrombolytic Therapy for Acute DVT: Clinical Description and Results (Section 1.9)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Browse et al[105]/ 1968	RCT, single center	10 patients with lower-extremity DVT confirmed by phlebography	Lysis: 600,000 U of streptokinase plus 100 mg of hydrocortisone for first hour, then continued every 6 h for 3 d (n = 5) Anticoagulation: 4- to 6-h doses of 5,000 U heparin for 48 h followed by warfarin (n = 5)	Clot lysis, PE, bleeding	7–10 d	Thrombolysis: Complete clot lysis: 3/5 (60%) Partial lysis: 1/5 (20%) No lysis: 1 (20%) PE: 0 Bleeding: 0 Anticoagulation: Complete clot lysis: 0/5 Partial lysis: 0/5 No lysis: 5/5 (100%) PE: 0 Bleeding: 0
Robertson et al[113]/ 1968	RCT, single center	16 patients with DVT	Thrombolysis: 200,000 U of streptokinase over 90 min, then 100,000 U as maintenance dose for 22.5 h; 500 mg of heparin administered over 24 h, plus prednisone (n = 8) Anticoagulation: heparin plus prednisone (n = 8)	Clot lysis, bleeding	7 d	Thrombolysis: Significant lysis: 5/8 (63%) Partial lysis: 2/8 (25%) No lysis: 1/8 (12%) Bleeding: Major: 2/8 (25%) Minor: 2/8 (25%) Anticoagulation: Significant lysis: 1/8 (12%) Partial lysis: 2/8 (25%) No lysis: 5/8 (63%) Bleeding: Major: 1/8 (12%) Minor: 1/8 (12%)
Kakkar et al[109]/ 1969	RCT, single center	30 patients with DVT of < 4 d	Thrombolysis: streptokinase at 500,000 U IV over 30 min, 900,000 U every 6 h for 5 d (n = 10) Arvin: arvin loading dose 80 U IV over 6 h, 80 U over 15 min, 40 to 80 U every 6 h for 5 d (n = 10) Anticoagulation: heparin at 10,000 U IV over 5 min, then 10,000–15,000 U every 6 h for 5 d (n = 10)	Clot lysis, PE, bleeding, death	6–12 mo	Thrombolysis: Complete clot lysis: 6/9 (67%) Partial lysis: 1/9 (11%) No lysis: 2/9 (22%) PE: 0 Bleeding: 4/10 (40%) Death: 2/9 (22%) [1 patient excluded from treatment] Arvin: Complete lysis: 1/10 (10%) Partial lysis: 3/10 (30%) No lysis: 6/10 (60%) PE: 0 Bleeding: 0 Death: 0 Anticoagulation: Complete clot lysis: 2/9 (22%) Partial lysis: 2/9 (22%) No lysis: 5/9 (55%) PE: 1/10 Death: 2/9 (22%) Bleeding: 2/9 (22%) [note:1 patient excluded from treatment]

Table 4—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Tsapogas et al[117]/ 1973	RCT, single center	34 patients with DVT of < 5 d	Thrombolysis: titrated initial dose of streptokinase IV, then streptokinase at 100,000 U/h maintained and adjusted up to 72 h; IV heparin for 1 wk 6–12 h after streptokinase (n = 19) Anticoagulation: heparin IV into affected limb, 7,000 U bolus then 1,500 U/h adjusted; continued for 7 d (n = 15)	Clot lysis, PE, bleeding	7 d	Thrombolysis: Complete/partial lysis: 10/19 (53%) No lysis: 9/19 (47%) PE: 0 Bleeding: minor: 3 (16%) Anticoagulation: Complete/partial lysis: 1/15 (7%) No lysis: 14/15 (93%) PE: 1/15 (7%) Bleeding: 0
Duckert et al[106]/ 1975	Prospective study	134 patients with acute or subacute DVT	Thrombolysis: initial dose of streptokinase calculated according to tolerance injected over 15–30 min; maintenance dose at 30 mL/h was two thirds of first dose (n = 92) Anticoagulation: 5,000 U heparin for initial dose followed by 25,000 U/24 h infusion (n = 42)	Clot lysis, PE, bleeding	Approximately 7 d	Thrombolysis: Significant lysis: 39/92 (42%) Partial lysis: 23/92 (25%) No lysis: 30/92 (33%) PE: 7 (8%) Bleeding: Major: 58 (62%) Minor: 24 (26%) Anticoagulation: Significant lysis: 0/42 (0%) Partial lysis: 4/42 (10%) No lysis: 38/42 (90%) PE: 5/42 (12%) Bleeding: Major: 2/42 (5%) Minor: 4/42 (10%)
Porter et al[112]/ 1975	RCT, single center	50 patients with DVT < 14 d in duration	Thrombolysis: streptokinase IV at 250,000 U over 30 min, then 100,000 U/h titrated for 72 h; followed by IV heparin titrated over 7 d (n = 23) Anticoagulation: IV heparin at 150 U/kg loading dose then titrated for 10 d (n = 26)	Clot lysis, PE, bleeding, death due to treatment	10 d	Thrombolysis: Complete lysis: 6/23 (26%) Partial lysis: 15/23 (65%) No lysis: 2/23 (9%) PE: 0 Bleeding: 4/23 (17%) Death: 1 (4%) Anticoagulation: Complete lysis: 1/26 (4%) Partial lysis: 20/26 (77%) No lysis: 5/26 (19%) PE: 0 Bleeding: 1/26 (4%) Death: 0
Marder et al[111]/ 1977	RCT, single center	24 patients with DVT	Thrombolysis: initial dose of 250,000 U of streptokinase for 20 min, followed by 100,000 U/h for 72 h (n = 12) Anticoagulation: initial IV heparin dose of 150 U/kg, followed by titrated infusion for 72 h Cotreatment: 100 mg bolus hydrocortisone prior to treatment	Clot lysis, death due to treatment	5 d	Thrombolysis: Significant lysis: 5/12 (42%) Partial lysis: 2/12 (16%) No lysis: 5/12 (42%) Death: 1/12 (8%) Anticoagulation: Significant lysis: 0/12 (0%) Partial lysis: 3/12 (25%) No lysis: 9/12 (75%) Death: 0

Table 4—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Arnesen et al[103]/ 1978	RCT, single center	42 patients with proximal DVT of < 5 d	Thrombolysis: 250,000 U loading of IV streptokinase, then 100,000 IU/h IV for 72–96 h (n = 21) Anticoagulation: 15,000 IU IV bolus heparin, then total of 30,000 IU IV infusion for 72–90 h (n = 21)	Clot lysis, PE, bleeding	21 d to 6 yr	Thrombolysis: Significant lysis: 15/21 (71%) No lysis: 6/21 (29%) PE: 1/21 (5%) Bleeding: 2/21 (9%) Anticoagulation: Significant lysis: 5/21 (24%) No lysis: 16/21 (76%) PE: 0 Bleeding: 2/21 (9%)
Elliot et al[107]/ 1979	RCT, single center	51 patients with clinical history of DVT of < 8 d	Thrombolysis: loading dose of 600,000 U of streptokinase infused over 30 min, followed by 100,000/h for 3 d; heparin for 4 d following streptokinase (n = 26) Anticoagulation: 10,000 U of IV heparin initially, followed by 10,000 U IV daily for a 6-h infusion to maintain clotting time of 2.5 to 3 times normal, for 7 d (n = 25)	Immediate: clot lysis, PE, bleeding Long term: symptom free	Immediate: 5 d Long-term: 19 mo (mean)	Immediate: Thrombolysis: Significant lysis: 17/26 (65%) Partial lysis: 1/26 (4%) No lysis: 8/26 (31%) PE: 0 Bleeding: 2 (8%) Anticoagulation: Significant lysis: 0/25 (0%) Partial lysis: 0/25 (0%) No lysis: 25/25 (100%) PE: 0 Bleeding: 2/21 (9%) Long-term Thrombolysis: Symptom free: 12/20 (60%) [four deaths, other causes, two unavailable for follow-up]; Treatment 2: Symptom free: 2/21 (9%) [four deaths, two PE, two other causes]
Watz et al[120]/ 1979	Prospective study	35 patients with DVT	Thrombolysis: initial dose of 250,000 U of streptokinase in 30 min, followed by maintenance of 100,000 U/h for how long????? (n = 18) Anticoagulation: 45,000 U of heparin daily with warfarin (n = 17)	Clot lysis, PE, bleeding	1–2 mo	Thrombolysis: Significant lysis: 8/18 (44%) Partial lysis: 4/18 (22%) No lysis: 6/18 (34%) PE: 1/18 (5%) Bleeding: minor: 3/18 (12%) Anticoagulation: Significant lysis: 1/17 (6%) Partial lysis: 5/17 (29%) No lysis: 11/17 (65%) PE: 1/17 (6%) Bleeding: minor 2/17 (12%)

Table 4—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Kiil et al[110]/ 1981	RCT, single center	20 patients with DVT of < 72 h	Thrombolysis: urokinase at 200,000 U IV for 24 h; after 18 h, heparin loading dose of 15,000 U, then 40,000 U/d for 5 d (n = 11) Anticoagulation: heparin at 40,000 U/d IV for 6 d (n = 9)	Clot lysis, PE, bleeding	2 wk	Thrombolysis: Partial lysis: 1/11 (9%) No lysis: 10/11 (91%) PE: 0 Bleeding: 3/11 (27%) Anticoagulation: Partial lysis: 1/8 (12%) No lysis: 7/8 (88%) PE: 0 Bleeding: 3/9 (33%) [note: 1 patient excluded from group]
Arnesen et al[104]/ 1982	Follow-up to RCT of Arnesen/1978 (n = 48)	35/42 patients from RCT	Phlebography and clinical examination by blinded evaluators	Normal legs, PTS symptoms	6.5 yr	Thrombolysis: Normal legs: 13/17 (77%) PTS: symptoms (moderate): 4/17 (24%) Anticoagulation: Normal legs: 6/18 (33%) PTS symptoms (moderate): 9/18 (50%)
Schulman et al[114]/ 1986	RCT, single center	36 patients with calf DVT of < 7 d	Thrombolysis: streptokinase at 50,000 IU IV over 15 min, then 100,000 IU over 12 h for up to 7 d, titrated; administered with 5,000 IU of heparin IV over 12 h (n = 17) Anticoagulation: heparin at 5,000 IU IV for 15 min then 30,000 IU/d, titrated over 7 d (n = 19)	Clot lysis, bleeding, PE	5 yr	Thrombolysis: Complete lysis: 7/17 (41%) Bleeding: 3/17 (18%); PE: 0 Anticoagulation: Complete lysis: 2/19 (10%) Bleeding: 1/19 (5%) PE: 0
Verhaeghe et al[119]/ 1989	Prospective cohort study (study A) and multicenter RCT (study B)	32 patients with DVT of < 10 d	Study A: Open-label study with IV rt-PA 100 mg over 8 h (day 1), 50 mg rt-PA over 8 h (day 2); 10% dose as bolus (n = 11) Study B: rt-PA at 100 mg: IV of 100 mL containing rt-PA 100 mg infused over 8 h (day 1), IV of 100 mL containing 50 mg of rt-PA infused over 8 h (day 2); 10% dose as bolus (n = 8) rt-PA 50 mg: IV of 100 mL containing rt-PA 50 mg infused over 8 h on both days 1 and 2; 10% dose as bolus (n = 6) Placebo: IV of 100 mL containing placebo infused over 8 h on both days 1 and 2 (n = 7) Cotreatment: heparin at 5,000 U IV bolus then continuous infusion 1,000 U/h for up to 72 h	Clot lysis, bleeding	72 h	Note: authors assigned veins a relative value reflecting degree of thrombosis (maximum of 40 U: complete thrombosis); the unit scores reflect the reduction in thrombosis after lysis Study A: Change in unit score −3.2 Study B: rt-PA 100 mg Change in unit score −24.3 Bleeding: 6 rt-PA: 50 mg Change in unit score −34.3 Bleeding: 3 Placebo: Change in unit score −2.8 Bleeding: 0

Table 4—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Goldhaber et al[108]/ 1990	RCT, multicenter	64 patients (65 randomizations) with DVT of < 14 d	rt-PA: rt-PA 0.05 mg/kg/h IV for 24 h, then heparin 100 U/kg bolus, then 1,000 U/h, adjusted (n = 36) rt-PA plus heparin: rt-PA as in group 1 plus heparin concomitantly (n = 17) Anticoagulation: heparin 100 U/kg bolus, then 1,000 U/h (n = 12)	Clot lysis, bleeding	36 h	rt-PA: Complete lysis: 2/32 (6%) Partial lysis: 18/32 (57%) No lysis: 12/32 (38%) Bleeding: 1/32 (3%) rt-PA plus heparin: Complete lysis: 1/17 (6%) Partial lysis: 8/17 (48%) No lysis: 8/17(48%) Bleeding: 0 Anticoagulation: Partial lysis: 2/11 (18%) No lysis: 9/11 (89%) Bleeding: 0 (note: 5 of 65 venograms were not analyzed)
Turpie et al[118]/ 1990	RCT, multicenter	83 patients with DVT of < 7 d	Phase 1: Lysis plus heparin: two-chain rt-PA 0.5 mg/kg IV for 4 h (n = 12) Placebo plus heparin (n = 12) Phase 2: Lysis plus heparin: one-chain rt-PA 0.5 mg/kg IV for 8 h and repeated in 24 h (n = 29) Placebo plus heparin (n = 30) Cotreatment: IV heparin 5,000 U bolus then 30,000 U/24 h, adjusted for 7–10 d	Clot lysis, bleeding	24–48 h	Phase 1: Lysis plus heparin: ≥50% lysis: 7/12 (58%) < 50% lysis: 2/12 (17%) No lysis: 3/12 (25%) Bleeding: 4/12 (33%) Placebo plus heparin: < 50% lysis: 2/12 (17%) No lysis: 10/12 (83%) Bleeding: 1/12 (8%) Phase 2: Lysis plus heparin: ≥50% lysis: 6/29 (21%); < 50% lysis: 7/29 (24%) No lysis: 15/29 (52%) Bleeding: 1/29 (3%) Placebo plus heparin: ≥50% lysis: 2/30 (7%); < 50% lysis: 5/30 (17%) No lysis: 23/30 (77%) Bleeding: 1/30 (3%)
Schweizer et al[115]/ 1998	RCT, single center	69 patients with DVT of < 7 d	rt-PA: 20 mg IV into pedal vein 4 h/d for 7 d; heparin IV administered concomitantly; warfarin day 7 to 12 mo Urokinase: 100,000 IU/h IV into pedal vein continuously 7 d; heparin IV 7 d; plasminogen monitored; warfarin day 7–12 mo Anticoagulation: heparin IV adjusted for 7 d;. warfarin, day 1 to 12 mo	7 d: clot lysis, bleeding 1 yr: PTS symptoms	7 d and 1 yr	rt-PA: Complete lysis: 6/22 (27%) Bleeding: 1/22 (5%) PTS symptoms: 14/22 (64%) Urokinase: Complete lysis: 11/22 (50%) Bleeding: 1/22 (5%) PTS symptoms: 9/22 (41%) Anticoagulation: Complete lysis: 0 Bleeding: 0 PTS symptoms: 15/22 (68%)

Table 4—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Schweizer et al[116]/ 2000	RCT, multicenter	250 patients with DVT of < 9 d	rt-PA: locoregional rt-PA 20 mg/d for 4 h via pedal vein for 4–7 d; IV heparin administered simultaneously at 1,000 IU/h; adjusted Urokinase: locoregional urokinase 100,000 IU/ infused continuously; fibrinogen and plasminogen monitored; IV heparin administered concomitantly Systemic streptokinase: 3,000,000 U/d for 6 h with heparin for up to 7 d; premedications: hydrocortisone at 100 mg, ranitidine at 50 mg, clemastine at 2 mg Systemic urokinase: 5,000,000 IU/d for 4 h up to 7 d; IV heparin administered concomitantly Anticoagulation: heparin IV, adjusted Cotreatment: bed rest, compression bandages, compression therapy, warfarin for 12 mo	Clot lysis, bleeding, mortality	1 yr	rt-PA: Complete lysis: 10/50 (20%) ≥50% lysis: 7/50 (14%) < 50% lysis: 16/50 (32%) No lysis: 13/50 (26%) Bleeding: 2/50 (4%) Urokinase: Complete lysis: 10/50 (20%) ≥50% lysis: 9/50 (18%); < 50% lysis: 17/50 (34%) No lysis: 11/50 (22%) Bleeding: 1/50 (2%) Systemic streptokinase: Complete lysis: 20/50 (40%) ≥50% lysis: 7/50 (14%) < 50% lysis: 13/50 (26%) No lysis: 8/50 (16%) Bleeding: 5/50 (10%) PE: 5/50 (10%) Systemic urokinase: Complete lysis: 17/50 (34%) ≥ 50% lysis:10/50 (20%) < 50% lysis: 13/50 (26%) No lysis: 8/50 (16%) Bleeding: 4/50 (8%) PE: 4/50 (8%)
Laiho et al[81]/ 2004	Retrospective study, single center	32 patients with iliofemoral DVT ≤ 14 d in duration received either CDT (n = 16) or systemic thrombolysis (n = 16)	Thrombolysis: 229 mg (mean) of rt-PA (n = 4) or 6.5 million U of streptokinase (n = 12) for 62 h (mean) plus LMWH and oral anticoagulants	Clot lysis, PE, bleeding, valvular competence	2–3 yr	Thrombolysis: Significant lysis: 5/16 (31%) PE: 5/16 (31%) Bleeding: 1/16 (6%) Valvular competence: 2/16 (13%) Any deep vein incompetence: 81%

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Recommendation

1.10.1. In selected patients with extensive proximal DVT (*eg*, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year) who have a low risk of bleeding, we suggest that systemic thrombolytic therapy may be used to reduce acute symptoms and postthrombotic morbidity if CDT is not available (Grade 2C)**.**

1.11 Percutaneous Venous Thrombectomy

Percutaneous mechanical venous thrombectomy refers to catheter-based fragmentation of thrombus (*eg*, with pulse-spray or rotational devices) with, or without, aspiration of thrombus fragments.[101] Percutaneous mechanical venous thrombectomy is often combined with CDT, which, collectively, are referred to as *pharmacomechanical thrombolysis*. Because pharmacomechanical thrombolysis was included in the preceding section on CDT (Section 1.9), the current section will be confined to percutaneous mechanical venous thrombectomy without concomitant thrombolysis.

No randomized trials have compared percutaneous mechanical venous thrombectomy with other catheter-based, or noncatheter-based, treatments for DVT. Small retrospective studies suggest that percutaneous mechanical venous thrombectomy alone often fails to remove much of the thrombus[94,101] and is associated with a high risk of PE.[122,123]

Recommendation

1.11.1. In patients with acute DVT, we suggest that they should not be treated with percutaneous mechanical thrombectomy alone (Grade 2C)**.**

1.12 Operative Venous Thrombectomy for Acute DVT

Operative venous thrombectomy is an alternative approach for thrombus removal that is generally reserved for patients with iliofemoral DVT. Contemporary operative techniques[124] and more effective anticoagulant regimens have improved outcomes compared to earlier reports.[125,126] Iliofemoral venous thrombectomy with a temporary arteriovenous fistula plus anticoagulation was compared with anticoagulation alone in a randomized trial of 63 patients who were followed for a long term.[73,82,83] Results at 6 months, 5 years, and 10 years were consistent with improved iliac vein patency, less leg swelling, and fewer leg ulcers (Table 5).[73,82,83] In nine nonrandomized studies[73,80,82,83,127–134] that evaluated venous thrombectomy in 520 limbs of 509 patients, sustained patency was achieved in 65 to 85%, and preservation of femoral-popliteal valve function occurred in 65 to 75% of operated patients. Although operative pulmonary embolization is a concern with this procedure, it is an infrequent complication.[130]

Recommendations

1.12.1. In selected patients with acute iliofemoral DVT (*eg*, symptoms for < 7 days, good functional status, and life expectancy ≥ 1 year), we suggest that operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B). **If such patients do not have a high risk of bleeding, we suggest that CDT is usually preferable to operative venous thrombectomy** (Grade 2C)**.**

1.12.2. In patients who undergo operative venous thrombectomy, we recommend the same intensity and duration of anticoagulant therapy afterwards as for comparable patients who do not undergo venous thrombectomy (Grade 1C)**.**

1.13 Vena Caval Filters for the Initial Treatment of DVT

IVCs (and rarely superior vena caval [SVC]) filters can be used instead of initial anticoagulation (*eg*, unacceptable risk of bleeding), or as an adjunct to anticoagulation, in patients with acute DVT. No randomized trial or prospective cohort study have evaluated IVC filters as sole therapy in patients with DVT (*ie*, without concurrent anticoagulation). Permanent IVC filter insertion as an adjunct to anticoagulant therapy has been evaluated in a single, large RCT of patients with acute DVT who were considered to be at high risk for PE (PREPIC study; Table 6). The findings of that study, which were reported after 2 years[29] and 8 years[135] of follow-up (Table 6), provide the strongest evidence to guide use of IVC filters in patients with acute VTE, and can be summarized as follows. First, routine insertion of filters in patients who are also anticoagulated does not alter the frequency of recurrent VTE (RR, 1.34 at 2 years; and RR, 1.03 at 8 years) or total mortality (RR, 1.08 at 2 years; and RR, 0.95 at 8 years). Second, filters reduce PE at 12 days (RR, 0.4; this estimate includes asymptomatic PE detected by routine lung scanning), 2 years (RR, 0.54), and at 8 years (RR, 0.41). Third, filters increase DVT at 2 years (RR, 1.8) and at 8 years (RR, 1.3; hazard ratio, 1.5; 95% CI, 1.02 to 2.3 in the original report[29]). Fourth, despite more frequent DVT during follow-up and frequent evidence of thrombosis at the filter site in those with recurrent VTE (43% of cases), filters were not associated with a higher frequency of PTS (defined as presence of at least one of edema, varicose veins, trophic disorders or ulcers) [hazard

Table 5—*Operative Venous Thrombectomy for Acute DVT: Clinical Description and Results (Section 1.12)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Kistner and Sparkuhl[130]/ 1979	Case series	70 patients (77 extremities) with acute iliofemoral DVT confirmed by venography	Operative venous thrombectomy	Patency, clinical success, operative PE	4 yr (mean)	Patency: 75% Clinical success: Excellent, 54% Good, 32% Fair, 7% Poor, 7% Operative PE: 8% (three asymptomatic)
Plate et al[73]/1984	RCT, multicenter	58 patients with acute iliofemoral venous thrombosis	Medical: 5,000 U bolus heparin followed by 500 U/kg/24 h adjusted to APTT, and oral anticoagulation (n = 31) Surgical: operative venous thrombectomy with temporary arteriovenous fistula plus anticoagulation as above (n = 27)	PTS sequelae: iliofemoral patency, valve competence	6 mo	Medical: PTS sequelae: 25/27 (93%) Iliofemoral patency: 9/26 (35%) Valve competence: 7/27 (26%) (PE in 1 patient) Surgical: PTS sequelae: 14/24 (58%; $p < 0.005$) Iliofemoral patency: 16/21 (76%, $p < 0.025$) Valve competence: 13/23 (52%; $p < 0.05$) (venous gangrene in 1 patient)
Einarsson et al[127]/ 1986	Prospective registry	70 patients (71 legs) with iliofemoral DVT (age of clot: mean 3 d)	Iliofemoral venous thrombectomy with temporary AVF closed at 6–8 wk, heparin before and after operativion, plus warfarin postoperatively	Venous patency, hematoma, AVF patency, PE, wound infection	56 d (mean)	Patent iliac vein: 88% Hematoma: 11% AVF patency: 86% PE: 4% Wound infection: 26%:
Einarsson et al[128]/ 1986	Follow-up to (66)	57 patients (58 limbs) with prior operative venous thrombectomy and AVF closed at 6–8 wk for iliofemoral DVT	Clinical PTS; venography; venous pressure; venous plethysmography, foot volumetry	Venous insufficiency: Good, fair, poor Venography (vein segment): Normal; postthrombotic, occluded Venous pressure: Normal; abnormal Plethysmography: Normal, abnormal Foot volumetry: Normal, abnormal	9–10 mo	Venous insufficiency: Good: 75% Fair: 20% Poor: 5% Venography (iliofemoral): Normal: 61% Postthrombotic: 23% Occluded: 39% IV pressure: Normal: 82% Abnormal: 18% Plethysmography: Normal: 29% Abnormal: 71% Foot volumetry: Normal: 29% Abnormal: 71%

Table 5—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Juhan et al[129]/ 1987	Retrospective study	41 patients with 42 iliofemoral (n = 24) or iliocaval (n = 18) recent thromboses	Operative venous thrombectomy with temporary arteriovenous fistula (n = 31), IVC interruption (n = 21)	Venous patency, PE, death, hematoma	4 yr	Immediate Patency: Iliac: 93% IVC: 100% Superficial femoral: 66% Popliteal: 82% PE: 0 Death: 0 Hematoma: 6 Late follow-up: 4 yr patency (33 patients): 93%
Torngren and Swendenborg[134]/ 1988	Retrospective study	60 patients with iliofemoral DVT	Operative venous thrombectomy with temporary AVF (closed at 3 mo) and anticoagulation for 6 mo	Venous patency	3 mo–5 yr	Early: Patency: 70% Follow-up: Patency: 54%
Plate et al[82]/ 1990	5-yr follow-up to RCT (Plate 1984, n = 10)	41/58 patients (22 medical, 19 surgical) available for evaluation at 5 yr	Prior treatment Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation	PTS sequelae, iliac patency, venous pressure	5 yr	Medical: PTS sequelae: 6/22 (27%) Iliac patency: 11/22 (50%) Venous pressure: 60 mm Hg (mean) Surgical: PTS sequelae: 2/19 (11%) Iliac patency: 15/19 (78%) Venous pressure: 43 mm Hg (mean; $p < 0.05$)
Neglen et al[132]/1991	Prospective registry	48 patients with iliofemoral DVT of 1–14 d	Operative venous thrombectomy with temporary AVF (closed 6–12 wk after operation) Adjunctive therapy: transvenous percutaneous dilatation of severe iliac stenosis (n = 3)	Patency, PE, clinical symptoms, normal photoplethysmography, successful AVF closure	24 mo (mean)	Patency: Iliofemoral: 88% Popliteal: 94% PE: 16% symptomatic, 31% asymptomatic Symptom free: 81% Normal photoplethysmography (no reflux): 56% AVF closure success rate: 87%
Meissner and Huszeza[131]/1996	Retrospective study	30 patients with acute DVT of the lower extremities	Operative venous thrombectomy with temporary AVF	Patency, PE, swelling	30 d–12 wk	Early: Patency: 100% PE: 0 Follow-up: Patency: 89%

Table 5—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Plate et al[83]/1997	10-yr follow-up to RCT (Plate 1984, n = 10; 1990, n = 20)	30/58 patients (17 from medical arm, 13 from surgical arm) available for evaluation	Prior treatment: Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation	PTS sequelae, iliac patency, venous pressure	10 yr	Medical: PTS sequelae: 15/17 (88%) Iliac patency: 7/17 (41%) Venous pressure: 63 mm Hg (mean) Surgical: PTS sequelae: 7/13 (54%) Iliac patency: 10/12 (83%) Venous pressure: 55 mm Hg (mean)
Juhan et al[80]/1997	Retrospective study	75 patients (77 limbs) with acute iliofemoral venous thrombosis	Operative venous thrombectomy with AVF ligated at 6–8 wk	Iliofemoral system patency, valvular competence, CVI	8.5 yr (mean)	5-yr results (44 limbs): Iliofemoral patency: 84% Valvular competence: 80% CVI, Grade 0/1: 93% 10-yr results (16 limbs): Iliofemoral patency: 84% Valvular competence: 56% CVI, Grade 0/1: 94%
Schwarzbach et al[133]/2005	Retrospective study	20 patients with acute iliofemoral or iliocaval thrombosis	Operative venous thrombectomy with endovascular correction of residual lesions	Primary and secondary patency, clinical outcome per CEAP stage	21 mo (mean)	Patency: Primary: 80% Secondary: 90% Clinical outcome: 13 patients, asymptomatic 1 patient; reticular veins 4 patients; asymptomatic edema 4 patients; symptomatic edema, pain

*AVF = arteriovenous fistula; CVI = chronic venous insufficiency; V-Q = ventilation-perfusion; CEAP = clinical etiologic anatomic pathophysiologic (classification). The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

ratio, 0.87; 95% CI, 0.66 to 1.13]. Fifth, 2.5% (five patients) of the nonfilter group and 1.0% (two patients) of the filter group died of PE during 8 years of follow-up. Sixth, other complications of filter placement are rare (none were reported).

A comprehensive review[136] of mostly retrospective case series of vena caval filter insertions (a total of 6,500 patients in 89 reports who had filters inserted for many different reasons) suggests that venous thrombosis at the site of filter insertion sites is common (*eg*, approximately 10% of patients), that filters can be placed above the renal veins if necessary, and that it is feasible to place filters in the SVC. Epidemiologic data suggest that IVC filters are not associated with an increased risk of recurrent VTE in patients who present with DVT.[137] If an IVC filter is being inserted in a patient with acute DVT or PE because anticoagulant therapy is temporarily contraindicated (*eg*, active bleeding), there is the option of inserting a retrievable filter and removing the filter when it is safe to start anticoagulant therapy. However, the risks and benefits of using a retrievable filter compared with a permanent filter in this setting are uncertain.

Recommendations

1.13.1. For patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (Grade 1A)**.**
1.13.2. For patients with acute proximal DVT if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an IVC filter (Grade 1C)**.**
1.13.3. For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C)**.**

1.14 Immobilization for the Treatment of Acute DVT

The early treatment of acute DVT with bed rest and anticoagulation has given way to anticoagulation with early mobilization. Randomized trials[138–142] and observational studies[143–145] show faster resolution of pain and swelling with early ambulation and leg compression compared with immobilization, and a similar incidence of new PE on routine repeat lung scanning after 10 days of treatment (Table 7). These observations suggest that mobile patients with DVT should remain ambulant.

Recommendation

1.14.1. In patients with acute DVT, we recommend early ambulation in preference to initial bed rest when this is feasible (Grade 1A)**.**

2.0 Long-term Treatment of Acute DVT of the Leg

In this review, long-term treatment refers to treatments that are continued after initial therapy, such as with heparin or thrombolytic agents, has been completed. Long-term therapy has two goals: (1) to complete treatment of the acute episode of VTE; and (2) to prevent new episodes of VTE that are not directly related to the acute event. During the early phase of long-term treatment (*ie*, first 3 months), treatment of the acute episode of VTE predominates. During the late phase of long-term treatment (*ie*, after the first 3 months), prevention of new episodes of VTE predominates. We will use the term *indefinite anticoagulation* to refer to anticoagulation that is continued without a scheduled stop date, but which may be stopped because of a subsequent increase in the risk of bleeding or change in patient preference.

The need for long-term anticoagulant treatment of DVT after 5 to 10 days of initial heparin therapy is supported by three lines of evidence from RCTs: (1) a randomized trial in which no long-term anticoagulant treatment was administered to patients with symptomatic calf-vein thrombosis, which documented a 20% rate of symptomatic extension and/or recurrence of thrombosis within 3 months[146]; (2) a randomized trial that evaluated SC low-dose UFH (5,000 U bid) as an alternative to VKA for long-term treatment after proximal DVT, in which the low-dose UFH regimen proved ineffective and resulted in a high rate of recurrent VTE (47% within 3 months)[147]; and (3) randomized trials in which reduced durations of treatment of 4 or 6 weeks resulted in clinically important increases in recurrent VTE, compared to conventional durations of treatment of 3 months or 6 months.[148–150]

In this section, we will address three issues relating to long-term anticoagulant therapy for DVT: (1) the optimal duration of treatment (usually with VKA), (2) the optimal intensity of treatment with VKA, and (3) the relative effectiveness and safety of alternative approaches to long-term VKA treatment, particularly LMWH. We will review studies that included patients with symptomatic DVT, or both symptomatic DVT and PE. Studies that only included patients with symptomatic PE, with or without concomitant symptomatic DVT, are considered in later sections of this

Table 6—*Randomized Trial of IVC Filter as an Adjunct to Anticoagulation in Patients With DVT: Clinical Description and Results (Section 1.13)**

Study/yr	Interventions	Patients Analyzed	Length of Follow-up	Recurrent VTE	Major Bleeding	Total Mortality	Comments
PREPIC[29]/ 1998	Permanent IVC filter (56% Vena Tech LGM; 26% Greenfield; 16% Cardial or Birds Nest; 2% no filter) No IVC filter	12 d 372 patients (reasons why 28 patients were not analyzed are described; estimated that 183 filter and 189 no filter were analyzed)	12 d	All PE at 12 d Filter: 2/183 (1.1%) No filter: 9/189 (4.8%) RR, 0.23 (95% CI, 0.05–1.05) Symptomatic PE at 12 d Filter: 2/183 (1.1%) No filter: 5/189 (2.6%) RR, 0.41 (95% CI, 0.08–2.1)	Major bleeding at 12 d Filter: 9/200 No filter: 6/200 RR: 1.5 (95% CI, 0.54–4.14)	Mortality at 12 d Filter: 5/200 No filter: 5/200 RR, 1.0 (95% CI, 0.29–3.40)	400 patients with proximal DVT: femoral or more proximal vein involved in 94%; concomitant symptomatic PE in 36%; mean age, 72 yr; all patients were treated with LMWH or UFH (randomized allocation; factorial design) followed by VKAs (INR 2–3) for at least 3 mo; primary outcome was symptomatic or asymptomatic PE at 12 d Other than thrombosis at the filter site that was detected in 16 of the 37 filter patients with recurrent VTE, "no other major complications were observed" in the filter group. Enrollment was stopped at 400 instead of 800 patients because of slow recruitment
		2 yr 399 patients analyzed for death; denominators are estimated from percentages and reason for differences are not described	2 yr	Symptomatic PE at 2 yr Filter: 6/176 (3.4%) No filter: 12/190 (6.3%) RR, 0.54 (95% CI, 0.21–1.41) Symptomatic DVT at 2 yr Filter: 37/178 (20.8%) No filter: 21/181 (11.6%) RR, 1.78 (95% CI, 1.09–2.94) Symptomatic VTE at 2 yr Filter: 37/178 (20.8%) No filter: 29/187 (15.5%) RR, 1.34 (95% CI, 0.86–2.08)	Major bleeding at 2 yr Filter: 17/193 (8.8%) No filter: 22/186 (11.8%) RR, 0.74 (95% CI, 0.41–1.36)	Mortality at 2 yr Filter: 43/199 (21.6%) No filter: 40/199 (20.1) RR, 1.08 (95% CI, 0.73–1.58)	

Table 6—*Continued*

Study/yr	Interventions	Patients Analyzed	Length of Follow-up	Recurrent VTE	Major Bleeding	Total Mortality	Comments
PREPIC[135]/ 2005	Same patients as for PREPIC 1998	399 analyzed for death Denominators are estimated from percentages and reason for differences are not described	8 yr	Symptomatic PE at 8 yr Filter: 9/145 (6.2%) No filter: 24/159 (15.1%) RR, 0.41 (95% CI, 0.20–0.86) Symptomatic DVT at 8 yr Filter: 57/160 (35.7%) No filter: 41/150 (27.5%) RR, 1.3 (95% CI: 0.93–1.82) Symptomatic DVT and PE at 8 yr Filter: 58/159 (36.4%) No filter: 55/155 (35.4%) RR, 1.03 (95% CI, 0.72–1.38)	Major bleeding at 8 yr Filter: 26/169 (15.4%) No filter: 31/168 (18.5%) RR, 0.83 (95% CI. 0.52–1.34)	Mortality at 8 yr Filter: 98/200 (49%) No filter: 103/200 (51%) RR, 0.95 (95% CI, 0.78–1.16) Fatal PE at 8 yr Filter: 2/200 (1.0%) No filter: 5/200 (2.5%) RR, 0.40 (95% CI, 0.08–2.04)	Long-term follow-up of PREPIC study; VKAs were stopped at 3 mo in 38% of filter group and 36% of no-filter group; VKAs were used throughout 8 yr follow-up by 35% of both groups; elastic stockings were worn throughout 8-yr follow-up by 45% of filter and 47% of no-filter group

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

chapter (Sections 4.0 and 5.0). However, for the reasons noted in Section 4.0, the results of all studies of VTE have been considered when formulating recommendations for long-term treatment of DVT and PE, and the main recommendations for long-term anticoagulant therapy do not differ for proximal DVT or PE.

2.1. Duration of Anticoagulant Therapy

Anticoagulant therapy for VTE should be continued for the following: (1) until its benefits (reduction of recurrent VTE) no longer clearly outweigh its risks (increase in bleeding), or (2) it is patient preference to stop treatment even if continuing treatment is expected to be of net benefit. In order to assess if the benefits of continuing anticoagulant therapy will outweigh its risks, the increase in recurrent VTE and the decrease in bleeding that will occur with stopping treatment need to be known or estimated. In addition, the consequences of a new episode of VTE and of an episode of bleeding need to considered.[151,152] In patients with an average risk of bleeding while receiving anticoagulant therapy, therefore, the decision to stop or continue therapy is dominated by the risk of recurrent VTE if treatment is stopped.

Current evidence suggests that the risk of recurrence after stopping therapy is largely determined by two factors: (1) whether the acute episode of VTE has been effectively treated; and (2) the patient's intrinsic risk of having a new episode of VTE (*ie*, not arising directly from the episode of thrombosis for which patients have been receiving treatment). If therapy is stopped before the acute episode of thrombosis is adequately treated, the risk of recurrent VTE will be higher than if anticoagulants were stopped after a longer course of treatment. If patients have a persistently high intrinsic risk for thrombosis, even if the acute episode of thrombosis has effectively been treated, they will have a high risk of recurrence once anticoagulant therapy is stopped; if this risk is sufficiently high relative to the patient's risk of bleeding, long-term anticoagulant therapy will be indicated.

During the past 15 years, a series of trials[148–150,153–162] have compared different durations of anticoagulant therapy for VTE (Table 8). Most of these studies[163–166] excluded patients with active cancer because they were judged to require long-term anticoagulant therapy because of a high risk of recurrence. The earlier trials,[148,149,162] in addition to comparing outcomes with different durations of treatment, identified that the risk of recurrent VTE after stopping VKA therapy was much lower if VTE had been provoked by a reversible risk factor, such as surgery, rather than if the episode

Table 7—*Immobilization for the Treatment of Acute DVT: Clinical Description and Results (Section 1.14)***

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Schellong et al[142]/ 1999	RCT, single center	126 patients with acute proximal DVT	Ambulation: leg elevation until day 2, then ambulation, compression (n = 64) Bed rest: Bed rest for 8 d with leg elevation, compression (n = 62)	PE by ventilation/ perfusion scan	10 d	Ambulation: PE: 10/59 (17%) Bed rest: PE: 14/63 (22%)
Partsch and Blattler[141]/ 2000	RCT, multicenter	45 patients with proximal DVT < 14 d duration	Ambulation plus bandages: inelastic Unna boot bandages plus walking exercises, (n = 15) Ambulation plus stockings: elastic compression stockings plus walking exercises (n = 15) Bed rest: bed rest, no compression, LMWH (n = 15)	Walking distance, pain levels, leg circumference, clinical scores, PE, side effects	9 d	Summary results between groups: Walking distance, pain, leg circumference and clinical scores significantly improved in groups A and B compared to group C PE, group A: 2/15 (13%) PE, group B: 1/15 (7%) PE, group C: 1/15 (7%)
Aschwanden et al[138]/2001	RCT, single center	129 patients with acute DVT	Ambulation: Ambulation ≥ 4 h/d for 4 d under supervision, LMWH (n = 69) Bed rest: Bed rest for 4 (n = 60)	New PE between baseline and day 4 by ventilation/ perfusion scan	3 mo	Ambulation: PE: 10/69 (14%) Bed rest PE: 6/60 (10%) Note: new PEs were asymptomatic; 12/16 patients had baseline PEs
Partsch[143]/2001	Prospective study	1,289 patients with acute DVT	All treated with LMWH, compression, and immediate ambulation	PE on ventilation/ perfusion scan at hospital admission and after 10 d of treatment	10 d	PE at admission: 629/1,270 (50%) PE at 10 d: 77/1,256 (61%) Note: initial lung scans were performed in 1,270/1,289 patients; f/u scans were performed in 1,256/1,289 patients.
Blattler and Partsch[139]/2003	RCT	53 patients with proximal DVT	Ambulation plus bandages: firm inelastic bandages, ambulation (n = 18) Ambulation plus stockings: elastic compression stockings, ambulation (n = 18) Bed rest only (n = 17)	Walking distance, well-being and DVT-related QOL, leg pain by VAS, edema, clinical scores, thrombus progression	9 d	Well-being/QOL: Improved with stockings ($p < 0.05$) bandages ($p < 0.01$) Leg pain: Decreased faster during first 4 d with bandages and stockings vs bed rest (p [lt 0.01); near absence of pain at 9 d achieved with bandages only Edema: Marked reduction in leg size with bandages and stockings vs bed rest ($p < 0.001$) Clinical scores: Improved with bandages and stockings vs bed rest ($p < 0.001$) Thrombus progression: Improved with bandages and stockings vs bed rest ($p < 0.01$) PE: No difference between groups

Table 7—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Partsch et al[144]/ 2004	2-yr follow-up to RCT (n = 77)	37 patients followed up 2 yr after RCT	Anticoagulation and bed rest vs Anticoagulation and ambulation with compression bandages or stockings	PTS assessment (Villalta-Prandoni scale) Pain assessment by VAS and modified Lowenberg test Thrombus regression	2 yr	PTS scores: Ambulatory group (mean score, 5.1) had improved outcome vs bed rest group (mean score, 8.2) [$p < 0.01$] Pain: Lower pain levels in mobile group vs bed rest (not significant) Thrombus extension: No difference in thrombus regression of thrombus remnants between groups
Trujillo-Santos et al[145]/2005	Prospective study	2,650 patients with acute DVT (n = 2038, 77%) or PE (n = 612 , 23%)	DVT group: bed rest or ambulation: 1,050 (52%) patients received bed rest and 988 patients (48%) were ambulated; all received LMWH. PE group, bed rest or ambulation: 385 patients (63%) received bed rest, and 227 patients (37%) were ambulated; all received LMWH	Symptomatic, confirmed PE during first 15 d of therapy	3 mo	DVT group: bed rest: PE: 7/1,050 (0.7%) DVT group: ambulate: PE: 4/988 (0.4%) PE group: bed rest: PE: 2/385 (0.5%) PE group: ambulate: PE: 2/227 (0.9%)
Junger et al[140]/ 2006	RCT, multicenter open design stratified by age	103 patients with proximal DVT	Bed rest: 50 patients received 5 d of strict bed rest, LMWH, compression bandages Ambulation: 52 patients ambulated for 5 d, LMWH, compression bandages	PE, progression of or new thrombosis, infection or serious adverse event	5 d	New PE Bed rest: 8/50 (16%) Ambulation: 2/52 (4%) Primary target variable Bed rest: 14/50 (28%) Ambulation: 7/52 (13%)

*VAS = visual analogue scale. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 8—*Comparisons of Durations and Intensities of Anticoagulant Therapy for DVT and PE: Clinical Description and Results (Section 2.1)**

Author/yr (Acronym)	Intervention	Pateints Analyzed, No.	Length of Follow-up	Recurrent DVT or PE, No. (Total)	Major Bleeding, No. (Total)	Total Mortality, No. (%)	Comments
Short (4 wk or 6 wk) vs intermediate (3 mo or 6 mo) durations of anticoagulation							
Kearon et al[157]/2004 (SOFAST)	VKA stopped (placebo)	84/84	11 mo	5/84 (6%)	0/84	0/84	Population: first DVT or PE: treated for 1 mo; VTE was asymptomatic in 9%, and isolated calf DVT in 18%; one VTE occurred while during warfarin treatment
	VKA (INR, 2.0–3.0) for 2 more mo	81/81	11 mo.	3/81 (4%) RR, 0.6 (95% CI, 0.1–2.5)	0/81 RR,1.0 (95% CI, 0.0–51.6)	1/81 (1%) RR 3.1 (95% CI, 0.1–74.4)	
Pinede et al[160]/2001 (DOTAVK)	VKA (INR, 2.0–3.0) for 1.5 mo.	105/105	15 mo	2/105 (2%)	1/105(1%)	Not specified	Population: first isolated calf DVT
	VKA (INR, 2.0–3.0) for 3 mo	92/92		3/92 RR, 1.7 (95% CI, 0.3–10.0)	3/92 RR,3.4 (95% CI, 0.4–33.4)		
Schulman et al[162]/1995 (DURAC 1)	VKA (INR, 2.0–2.85) for 1.5 mo	443/443	2 yr	80/443 (18%)	1/443	22/443 (5%)	First VTE: DVT (distal or proximal) or PE; only asked about bleeding while receiving VKAs
	VKA (INR, 2.0–2.85) for 6 mo	454/454		43/454 (9%) RR, 0.5 (95% CI, 0.4–0.7)	5/454 (1%) RR, 4.9 (95% CI, 0.6–41.6)	17/454 (4%) RR 0.75 (95% CI, 0.4–1.4)	
Levine et al[148]/1995	VKA stopped (placebo)	105/107	9 mo	12/105 (11%)	0/105	9/105 (9%)	Proximal DVT (first episode in 91%); cancer in 21%
	VKA (INR, 2.0–3.0) for 2 more mo	109/113		7/109 (6%) RR, 0.6 (95% CI, 0.2–1.4)	1/109 (1%) RR, 2.9 (95% CI, 0.1–70.2) within 2 mo of randomization	9/109 (8%) RR, 1.0 (95% CI, 0.4–2.5)	
British Thoracic Society[149]	VKA (INR, 2.0–3.0) for 1 mo	358/358	1 yr	28/358 (11%)	5/358 (1%)	26/358 (7%)	Population: DVT or PE; only 71% objectively diagnosed; proportion with a previous VTE not known.
	VKA (INR, 2.0–3.0) for 3 mo	354/354	1 yr	14/354 (4%) RR, 0.5 (95% CI, 0.3–0.9)	4/354 (1%) RR, 0.8 (95% CI, 0.2–3.0)	28/354 (8%) RR, 1.1 (95% CI, 0.6–1.8)	All bleeds were receiving VKA; only one recurrent VTE among 116 patients with postoperative VTE
Summary		2,198		RR 0.53 (0.40, 0.70)	RR 1.84 (0.76, 4.50)	RR 1.04 (0.74, 1.48)	For all analyses, p = >0.1 for heterogeneity. SOFAST[80] not included in estimate for major bleeding as no events in either group

Table 8—*Continued*

Author/yr (Acronym)	Intervention	Pateints Analyzed, No.	Length of Follow-up	Recurrent DVT or PE, No. (Total)	Major Bleeding, No. (Total)	Total Mortality, No. (%)	Comments
Different intermediate durations (6 mo or 12 mo vs 3 mo) of anticoagulation							
Campbell et al[155]/2007	VKA (INR 2..0–3.5) for 3 mo	369/396	1 yr	31/369 (8%)	0/369 (during 3 mo of treatment) 8/380 (2%) during 6	15/369 (4%)	Population: DVT or PE; proportion with calf DVT not known;
	VKA (INR 2.0–3.5) for 6 mo	380/414	1 yr	29/380 (8%) RR, 0.9 (95% CI, 0.6–1.5)	mo of treatment RR, 16.5 (95% CI, (1.0–285)	9/369 (5%) RR,1.3 (95% CI, 0.6–2.5)	Only bleeding during treatment is reported. 20% of VTE outcomes were not objectively verified
Agnelli et al[153]/2003 (WODIT-PE)	VKA stopped	91/91	2.6 yr (mean) 2.9 yr (mean)	11/91 (12%)	1/91 (1%)	7/91 (8%)	Population: first unprovoked PE; treated for ≥ 3 mo; among the four groups, only one recurrent VTE while receiving VKA
	VKA (INR, 2.0–3.0) for 9 more mo	90/90		11.90 (12%) RR, 1.0 (95% CI, 0.5–2.2)	2/90 (2%) RR, 2.0 (95% CI, 0.5–21.9)	8/90 (9%) RR,1.16 (95% CI, 0.4–3.0)	
	VKA stopped	70/70	2.8 yr (mean) 2.9 yr (mean)	7/70 (10%)	0/70 (0%)	0/70 (0%)	Population: first provoked PE; treated for ≥ 3 mo (see previous)
	VKA (INR, 2.0–3.0) for 3 more mo	75/75		4/75 (5%) RR, 0.5 (95% CI, 0.2–1.7)	1/75 (1%) RR, 1.9 (95% CI, 0.1–56)	4/75 (5%) RR, 8.4 (95% CI, 0.5–153)	
Agnelli et al[154]/2001 (WODIT – DVT)	VKA stopped	133/133	3.2 yr (mean) 3.1 yr (mean)	21/133 (16%)	2/133 (2%)	7/133 (5%)	Population: First unprovoked proximal DVT treated for 3 mo; one patient had recurrent VTE while receiving VKA; bleeding in the intervention group was while receiving VKA
	VKA (INR, 2.0–3.0) for 9 mo	134/134		21/134 (16%) RR, 1.0 (95% CI, 0.6–1.7)	4/134 (3%) RR, 2.0 (95% CI, 0.4–10.7)	7/134 (5%) RR, 1.0 (95% CI, 0.4–2.8)	
Pinede et al[160]/2001 (DOTAVK)	VKA (INR, 2.0–3.0) for 3 mo	270/270	15 mo	21/270 (8%)	5/270 (2%)	Not specified	Population: first proximal DVT or PE; recurrent VTE occurred after VKA in 26/28 of the short-duration groups and 21/27 of the long-duration groups
	VKA (INR, 1.0–3.0) for 6 mo	269/269		23/269 (9%) RR, 1.1 (95% CI, 0.6–1.9)	7/269 (3%) RR, 1.4 (95% CI, 0.4–4.4)		
Summary		1,881		RR, 0.95 (95% CI, 0.72–1.26)	RR, 2.53 (95% CI, 1.18–5.46)	RR, 1.3 (95% CI, 0.82–2.08)	For all analyses, $p > 0.1$ for heterogeneity
Indefinite vs intermediate durations of anticoa gulation (INR, approximately 20–3.0)							
Palereti et al[159]/2006 (PROLONG)	Remain off (stop) VKA	103/105	1.4 yr (mean), maximum 1.5 yr	18/103 (17%)	0/103	1/103 (1%)	Population: First unprovoked proximal DVT or PE; treated for ≥ 3 mo; VKA stopped and d-dimer positive 1 mo later Eight control patients; restarted VKA, some after superficial phlebitis; one recurrent VTE in VKA group after VKA stopped.
	Restart Indefinite VKA (INR, 2.0–3.0) not blinded	120/122		2/120 (2%) RR, 0.1 (95% CI, 0.0–0.4)	1/120 (1%) RR, 2.6 (95% CI, 0.1–62.6)	1/120 (1%) RR, 0.9 (95% CI, 0.1–13.6)	

Table 8—*Continued*

Author/yr (Acronym)	Intervention	Pateints Analyzed, No.	Length of Follow-up	Recurrent DVT or PE, No. (Total)	Major Bleeding, No. (Total)	Total Mortality, No. (%)	Comments
Kearon et al[156]/1999 (LAFIT)	VKA stopped	83/83	10 mo (mean), maximum 2 yr)	17/83 (20%)	0/83	3/83 (4%)	Population: first unprovoked proximal DVT or PE (5%) had previous provoked VTE; recurrent VTE in the VKA patient was after stopping VKA
	(Placebo)	79/79					
	VKA (INR, 2.0–3.0) for 2 more yr			1/79 (1%) RR, 0.1 (95% CI, 0.0–0.5)	3/79 (4%) RR, 7.4 (95% CI, 0.4–140)	1/79 (1%) RR, 0.3 (95% CI, 0.0–3.3)	
Schulman et al[150]/1997 (DURAC 2)	VKA (INR, 2.0–2.85) for 6 mo	111/111	4 yr	23/111 (2%)	3/111 (3%)	16/111 (14%)	Second VTE: DVT (distal or proximal) or PE; all recurrent VTEs in the indefinite VKA group were after stopping VKAs; bleeding during the first 6 mo of VKA in one patients in 6-mo group and six patients in indefinite group (only asked about bleeding while receiving VKAs)
	VKA (INR, 2.0–2.85) Indefinitely	116/116		3/116 (3%) RR, 0.1 (95% CI, 0.0–0.4)	10/116 (9%) RR, 3.2 (95% CI, 0.9–11.3)	10/116 (9%) RR, 0.6 (95% CI, 0.3–1.3)	
Summary				RR, 0.1 (95% CI, 0.04–0.22)	RR, 3.61 (95% CI, 1.22–10.7)	RR, 0.58 (95% CI, 0.29–1.14)	For all analyses, $p > 0.1$ for heterogeneity
Indefinite vs intermediate durations of anticoagulation (INR, approximately 5–2.0 after initial INR of 2.0–3.0 in both groups)							
Ridker[161]/2003 (PREVENT)	VKA stopped or not restarted	253/253	2.1 yr (mean), maximum, 4.3 yr	37/253 (15%)	2/253 (1%)	8/253 (3%)	Population: Unprovoked DVT (distal or proximal) or PE (first episode in 38%); eight recurrent VTEs in the VKA group after stopping VKAs
	(Placebo)	255/255		14/255 (5%) RR, 0.4 (95% CI, 0.2–0.7)	5/255 (2%) RR, 2.5 (95% CI, 0.5–12.7)	4/255 (2%) RR, 0.5 (95% CI, 0.1–1.6)	
	VKA (INR, 1.5–2.0)						
Low-intensity (INR, 1.5–1.9) vs conventional intensity (INR, 2.0–3.0)							
Kearon[185]/2003 (ELATE)	VKA (INR, 1.5–1.9)	369/369	2.4 yr (mean)	16/369 (4%)	9/369 (2%)	16/369 (4%)	Population: Unprovoked proximal DVT or PE (first episode in 31%); treated for ≥ 3 mo. VKA (INR, 2.0–3.0); mean, 12 mo; five recurrent VTEs in INR of 1.5–1.9 and three in INR of 2.0–3.0 group after stopping VKAs
	VKA (INR, 2.0–3.0), blinded	369/369		6/369 (2%) RR, 0.4 (95% CI, 0.1–0.9)	8/369 (2%) RR, 0.9 (95% CI, 0.3–2.3)	8/369 (2%) RR, 0.5 (95% CI, 0.2–1.2)	

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

of VTE was unprovoked (also called *idiopathic VTE*). This observation was also made in a number of other prospective studies[166,167] during the same period. Consequently, many of the more recent trials that compared durations of VKA therapy selectively enrolled patients with either unprovoked VTE,[153,154,156,158,159,161] or VTE that was provoked by a reversible risk factor[157] (Table 8). Longer or indefinite durations of anticoagulant therapy were generally evaluated in patients with unprovoked VTE, and shorter durations of therapy were evaluated in patients with a reversible provoking factor. Because the presence of a reversible provoking risk factor,[148,149,160,162,163,165–170] unprovoked VTE,[148,149,160,162,163,165–170] and presence of active cancer[163–166] were used to select patients for many of the studies, and have been shown to be the most important factors that influence risk of recurrent VTE after stopping VKA, separate recommendations for duration of anticoagulant therapy will be made for each of these three categories of patients with VTE. Reversible provoking risk factors include the following: major factors such as surgery, hospitalization, or plaster cast immobilization, all within 1 month; and minor factors such as estrogen therapy, pregnancy, prolonged travel (*eg*, >8 h), or the previously noted major factors when they have occurred 1 to 3 months before diagnosis of VTE. The greater the provoking reversible risk factor (*eg*, such as recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.[168] Within each of these three groups, we will consider if there are additional factors that influence the risk of recurrence enough to modify recommendations about duration of therapy. The most important of such factors are the following: (1) whether DVT was confined to the distal veins (often called *isolated calf* DVT) or involved the proximal veins,[160,162,170] and (2) whether the DVT was a first episode of VTE or a second or subsequent episode of VTE.[161,164,171] The presence of hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies[156,161,168,169,172–180] suggests that these factors are not major determinants of the risk of recurrence.

VKAs for the Long-term Treatment of DVT

Clinical trials that have evaluated different durations of anticoagulant therapy can be divided into three categories according to the durations of therapy that were compared: (1) short vs intermediate durations, (2) different intermediate durations, and (3) indefinite therapy vs intermediate durations. Within each of these categories we will first consider studies that included heterogeneous (*ie*, less selected) patients with VTE, and then studies that enrolled subgroups of (*ie*, selected) patients who were expected to have either a lower (*eg*, associated with reversible risk factors) or a higher (*eg*, unprovoked, or second episodes, of VTE) risk of recurrence.

Short (4 Weeks or 6 Weeks) vs Intermediate (3 Months or 6 Months) Durations of Therapy

Five trials[148,149,160,162] have evaluated shortening the duration of oral anticoagulant therapy from 3 or 6 months to 4 or 6 weeks in patients with mostly first episodes of VTE (Table 8). The first three studies (British Thoracic Society, Levine, DURAC 1; Table 8), which mainly enrolled unselected patients with proximal DVT or PE, found that shortening the duration of anticoagulation was associated with about double the frequency of recurrent VTE during follow-up of 1 to 2 years (an absolute risk increase of approximately 5%).[148,149,162] Major bleeding was uncommon during the incremental period of anticoagulation in these three studies (estimated at seven episodes among 1,009 patients during 259 patient-years of additional treatment [2.7%/yr]).[148,149,162] Therefore, the main finding of these studies was that anticoagulant therapy should not be shortened to 4 or 6 weeks in patients with VTE.

Subgroup analyses of one of the above studies (DURAC 1) suggests that isolated distal DVT provoked by a major transient risk factor can safely be treated with only 6 weeks of therapy.[162] A subsequent study,[160] (component of DOTVAK), which compared 6 vs 12 weeks of therapy in patients with isolated calf DVT (unprovoked or provoked; mostly diagnosed by ultrasound), found no suggestion that shortening therapy increased the risk of recurrence (RR, 0.6; 95% CI, 0.01 to 3.4) and, in general, observed a low frequency of recurrent VTE with isolated calf DVT (approximately 2% in the first year) compared to proximal DVT or PE (approximately 6% in the first year). These findings suggest that if anticoagulants need to be stopped after 6 weeks of therapy in patients with isolated distal DVT, the subsequent risk of recurrence is not expected to be excessive. The fifth of these studies[157] enrolled only patients with VTE associated with a major reversible risk factor (SOFAST; Table 8); however, because only 165 patients were enrolled, its findings were not definitive. A metaanalysis of five studies (retrospective identification of the patient's subgroup in four studies,[148,149,162,181] selective enrollment of patients in 1 study[157]) that compared 4 or 6 weeks with 3 or 6 months of treatment among 725 patients with VTE provoked by a reversible risk factor found that the shorter durations of therapy were associated with more

than double the risk of recurrent VTE during the next year (OR, 2.9; 95% CI, 1.2 to 6.9; absolute increase of approximately 3.4%).[157]

Different Intermediate Durations of Therapy (6 Months or 12 Months vs 3 Months)

Two studies[155,160] have compared 6 months vs 3 months of anticoagulant therapy in patients with predominantly first episodes of DVT or PE (unprovoked, or provoked by a reversible risk factor) [DOTAVK, Campbell; Table 8]. There was no difference in the risk of recurrence during follow-up in both studies, and one study[155] reported a lower risk of bleeding in the 3-month group (Campbell; Table 8).

Agnelli and colleagues[154] compared stopping anticoagulant therapy at 3 months with continuing it for another 9 months after a first episode of unprovoked proximal DVT (WODIT-DVT; Table 8). At the end of the first year, recurrent VTE was less frequent in the group that remained on anticoagulant therapy (3.0% vs 8.3%), but this benefit was lost 2 years after these patients stopped anticoagulant therapy (RR, 1.0; 95% CI, 0.6 to 1.7). The same investigators obtained similar results in a comparable study[153] of patients with unprovoked PE (WODIT PE; Section 5.1, Table 8).

Based on the findings of these five studies (the "provoked" and "unprovoked" components of the WODIT-PE study are have been condidered separate studies),[153–155,160] anticoagulants are very effective at preventing recurrence while patients are receiving therapy; but, at the end of extended follow- up after stopping treatment, a similar risk of recurrence is expected if anticoagulants are stopped at 6 or 12 months, compared to at 3 months (RR for the five studies, 0.95; 95% CI, 0.72 to 1.26; Table 8), including among patients with unprovoked proximal DVT or PE.

Indefinite vs Intermediate Durations of Anticoagulant Therapy

Four trials have compared indefinite (where *indefinite* refers to extended therapy without scheduled stopping of treatment) anticoagulation (target INRs, 2.0 to 2.85,[150] 2.0 to 3.0,[156,159] and 1.5 to 2.0[161]) with stopping therapy in patients with VTE who were believed to have a high risk of recurrence because thrombosis was a second episode,[150] unprovoked,[156,161] or was unprovoked and had a positive d-dimer result 1 month after stopping therapy[159] (DURAC 2, LAFIT, PREVENT, PROLONG; Table 8). The results indicate that randomization to indefinite treatment with conventional-intensity VKA (target INR, 2.5) reduces recurrent VTE by approximately 90% (RR for the three studies, 0.10; 95% CI, 0.04 to 0.22; Table 8),[150,156,159] and randomization to low-intensity therapy (target INR, 1.75) reduces VTE by 64% (95% CI for HR, 23 to 81%)[161] (Table 8; both RRs are appreciably greater among patients who remain on VKA therapy).

The benefit of indefinite treatment with VKA is partially offset by the risk of major bleeding. In the two initial studies[150,156,182] of extended treatment (DURAC 2, LAFIT; Table 8), the incidence of major bleeding was approximately 3%/yr during extended treatment with conventional-intensity warfarin (included bleeding during the first 6 months of therapy in DURAC 2). However, in the more recent PROLONG study[159] and a randomized comparison of conventional-intensity and low-intensity VKA (ELATE; Table 8),[158] extended treatment with conventional-intensity VKA was associated with a risk of major bleeding of approximately 1% per patient-year (low-intensity VKA is considered in Section 2.2). A meta-analysis[184] of seven studies[115,148,154,156,161,171,183] that compared durations of conventional-intensity anticoagulant therapy for VTE estimated the rate of major bleeding to be 1.1% per patient-year (18 episodes in 1,571 patient-years) during the extended phase of anticoagulation compared with 0.6% per patient-year (9 episodes during 1,497 patient-years) without anticoagulation (RR, 1.80; 95% CI, 0.72 to 4.51). Thus, for patients with unprovoked DVT (and PE), the benefit of long-term treatment is partially offset by a higher risk of bleeding, and patients lose protection against recurrent VTE if anticoagulants are withdrawn. For these reasons, values and preferences regarding preventing recurrent thromboembolism, avoiding bleeding complications and inconvenience of treatment, bear on the recommendation for long-term anticoagulant treatment for unprovoked VTE, particularly after a first episode of DVT (lower risk of recurrence than after a second episode of VTE,[161,164,171] and expected to have a lower risk of death with a recurrence than after a first episode of PE[164,185]).[186] Individual patient risk of recurrent VTE and of major bleeding may differ from the average values that have been reported in the previously noted trials and, in selected patients, may influence the decision to continue or stop anticoagulant therapy once 3 months of initial treatment has been completed, or subsequently.

Of factors that have been evaluated as risk factors for recurrent VTE among patients with unprovoked DVT, the following appear to have the greatest potential to be clinically useful: isolated calf DVT vs proximal DVT (RR, approximately 0.5)[160,162,170]; one or more previous episodes of VTE (RR, approximately 1.5)[161,164,171]; negative d-dimer findings 1 month after withdrawal of VKA (RR, approximately 0.4)[159,177,187,188]; antiphospholipid antibody (RR, approximately 2)[156,179,189];

hereditary thrombophilia (RR, approximately 1.5)[156,161,168,169,173–175,177]; males vs females (relative risk ~ 1.6)[190]; Asian ethnicity (RR, approximately 0.8)[191]; and residual thrombosis in the proximal veins (RR, approximately 1.5).[153,156,157,192–194]

Of factors that have been evaluated as risk factors for major bleeding during anticoagulant therapy, the following appear to have the greatest potential to be clinically useful markers of increased risk: older age, particularly after 75 years; previous GI bleeding, particularly if not associated with a reversible cause; previous noncardioembolic stroke; chronic renal or hepatic disease; concomitant antiplatelet therapy (to be avoided if possible); other serious acute or chronic illness; poor anticoagulant control; suboptimal monitoring of anticoagulant therapy (see chapter on Hemorrhagic Complications of Anticoagulant and Thrombolytic Therapy[195]).[158,195–202]

Recommendations

2.1.1. For patients with DVT secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A)**.**

2.1.2. For patients with unprovoked DVT, we recommend treatment with a VKA for at least 3 months (Grade 1A)**. We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-to-benefit ratio of long-term therapy** (Grade 1C)**. For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment** (Grade 1A)**.** *Values and preferences:* This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A)**. For patients with a first isolated distal DVT that is unprovoked, we suggest that 3 months of anticoagulant therapy is sufficient rather than indefinite therapy** (Grade 2B)**.**

2.1.3. For patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A)**. For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4)** [Grade 1C]**.**

2.1.4. For patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C)**.**

2.2 Intensity of Anticoagulant Effect

The preferred intensity of the anticoagulant effect of treatment with VKA has been established by the results of randomized trials.[158,203–205] The ELATE study was a randomized, blinded trial that compared low-intensity VKA (target INR, 1.5 to 1.9) with conventional-intensity VKA (INR, 2.0 to 3.0) for indefinite treatment of patients with unprovoked VTE who had completed at least 3 months of initial conventional-intensity anticoagulation (Table 8). The incidences of recurrent VTE were 1.9% per patient-year in the low-intensity group, and 0.6% per patient-year in the conventional-intensity group (hazard ratio, 3.3; 95% CI, 1.2 to 9.1).[158] The incidences of major bleeding were 0.96% per patient-year in the low-intensity group and 0.93% per patient-year in the conventional-intensity group; the corresponding incidences of all bleeding (major and minor) were 4.9% per patient-year and 3.6% per patient-year. Thus, low-intensity VKA treatment was less effective than conventional-intensity therapy and did not provide a safety advantage.[158] The observed incidence of recurrent VTE of 1.9% per patient-year in the low-intensity group is similar to the incidence of 2.6% per patient-year in the PREVENT study,[161] which compared low-intensity warfarin therapy (INR, 1.5 to 2.0) with placebo (the latter group had an incidence of recurrent VTE of 7.2% per patient-year; hazard ratio, 0.36 compared with placebo; 95% CI, 0.19 to 0.67). Taken together, the results of these two randomized trials[158,161] indicate that after 3 months of conventional-intensity therapy, although low-intensity warfarin therapy is much more effective than placebo, it is less effective than conventional-intensity therapy and does not appear to reduce the incidence of bleeding complications.

In the PREVENT trial,[161] low-intensity anticoagulation was delivered using a dosing nomogram that scheduled INR measurements 8 weeks apart, provided the current INR result was 1.3 to 3.0. This nomogram resulted in an average interval between INR tests of 61 days compared with an average interval of 26 days in the conventional-intensity group of the ELATE trial,[158] in which ordering of INR measurements was at the discretion of the responsible clinician. Thus, the findings of the PREVENT trial suggest that anticoagulant monitoring can be simplified, and made less burdensome to patients and health-care providers, when the target INR is 1.75 (range, 1.5 to 2.0) rather than 2.5 (range, 2.0 to 3.0). Some patients may prefer to be treated with a lower intensity of VKA therapy that is delivered with less frequent INR monitoring that to

receive conventional-intensity therapy that, although more effective, requires more frequent INR monitoring.

Additional important evidence regarding the optimal intensity of anticoagulant therapy with VKA is provided by the PAPRE[203] and WAPS[204] randomized trials that compared conventional-intensity VKA therapy (INR, 2.0 to 3.0) with high-intensity warfarin therapy (INR, 3.1 to 4.0[203] and 3.0 to 4.5[204]) for the prevention of recurrent thromboembolism in patients with antiphospholipid antibodies and a history of venous or arterial thromboembolism (Table 9). In the two studies combined, there was no evidence that the higher intensity of anticoagulation was associated with a lower frequency of recurrent thromboembolism (OR, 2.49; 95% CI, 0.93 to 6.67), and no difference in major bleeding (OR, 0.73; 95% CI, 0.23 to 2.31), or minor bleeding (OR, 1.75; 95% CI, 0.93 to 3.31).[204] However, high-intensity VKA therapy has previously been shown to be associated with high rates of bleeding in patients with VTE.[147,205,206] The evidence outlined above provides the basis for the recommendation of an INR of 2.0 to 3.0 as the preferred intensity of long-term anticoagulant treatment with VKA in all patients with VTE.

Recommendation

2.2.1. In patients with DVT, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 to 3.0) for all treatment durations (Grade 1A)**. For patients with unprovoked DVT who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of conventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (INR range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment** (Grade 1A)**. We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared to an INR range of 2.0 to 3.0** (Grade 1A)**.**

2.3 SC UFH for the Long-term Treatment of DVT

Adjusted-dose SC UFH is an effective approach for the long-term treatment of DVT,[206] whereas low-dose UFH (5,000 U bid) is inadequate for this purpose.[147,207] In a study[208] of 80 patients with DVT and contraindications to VKA therapy that compared 10,000 U of UFH with 5,000 IU of dalteparin, each administered SC twice daily for 3 months, there was a similar low frequency of recurrent VTE and bleeding in both groups, but less frequent spinal fracture in the LMWH group. Because of the lower potential for osteoporosis with LMWH and because it can be administered once daily without the need for anticoagulant monitoring, LMWH is preferred to UFH for long-term therapy.

2.4 LMWH for the Long-term Treatment of DVT

Twelve randomized trials have compared VKA (INR, 2.0 to 3.0) with widely differing regimens of five LMWH preparations (dalteparin,[209–211] enoxaparin,[167,212–214] nadroparin,[215,216] tinzaparin,[217,218] bemiparin[34]). In these studies, the daily LMWH dose was as low as 4,000 IU[167,212] to as high as 200 IU/kg[211,216]; approximately a 3.5-fold difference. Two metaanalyses of studies that compared LMWH with VKAs, each administered for 3 months after initial heparin therapy, have been performed.[219,220] In the analysis by Iorio and colleagues,[219] which includes seven studies[167,209,212,214–217] and a total of 1,379 patients, there were trends toward less recurrent VTE (OR, 0.66; 95% CI, 0.41 to 1.07) and less major bleeding (OR, 0.45; 95% CI, 0.18 to 1.11) with 3 months of LMWH compared with VKA. Compared with outcomes in patients who received VKA therapy, between study differences of mean daily dose of LMWH had little effect on efficacy but did appear to influence the risk of major bleeding (OR, approximately 0.2 with approximately 4,000 IU/d to approximately 0.7 with 12,000 IU/d, relative to the VKA groups [$p = 0.03$]).[219] Three subsequent studies that selectively enrolled a total of 1,029 patients with VTE in association with active cancer found that, compared to VKA therapy, 3 months[213,221] or 6 months[211] of therapeutic-dose LMWH was associated with less recurrent VTE in one study[211] and less bleeding in another study[213] (Table 10) [RR for the three studies: recurrent VTE, 0.56; 95% CI, 0.38 to 0.82; major bleeding, 1.01; 95% CI, 0.62 to 1.64; mortality, 0.92; 95% CI, 0.78 to 1.10; Table 4].[213,219,221] Randomized trials have not evaluated approaches to anticoagulant therapy after the first 6 months of VKA or LMWH therapy in patients with VTE and cancer, either to assess duration of therapy or to compare extended therapy with VKA or LMWH. Observational studies[163–166] suggest that the risk of recurrent VTE is unacceptably high in patients with active cancer who stop anticoagulant therapy.

2.5 New Antithrombotic Agents for Long-term Treatment of DVT

Ximelagatran (since withdrawn because of hepatic toxicity) has been evaluated for both short-term and long-term treatment of VTE.[61,171] In the short-term treatment study,[61] 2,491 patients with acute DVT were treated for 6 months with ximelagatran, 36 mg bid, or LMWH followed by VKA therapy (INR, 2.0 to 3.0), using a blinded design. The frequency of recurrent VTE at 6 months was similar with ximelagatran (2.1%)

and usual therapy (2.0%), and an "on treatment" analysis ("intention to treat" analysis was not reported) suggested less major bleeding with ximelagatran (1.3% vs 2.2%; 95% CI for difference, − 2.0% to + 0.2%). In the long-term treatment study,[171] 18 months of ximelagatran (24 mg bid) was compared with placebo in 1,224 patients with DVT or PE who had completed 6 months of initial treatment with VKA. Ximelagatran reduced recurrent VTE by 84% (95% CI, 70 to 91%) without an apparent increase in major bleeding (hazard ratio, 1.2; 95% CI, 0.4 to 3.8). Many new anticoagulants are being evaluated in ongoing trials (see chapter by Weitz et al[222] on new anticoagulant drugs).

The long-acting pentasaccharide idraparinux was reported to be as effective and as safe as VKA for the first 3 or 6 months of treatment of DVT (but less effective that VKA in patients with PE).[223] After an initial 6 months of treatment with either idraparinux or warfarin (52% of patients initially presented with symptomatic DVT), compared with placebo, 6 months of extended therapy with idraparinux markedly reduced recurrent VTE and increased bleeding.[223]

2.6 Treatment of Asymptomatic DVT of the Leg

Screening of postoperative patients for the presence of asymptomatic DVT is not recommended[224]; instead, surgical patients should receive appropriate primary prophylaxis for VTE. If asymptomatic proximal DVT is detected, for example, in patients who have screening performed because they could not receive recommended VTE prophylaxis or in patients who have imaging studies performed for other reasons (*eg*, staging of cancer), care should be taken to ensure that DVT is truly present and patients should be treated as described elsewhere in this chapter (also see Section 5.4, "Treatment of Asymptomatic PE"). Asymptomatic proximal DVT detected by routine ultrasound screening in the setting of a clinical trial evaluating VTE prophylaxis in hospitalized medical patients has been shown to be associated with increased mortality at 3 months.[225]

Recommendation

2.6.1. In patients who are unexpectedly found to have asymptomatic DVT, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 1C)**.**

Table 9—*Comparison of High-Intensity and Conventional-Intensity VKA Therapy in Patients With Venous or Arterial Thrombosis and an Antiphospholipid Antibody: Clinical Description and Results (Section 2.2)**

Author/yr (Acronym)	Interventions	Patients Analyzed, No. (%)	Length of Follow-up	Recurrent Venous or Arterial Thrombosis, No. (Total)	Major Bleeding, No. (Total)	Total Mortality, No. (%)	Comments
Crowther et al[203]/2003 (PAPRE)	VKA (INR, 2.0–3.0)	58/58	2.7 yr (mean)	2/58 (3.4%)	4/58 (6.9)	0/58	Population: 76% had VTE and 24% had arterial thromboembolism only, acutely or remotely; all had an antiphospholipid antibody on two occasions 3 mo apart; four of eight thrombotic episodes were arterial
	VKA (INR, 3.1–4.0)	56/56	2.6 yr (mean)	6/56 (10.7%) RR, 3.1 (95% CI, 0.6–15)	3/56 (5.4) RR, 0.8 (95% CI, 0.2–3.3)	0/56 RR, 1.0 (95% CI, 0.0–48)	
Finazzi et al[204]/2004 (WAPS)	VKA (INR, 2.0–3.0), n = 52, or aspirin at 100 mg/d if no VTE or cardioembolism (n = 3)	55/55	Median of 3–6 yr for all patients	3/55 (5.5%)	3/55 (5.5%)	2/55 (3.6)	Population: 69% have VTE and 405 had arterial thromboembolism, acutely or remotely All had an anticardiolipin antibody on two occasions 6–8 wk apart; of nine thrombotic episodes, six were arterial and one was superficial phlebitis
	VKA (INR, 3.0–4.5)	54/54		6/54 (11.1%) RR, 2.0 (95% CI, 0.5–7.7)	2/54 (3.7%); RR, 0.7 (95% CI, 0.1–3.9)	3/54 (5.6) RR, 01.64 (95% CI, 0.3–8.8)	

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

3.0 Postthrombotic Syndrome

PTS is a cluster of leg symptoms and signs in patients with previous DVT. PTS occurs in 20 to

50% of patients after acute DVT.[226] The initial treatment of acute DVT may influence the presence and severity of PTS, as discussed earlier (Section 2.0). The most prominent symptoms are chronic postural dependent swelling and pain, ambulatory discomfort, and skin pigmentation. The severity of symptoms may vary over time, and the most extreme manifestation is a venous ulcer of the lower leg. First, the studies on the prevention of PTS are discussed, followed by the trials on the treatment of this syndrome, with and without venous ulcers.

3.1 Elastic Stockings and Compression Bandages To Prevent PTS

Four randomized trials[144,227–229] have evaluated the efficacy of compression stockings for the prevention of PTS following DVT (Table 11). Two trials, namely those of Brandjes et al[227] and Prandoni et al,[229] randomized patients to stockings (30 to 40 mm Hg ankle gradient) or no stockings after a first episode of acute symptomatic proximal DVT. A third trial by Ginsberg et al[228] evaluated 47 asymptomatic patients with evidence of venous valvular incompetence 1 year following their acute DVT. Twenty-six percent of the patients had asymptomatic DVT detected by phlebography after orthopedic surgery. A lower compression stocking of 20 to 30 mm Hg ankle pressure was compared with a placebo stocking.

Blattler and Partsch[139] randomized 53 patients with acute symptomatic DVT to anticoagulation and bed rest for 9 days or anticoagulation and ambulation with either inelastic bandages or compression stockings (30 mm Hg). Early and long-term results favored the ambulation-with-compression group (Table 11).[144]

Brandjes et al[227] demonstrated that 47% of the control group had mild-to-moderate PTS compared with 20% of patients in the stocking group. Twenty-three percent of patients in the control group vs 11% of patients in the stocking group had severe PTS. Prandoni et al[229] made similar observations, in that PTS developed in 49% of control patients compared with 25% in the treatment group after 2 years.

Ginsberg et al[228] observed no difference in the 47 patients who were randomized to 20 to 30 mm Hg compression stockings compared with a placebo stocking. Since all patients were asymptomatic at entry into the study 1 year after diagnosis, and as 26% initially had asymptomatic DVT, it appears that the patients in this trial were unlikely to benefit from any measure to prevent PTS, since PTS was unlikely to develop without treatment.

A Cochrane review[230] that combined the findings of Brandjes, Prandoni, and Ginsberg (421 patients) estimated that stockings markedly reduced the cumulative incidence of PTS at 2 years (OR, 0.3; 95% CI, 0.2 to 0.5). An ongoing placebo-controlled study is further evaluating whether routine wearing of graduated compression stockings prevents the development of PTS.[231]

Recommendation

3.1.1. For a patient who has had a symptomatic proximal DVT, we recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A)**. Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum of 2 years, and longer if patients have symptoms of PTS. (Note: feasibility, both short-term and long-term, refers to ability of patients and their caregivers to apply and remove stockings.)**
Values and preferences: This recommendation attaches a relatively high value to long-term prevention of the PTS and a low value to the burden (*eg*, inconvenience or discomfort) associated with wearing stockings.

3.2 Physical Treatment of PTS Without Venous Leg Ulcers

The treatment of PTS has been evaluated only in small or methodologically flawed trials. Treatment is usually based on physical methods designed to counteract the raised venous pressure. Of these approaches, elastic stockings have been evaluated in asymptomatic and symptomatic patients in a small underpowered trial[228]; the results failed to show a benefit, possibly due to mild disease and small patient numbers. In a cross-over study[232] of 15 patients with a severe PTS, intermittent pneumatic compression (IPC) at 40 mm Hg was more effective than a lower (placebo) pressure. Twelve of 15 patients preferred the therapeutic pressure.

Recommendations

3.2.1. For patients with severe edema of the leg due to PTS, we suggest a course of IPC (Grade 2B)**.**
3.2.2. For patients with mild edema of the leg due to PTS, we suggest the use of elastic compression stockings (Grade 2C)**.**

3.3 Physical Treatment of Venous Leg Ulcers

Venous leg ulcers represent the most severe complication of PTS. While most reports of venous leg ulcers fail to differentiate a postthrombotic etiology from primary venous insufficiency, it is recognized that the postthrombotic limb is likely to have higher venous

Table 10—*LMWH vs VKA for Long-Term Treatment of VTE in Patients With Active Cancer: Clinical Description and Results (Section 2.4)**

Author/yr (Acronym)	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Recurrent DVT or PE, No./Total (%)	Major Bleeding, No./Total (%)	Total Mortality, No./Total (%)	Comments
Meyer et al[213]/2002	VKA (INR, 2.0–3.0) for 3 mo after initial enoxaparin	75/75	3 mo	3/75 (4%)	12/75 (16%)	17/75 (23%)	Population: DVT (proportion with calf DVT not known) or PE and active cancer; all fatal bleedings (n = 6) were in VKA group.
	Enoxaparin at 1.5 mg/kg once daily for 3 mo	71/71	3 mo.	2/71 (3%) RR, 0.7 (95% CI, 0.1–4.1)	5/71 (7%) RR, 0.4 (95% CI, 0.2–1.2)	8/71 (11%) RR, 0.5 (95% CI, 0.2–1.1)	
Lee et al[211]/2003 (CLOT)	VKA (INR, 2.0–3.0) for 6 mo after initial dalteparin	336/338	6 mo	53/336 (16%)	12/335 (4%)	136/336 (40%)	Population: Proximal DVT or PE and active cancer
	Dalteparin at 200 U/kg once daily for 1 mo followed by 150 U/kg for 5 mo	336/338	6 mo	27/336 (8%) RR, 0.5 (95% CI, 0.3–0.8)	19/338 (6%) RR, 1.6 (95% CI, 0.8–3.2)	130/336 (37%) RR, 1.0 (95% CI, 0.8–1.2)	Difference in efficacy mainly due to recurrent DVT (14 vs 37 episodes)
Hull et al[221] /2006 (Main LITE-cancer)	VKA (INR 2.0–3.0) for 3 mo after initial IV UFH	100/100	3 mo	10/100 (10%)	7/100 (7%)	19/100 (19%)	Population: Proximal DVT and active cancer
	Tinzaparin at 175 mg/kg once for 3 mo	100/100	3 mo.	6/100 (6%) RR, 0.6 (95% CI, 0.2–1.6)	7/100 (7%) RR, 1.0 (95% CI, 0.4–2.8)	20/100 (20%) RR, 1.0 (95% CI, 0.6–1.9)	Prespecified, stratification, subgroup within a larger trial; Outcomes at 12 mo were also reported
Summary				RR, 0.7 (95% CI, 0.4–0.8)	RR, 1.0 (95% CI, 0.6–1.6)	RR, 0.9 (95% CI, 0.8–1.1)	

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 11—*Elastic Stockings for the Prevention of PTS: Clinical Description and Results (Section 3.1)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Brandjes et al[227]/ 1997	RCT	194 patients with first symptomatic, proximal DVT	Compression stockings: below-knee customized elastic compression stockings with ankle pressure 30–40 mm Hg (96 patients) Control group: no intervention (n = 98)	Cumulative incidence of mild-to-moderate and severe PTS	3 mo and 6 mo, then every 6 mo to a median of 76 mo	Compression stockings: Mild-to-moderate PTS: 20% (RR, 0.42; 95% CI, 0.27–0.66; $p < 0.001$) Severe PTS: 11% (RR, 0.49; 95% CI, 0.25–0.95; $p < 0.001$) Control group: Mild-to-moderate PTS: 47% Severe PTS: 23%
Ginsberg et al[228]/ 2001	RCT	47 asymptomatic patients with valvular incompetence 1 yr after DVT	Compression stockings: below-knee elastic compression stockings 20–30 mm Hg (n = 24) Placebo: placebo stocking (n = 23)	PTS symptoms	57 mo (mean)	Compression stockings: PTS symptoms: 0% Placebo: PTS symptoms: 4%
Prandoni et al[229]/ 2004	RCT	180 patients with first episode of symptomatic, acute proximal DVT	Compression stockings: below-knee elastic compression stockings 30–40 mm Hg (n = 90) Control group: no intervention (n = 90)	Cumulative incidence of mild-to-moderate and severe PTS	3 to 5 yr	Compression stockings: PTS symptoms: 25% (95% CI, 15.6–33.4%) Control group: PTS symptoms: 49% (95% CI, 38.7–59.4%)
Partsch et al[144]/ 2004	2-yr follow-up to RCT[141]	37 symptomatic patients with acute DVT followed up long term	All anticoagulated with LMWH followed by oral anticoagulation Inelastic bandages plus early ambulation (n = 13) Elastic stockings (30 mm Hg) plus early ambulation (n = 13) Bed rest for 9 d, no compression (n = 11)	Overall leg pain, leg circumference, PTS score (Villalta-Prandoni)	2 yr	Leg pain No difference between groups Calf circumference No difference between groups PTS score Significantly better outcome with ambulation and bandaging or stockings compared to bed rest ($p < 0.01$)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

pressures and, therefore, more likely to have ulceration than patients with primary venous insufficiency.[65]

Smith et al[233] demonstrated that in patients with venous leg ulcers, IPC for 4 h daily added to standard wound care and compression significantly increased healing ($p = 0.009$) [Table 12]. Kumar et al[234] found that IPC in addition to standard four-layered compression increased rate of ulcer healing ($p = 0.046$) and reduced time to a healed ulcer ($p < 0.05$) [Table 12]. In 10 patients with postthrombotic venous ulcers, 60 min of IPC was found to increase transcutaneous oxygen tension, reduce edema, and increase skin temperature in the short-term (Table 12).[235] As compression pressures and cycles have varied in the studies that have been performed, IPC prescription for treatment of PTS and venous ulcers has not been standardized. Surgical correction of superficial venous reflux in addition to compression bandaging was shown to reduce recurrent ulceration compared with compression therapy alone in a randomized trial[236,237] of 500 patients with open or recently healed leg ulcers and ultrasound-confirmed superficial venous reflux (recurrent ulceration of 31% vs 56% at 4 years; $p < 0.01$).

Recommendation

3.3.1. In patients with venous ulcers resistant to healing with wound care and compression, we suggest the addition of IPC (Grade 2B)**.**

Table 12—*Physical Treatment of PTS With Venous Ulcers: Clinical Description and Results (Section 3.3)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Kolari et al[235]/ 1988	Prospective study	10 patients (study group) with PTS leg ulcers, and 9 patients with no evidence of peripheral arterial disease	1 h of IPC at 50 mm Hg (inflation time of 12 s, deflation time of 18 s); leg volume and skin temperature measured before and after compression	Before/after intervention $TcPO_2$ (supine at ulcer edge), leg volume (water displacement), skin temperature	Immediately after procedure	Before/after $TcPO_2$: Study group: before, 26.2 ± 7.0, after, 42.7 ± 6.4 ($p < 0.005$) Control subjects: before, 59.7 ± 2/9; after, ND Change in $TcPO_2$ correlated significantly with reduction in edema and inverse change in skin temperature ($R = 0.912$, $p < 0.002$)
Smith et al[233]/ 1990	RCT	45 patients with nonhealing venous ulcers	Stockings: ulcer debridement, cleaning, nonadherent dressing, graduated compression stockings 30–40 mm Hg Stockings plus IPC: same protocol as compression group plus IPC 4 h/d	Healed ulcer, median rate of healing per week	3.7 yr (mean)	Stockings Healed ulcer: 1/24 (4%) Median healing rate: 2.1% Stockings plus IPC Healed ulcer: 10/21 (48%) [$p = 0.009$] Median healing rate: 19.8% ($p = 0.046$)
Kumar et al[234]/ 2002	RCT	47 patients with nonhealing venous ulcers	Bandages: weekly four-layer bandaging Bandages plus IPC: weekly four-layer bandaging plus IPC for 1 h bid at 60 mm Hg	Mean number of days to healed ulcer, mean rate of healing	4 mo	Bandages Mean days to healed ulcer: 73.7 d Mean rate of healing: 0.05 cm^2/d (95% CI, 0.03–0.07; SD = 0.046) Bandages plus IPC Mean days to healed ulcer: 53.5 d Mean rate of healing: 0.14 cm^2/d (95% CI, 0.03–0.25; SD = 0.22) [$p < 0.05$]

*$TcPO_2$ = transcutaneous oxygen pressure; ECS = elastic compression stocking; IPC = intermittent pneumatic compression; ND = not determined. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

3.4 Hyperbaric Oxygen and the Management of Patients With Venous Ulcers

Only one small trial[238] of acceptable methodologic quality has evaluated hyperbaric oxygen in the treatment of patients with venous leg ulcers, and this study of 16 patients failed to show any benefit on the rate of healing.

Recommendation

3.4.1. For patients with venous ulcers, we suggest that hyperbaric oxygen not be used (Grade 2B)**.**

3.5 Pharmacologic Treatment of Venous Ulcers

Not all venous ulcers heal in a timely manner with compression and/or IPC, and such patients may benefit from the addition of pharmacologic agents.

Pentoxifylline

Pentoxifylline affects the membrane of blood cells, resulting in changes in the rheology of blood and the microcirculation.[239] A Cochrane review evaluated eight randomized studies[240–247] with a total of 547 patients with venous leg ulcers who were treated with pentoxifylline vs placebo and in which there was objective measurement of wound healing (Table 13). Compression therapy was used in five of the eight trials,[241–244,246] and in three trials no compression was used.[240,245,247] There was a tendency for complete healing or significant improvement to occur more frequently in pentoxifylline-treated patients (RR, 1.5; 95% CI, 1.1 to 2.0). In the five studies in which compression was used, the addition of pentoxifylline resulted in an RR of healing of 1.3 (95%

CI, 1.1 to 1.5). In the three studies in which compression was not used as standard therapy, pentoxifylline also promoted healing (RR, 2.4; 95% CI, 1.3 to 4.3). A subsequent trial[248] of 80 patients showed similar results.

Micronized Purified Flavonoid Fraction or Sulodexide for the Treatment of Venous Leg Ulcers

Hydroxyrutosides are a class of flavonoid drug produced from plant glycosides. Although their mechanism of action is not entirely known, they appear to reduce capillary permeability, reduce inflammation, improve lymphatic function, and improve symptoms relating to chronic venous insufficiency[249,250] (Table 14). Micronization of the flavonoid compound improves intestinal absorption and bioavailability and, therefore, is thought to improve clinical effects.[251] A meta-analysis[252] of five studies evaluated micronized purified flavonoid fraction (MPFF) in the management of patients with venous ulceration who were all treated with compression. Two of the five studies were placebo-controlled trials, whereas three studies did not incorporate a placebo. At 6 months, complete ulcer healing had occurred in 61% of the MPFF patients and in 48% of the control patients (RR reduction for persistent ulceration, 32%; 95% CI, 3 to 70%; $p = 0.03$). Subgroup analyses suggested that the benefits of MPFF were greatest in ulcers ≥ 5 cm^2 and > 6 months in duration. Sulodixide, a glycosaminoglycan preparation that is administered intraamuscularly or orally, was shown to increase venous ulcer healing in a placebo-controlled trial[253] of 235 patients (RR for healing, 1.37; 95% CI, 1.07 to 1.74) without an apparent increase in side effects.

Recommendations

3.5.1. In patients with venous leg ulcers, we suggest pentoxifylline, 400 mg po tid, in addition to local care and compression and/or IPC (Grade 2B)**.**

3.5.2. In patients with persistent venous ulcers, we suggest that rutosides, in the form of MPFF adminstered orally, or sulodexide administered intramuscularly and then orally, be added to local care and compression (Grade 2B)**.**

4.0 Initial Treatment of Acute PE

Treatment regimens for DVT and PE are similar because the two conditions are manifestations of the same disease process. When patients with VTE are carefully studied, the majority of those with proximal DVT also have PE (symptomatic or asymptomatic) and vice versa.[185] Furthermore, clinical trials of anticoagulant therapy have yielded similar estimates for efficacy and safety in patients with DVT alone, in those with both DVT and PE, and in patients with only PE. The risk of recurrence also appears to be similar after PE and after proximal DVT.[164,185] The vast majority of patients with VTE who receive adequate anticoagulation survive. However, there are some important differences between patients who present with PE and those who present with DVT that justify separate consideration of treatment for PE. First, the risk of early death (within 1 month) from VTE, due to either the initial acute episode or recurrent VTE, is much greater after presenting with PE than after DVT[164]; this difference may justify more aggressive initial treatment for PE (*eg*, thrombolytic therapy, insertion of an IVC filter, more intensive anticoagulant therapy) compared with DVT. Second, recurrent episodes of VTE are about three times as likely to be PE after an initial PE than after an initial DVT (*ie*, approximately 60% after a PE vs 20% after a DVT)[164,185]; this difference may justify more aggressive, or more prolonged, long-term therapy. Third, the long-term sequelae of PE are cardiorespiratory impairment, especially due to pulmonary hypertension, rather than PTS of the legs or arms. As the recommendation for anticoagulant therapy and IVC filter insertion in patients with PE are partly based on studies that enrolled DVT patients alone, or both DVT and PE patients, see corresponding sections for treatment of patients with DVT.

4.1 IV or SC UFH, SC LMWH, SC Fondaparinux, and VKA for the Initial Treatment of PE

Anticoagulant Therapy vs No Anticoagulant Therapy

In their landmark RCT, Barritt and Jordan[1] showed that short-term treatment with intermittent boluses of IV UFH and VKA therapy was effective in patients with a clinical diagnosis of PE (Table 15); this trial also reported very favorable outcomes in a cohort of 38 patients with severe PE who were all treated with anticoagulants (one nonfatal recurrent PE, and one death not due to PE or bleeding) after the RCT was stopped early because of benefit from active therapy.

SC LMWH vs IV UFH

Consistent with findings in patients with DVT, LMWH has been found to be at least as effective

and safe as IV UFH in studies that included both patients with PE and/or DVT, or only patients with PE (Table 15). In a metaanalysis[259] of 12 studies[29,30,33,35,39,43,44,254–258] that included a total of 1,951 patients with either submassive symptomatic PE, or asymptomatic PE in conjunction with symptomatic DVT, at the end of treatment (5 to 14 days), LMWH was associated with a tendency to less recurrent VTE (OR, 0.63; 95% CI, 0.33 to 1.18), less major bleeding (OR, 0.67; 95% CI, 0.36 to 1.27), and similar all-cause mortality (OR, 1.20; 95% CI, 0.59 to 2.45).

SC UFH vs SC LMWH

Two recent large studies of patients with acute VTE (total of 1,478 patients, of whom 253 presented with PE) found no difference in recurrent VTE, bleeding, or all-cause mortality between patients who were treated with either partially[24] or fully[25] weight-adjusted SC UFH (dose adjusted to APTT results in one study,[24] and in fixed-doses without APTT monitoring in the other study[25]), compared with those who were treated with LMWH (Galilie, FIDO; Table 2) [judged Grade 1B evidence for noninferiority of monitored and fixed-dose SC UFH compared with LMWH].

Fondaparinux vs IV UFH

The Matisse PE study,[60] an open-label trial that enrolled 2,213 patients with acute PE (including major PE, provided thrombolytic therapy was not required), found that partially weight-adjusted, fixed-dose, SC fondaparinux was associated with a similar frequency of recurrent VTE (3.8% vs 5.0% at 3 months) and major bleeding (1.3% vs 1.1% during initial treatment) as adjusted-dose IV UFH (Table 15) [judged Grade 1A evidence for noninferiority of fondaparinux compared with IV UFH or SC LMWH].

Treatment of PE on an Outpatient Basis

No published trials have specifically randomized patients with acute PE to either be treated in hospital or at home. Two randomized trials[25,57] included patients with acute PE who were treated as outpatients. The first trial,[57] which compared two LMWH preparations for outpatient treatment of acute VTE, included 90 patients with acute PE. The second trial,[25] which compared subcutaneous fixed-dose UFH and LMWH in patients with acute VTE, included 52 patients with acute PE who were treated entirely as outpatients. Among the 142 patients, there was a low frequency of recurrent VTE (3.5%) and major bleeding (1.4%). The feasibility of treating a substantial proportion of patients with symptomatic PE with LMWH at home is also supported by the findings of three observational studies[260–262] in which 158 patients (35% of total) with PE were treated entirely at home. Two prediction rules have been developed to aid with selection of patients with acute PE who are suitable for treatment out of hospital.[263–265] Recommendations about the initiation of UFH or LMWH as well as the overlap with VKA and monitoring of the anticoagulant effects are largely based on the findings in patients with DVT and, therefore, are the same as for DVT (see Section 1).

Recommendations

4.1.1. For patients with objectively confirmed PE, we recommend short-term treatment with SC LMWH (Grade 1A)**, IV UFH** (Grade 1A)**, monitored SC UFH** (Grade 1A)**, fixed-dose SC UFH** (Grade 1A), **or SC fondaparinux** (Grade 1A) **rather than no such short-term treatment. Patients with acute PE should also be routinely assessed for treatment with thrombolytic therapy (see Section 4.3 for related discussion and recommendations).**

4.1.2. For patients for whom there is a high clinical suspicion of PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C)**.**

4.1.3. In patients with acute PE, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for at least 24 h (Grade 1C)**.**

4.1.4. In patients with acute PE, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A)**.**

4.1.5. In patients with acute PE, if IV UFH is chosen, we recommend that after an initial IV bolus (80 U/kg or 5,000 U), it be administered by continuous infusion (initially at dose of 18 U/kg/h or 1,300 U/h) with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C)**.**

4.1.6. In patients with acute PE, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of about 250 U/kg bid, with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of

Table 13—*Pentoxifylline for the Treatment of PTS With Venous Ulcers: Clinical Description and Results (Section 3.5.1)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Weitgasser[247]/ 1983	RCT	60 patients with nonhealing venous leg ulcers	Pentoxifylline: 400 mg tid (n = 30) Placebo (n = 30)	Healed ulcer (ulcer closed or size considerably reduced)	6–8 wk	Pentoxifylline Complete ulcer healing: 20/30 (67%) Placebo Complete ulcer healing: 7/29 (24%)
Schürman et al[246]/1986	RCT	24 patients with nonhealing venous ulcers	Pentoxifylline plus compression: 400 mg TID plus compression (n = 12) Placebo plus compression (n = 12)	Healed ulcer	8 wk	Pentoxifylline plus compression Complete ulcer healing: 2/12 (16%) Placebo plus compression: Complete ulcer healing: 3/12 (25%)
Arenas and Atoche[240]/ 1988	RCT	30 patients with nonhealing venous ulcers	Pentoxifylline: 400 mg TID (n = 18) Placebo (n = 12)	Healed ulcer	6 mo	Pentoxifylline Complete ulcer healing: 7/18 (39%) Placebo Complete ulcer healing: 3/12 (25%)
Colgan[242]/ 1990	RCT, multicenter	80 patients with nonhealing venous ulcers	Pentoxifylline plus compression: 400 mg TID plus layered compression (n = 38) Placebo plus compression: placebo plus layered compression (n = 42)	Healed ulcer	24 wk	Pentoxifylline plus compression Complete ulcer healing: 23/38 (60%) Placebo plus compression Complete ulcer healing: 12/42 (29%)
Barbarino[241]/ 1992	RCT	12 patients with nonhealing venous ulcers	Pentoxifylline plus compression: 400 mg TID plus layered compression (n = 6) Placebo plus compression: placebo plus layered compression (n = 6)	Healed ulcer	2–3 mo	Pentoxifylline plus compression Complete ulcer healing: 4/6 (66%) Placebo plus compression Complete ulcer healing: 1/6 (17%)
Apollonio and Angeletti[385]/ 1992	RCT	23 patients with nonhealing venous ulcers	Defibrotide: 800 mg in two doses daily (n = 12) Pentoxifylline: 400 mg of pentoxifylline tid (n = 11)	Healed ulcer	6 mo	Defibrotide Complete ulcer healing: 11/12 (92%) Pentoxifylline Complete ulcer healing: 9/11 (82%)
Herdy et al[245]/ 1997	RCT	12 patients with nonhealing venous ulcers	Pentoxifylline: 400 mg pentoxifylline TID (n = 6) Placebo (n = 6)	Reduction in ulcer area	12 wk	Pentoxifylline Ulcer reduction: 2.2 cm^2 Placebo Ulcer reduction: 0.4 cm^2
Dale et al[243]/ 1999	Factorial RCT, multicenter	200 patients with nonhealing venous ulcers	Pentoxifylline plus compression: 400 mg TID plus compression plus wound dressing (n = 101) Placebo plus compression: placebo plus compression plus wound dressing (n = 99)	Healed ulcer	24 wk	Pentoxifylline plus compression Complete ulcer healing: 65/101 (64%) Placebo plus compression Complete ulcer healing: 52/99 (52%)

Table 13—*Continued*

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Falanga et al[244]/1999	RCT	129 patients with nonhealing venous ulcers	Placebo plus compression (n = 45) Pentoxifylline plus compression: 400 mg TID plus compression (n = 41) Pentoxifylline plus compression: 800 mg TID plus compression (n = 43)	Healed ulcer	24 wk	Placebo plus compression Complete ulcer healing: 28/45 (63%) Pentoxifylline 400 mg tid plus compression: Complete ulcer healing: 31/41 (75%) Pentoxifylline 800 mg tid plus compression Complete ulcer healing: 31/43 (73%)
Belcaro et al[386]/2002	RCT	172 patients with nonhealing venous ulcers	Pentoxifylline: 400 mg tid (n = 82) Placebo (n = 88)	Healed ulcer	6 mo	Pentoxifylline Complete ulcer healing: 67% Placebo Complete ulcer healing: 31%
De Sanctis et al[387]/2002	RCT	85 patients with nonhealing venous ulcers	Pentoxifylline: 400 mg tid (n = 41) Placebo (n = 39)	Healed ulcer	12 mo	Pentoxifylline Complete ulcer healing: 88% Placebo Complete ulcer healing: 44%
Nikolovska et al[248]/2002	RCT	80 patients with nonhealing venous ulcers	Pentoxifylline: 400 mg tid (n = 40) Placebo (n = 40)	Healed ulcer	6 mo	Pentoxifylline Complete ulcer healing: 23/40 (58%) Placebo Complete ulcer healing: 11/40 (28%)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (Grade 1C).

4.1.7. In patients with acute PE, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/Kg followed by a twice-daily dose of 250 U/kg rather than non–weight-based dosing (Grade 1C).

4.1.8. In patients with acute nonmassive PE, we recommend initial treatment with LMWH over IV UFH (Grade 1A). **In patients with massive PE, in other situations where there is concern about SC absorption, or in patients for whom thrombolytic therapy is being considered or planned, we suggest IV UFH over SC LMWH, SC fondaparinux, or SC UFH** (Grade 2C).

4.1.9. In patients with acute PE treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A).

4.1.10. In patients with acute PE and severe renal failure, we suggest UFH over LMWH (Grade 2C).

4.2 New Antithrombotic Agents for the Initial Treatment of PE

In addition to the synthetic pentasaccharide fondaparinux (Section 4.1), several other new antithrombotic agents have recently been developed (see chapter by Weitz et al[222] in this supplement). As previously noted (Section 2.5), ximelagatran has been compared with LMWH and VKA therapy for the initial 6 months of short-term treatment of DVT, and one third of these patients had concomitant PE (not available for clinical use because of associated liver toxicity).[61] The long-acting pentasaccharide idraparinux was reported to be less effective than standard therapy with heparins and VKA for the first 3 to 6 months of treatment of PE.[62]

4.3 Systemically and Locally Administered Thrombolytic Therapy for PE

Thrombolytic therapy for PE remains controversial. The fundamental problem is that < 800 PE

Table 14—*MPFF for the Treatment of PTS With Venous Ulcers: Clinical Description and Results (Section 3.5)**

Author/yr	Type of Study	Participants	Interventions	Outcomes	Follow-up	Results
Guilhou et al[388]/1997	RCT, placebo controlled, multicenter	105 patients with venous ulcers, stratified by ulcer size: ≤10 cm (n = 91), > 10 cm (n = 14)	MPFF plus compression: 500 mg bid plus compression Placebo plus compression	Complete ulcer healing Symptoms of CVI, time to heal	2 mo	Healed ulcers Treatment: 14/44 (32%) Control: 6/47 (13%) p = 0.028; No ulcer > 10 cm^2
Glinski et al[389]/2001	RCT, open label	140 patients with venous leg ulcers, stratified by ulcer size: < 3 cm, 3–6 cm, > 6 cm	MPFF plus compression: 500 mg bid plus compression Compression alone	Complete ulcer healing Reduction in ulcer size, cost-effectiveness	6 mo	Healed ulcers Treatment: 47% Control: 28% (p < 0.05; RR, 2.3; 95% CI, 1.1–4.6) Ulcer: < 3 cm Treatment: 71% Control: 50% Ulcer 3–6 cm Treatment: 60% Control: 32% Ulcer > 6 cm Treatment: 9% Control: 13% Cost per healed ulcer Treatment: €1026.20 Control: €1871.80
Roztocil et al[390]/2003	RCT, open label, multicenter	150 patients with venous leg ulcers 2–10 cm in diameter	MPFF plus compression	Complete healing at 6 mo	6 mo	Healed ulcers Treatment: 65% Control: 41% (p = 0.004) Days to achieve healing Treatment: 137 d Control: 166 d (p = 0.004)
Coleridge-Smith et al[252]/2005	Metaanalysis, three trials summarized above, plus two unpublished trials	723 patients with venous leg ulcers	Two studies MPFF plus compression vs compression plus placebo Three studies MPFF plus compression vs compression alone	Complete healing	2–6 mo	Healing increased by 32% (RR, 1.3.2; 95% CI, 1.03–1.70) at 6 mo Healing time shortened by 5 wk Healing increased in ulcers > 5 cm^2 (RR, 1.53; 95% CI, 1.15–2.03) and > 6 mo old (RR, 1.41; 95% CI, 1.09–1.81)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

patients have been enrolled in randomized trials of thrombolysis plus anticoagulation vs anticoagulation alone (Table 16). The results of such trials have been summarized in three recently published metaanalyses.[266–268] In one overview, which included 11 studies[269–278] totalling 748 patients with PE of varying severity, thrombolysis was associated with trends toward reduction in recurrent PE (2.7% vs 4.3%; OR, 0.67; 95% CI, 0.33 to 1.37), reduction in all-cause mortality (4.3% vs 5.9%; OR, 0.70; 95% CI, 0.37 to 1.30), and an increase in major bleeding (9.1% vs 6.1%; OR, 1.42; 95% CI, 0.81 to 2.46). In the subset of five trials[269,271,273,275,278] (total of 254 patients) that focused on patients with more severe PE, the reduction in mortality (6.2% vs 12.7%; OR, 0.47; 95% CI, 0.20 to 1.10) and the

increase in major bleeding (21.9% vs 11.9%; OR, 1.98; 95% CI, 1.00 to 3.92) were more marked with thrombolytic therapy.[268]

MAPPET-3,[279] the largest and most recent randomized trial of thrombolytic therapy vs heparin alone, studied patients with the combination of normal BP and either echocardiographic or ECG evidence of right ventricular dysfunction (Table 16). The principal end point was escalation of therapy, defined as the need for pressors, mechanical ventilation, cardiopulmonary resuscitation, or open-label thrombolysis. Tissue plasminogen activator (tPA), compared with placebo, halved the frequency of escalation of therapy and did not increase major bleeding. However, open-label thrombolysis as rescue therapy was the main form of escalation of therapy, and as the decision to use open label "rescue thrombolysis" was subjective and could be make after unblinding, this component of the primary outcome has been criticized.[279]

In the International Cooperative Pulmonary Embolism Registry, which enrolled 2,454 PE patients from 52 hospitals in seven countries, intracranial bleeding occurred in 3.0% of the 304 patients who received thrombolytic therapy, compared with 0.3% of the nonthrombolysis treated patients.[280] The overall mortality rate from PE was approximately 8% after 3 months,[281] about double the frequency reported in randomized trials; this higher mortality rate probably reflects exclusion of the sickest patients from participating in randomized trials[43,60] (Table 16). There was no apparent survival benefit from thrombolysis in this registry, even among the sickest patients with massive PE.[280]

There is widespread agreement that thrombolytic therapy should be used to treat PE associated with hemodynamic compromise. Justification for this is that, compared with anticoagulation alone, thrombolytic therapy has demonstrated the following: (1) acceleration of thrombus lysis as evidenced by more rapid resolution of perfusion scan abnormalities, decrement in angiographic thrombus, reduction in elevated pulmonary artery pressures, and normalization of right ventricular dysfunction (Table 16); and (2) trends toward improved clinical outcomes in subgroups of patients with hemodynamic compromise. However, delaying thrombolytic therapy until patients with PE are pressor dependent is detrimental because prolonged inadequate tissue perfusion can cause irreversible multisystem organ failure. Consequently, selection of patients with PE to receive thrombolytic therapy requires rapid and accurate risk stratification of the competing risks of death from PE and of bleeding.

The risk of death is very high in the presence of sustained hypotension and cardiogenic shock.[280,281] However, such patients are rare, accounting for approximately 5% of patients with a diagnosis of PE.[280,281]

In the presence of normal systemic arterial pressure, prognostication depends on the following: (1) clinical evaluation,[281] (2) cardiac biomarkers such as troponin,[282–286] and (3) assessment of right ventricular size and function.[280,283,285,287–289] Clinical evaluation begins with general appearance, BP, heart rate, respiratory rate, temperature, and pulse oximetry. The next step is physical examination to detect findings of right ventricular dysfunction such as distended jugular veins, a systolic murmur of tricuspid regurgitation, or an accentuated P2. Clues on the ECG include right-bundle-branch block, $S_IQ_{III}T_{III}$, and T wave inversion in leads V1 through V4. Elevation of cardiac troponins indicates right ventricular microinfarction; echocardiography may show right ventricular hypokinesis; both are independent risk factors for early mortality and are associated with a worse outcome when they occur together.[282–286] Right ventricular enlargement on the CT pulmonary angiogram, defined as a right ventricular diameter $\geq 90\%$ than the left ventricular diameter, appears to be an independent risk factor for death and nonfatal clinical complications.[280,288]

Among patients without hemodynamic compromise, poor prognostic indicators include the following: (1) patients who appear ill, with marked dyspnea, anxiety, and low oxygen satuartion; (2) elevated troponin, indicating right ventricular microinfarction; (3) right ventricular dysfunction on echocardiography; and (4) right ventricular enlargement on chest CT. These sick patients are at high risk for an adverse outcome and may derive benefit from thrombolytic therapy, even if they initially maintain systemic arterial pressure. Consequently, in distinction to the last version of these guidelines that generally discouraged treatment of PE with thrombolytic therapy unless there was hemodynamic compromize, we suggest administration of thrombolytic therapy in selected high-risk patients without hypotension who are judged to have a low risk of bleeding.

Assessment of bleeding risk with thrombolytic therapy is similar in patients with PE and with acute ST-segment elevation myocardial infarction.[290,291] Major contraindications to thrombolytic therapy include intracranial disease, uncontrolled hypertension at presentation, and recent major surgery or trauma.[291]

Because of the inadequacy of currently available data, further studies are required to determine the risk and benefits of thrombolytic therapy in patients with severe PE who do not have hemodynamic compromise. In 2007, a European trial began enrolling patients with submassive PE who had preserved systolic BP, elevated troponin levels, and right ven-

Table 15—*RCTs of Initial Treatment of Acute PE: Clinical Description and Results (Section 4.1.1)**

Author/yr	Interventions	Patients Analyzed, No./Total	Length of Follow-up	Recurrent DVT and PE, No./Total	Major Bleeding, No./Total	Total Mortality, No./Total	Comments
Anticoagulation vs no anticoagulation							
Barritt and Jordan[1]/ 1960	UFH at 10,000 U IV q6h for 1.5 d and nicoumalone adjusted to prothrombin time for 14 d	16/16	Approximately 14 d	Recurrent PE Int: 0/16 Contr: 10/16 RR, 0.05 (95% CI, 0.00–0.75)	NR (1/16 fatal bleeds)	Int: 1/16 Contr: 5/19 RR, 0.32 (95% CI, 0.06–1.73)	Population: clinical diagnosis of acute PE (right heart failure, pulmonary infarction)
	Untreated controls	19/19		Fatal PE Int: 0/16 Contr: 5/19 RR, 0.11 (95% CI, 0.01–1.80)	NR (0/19 fatal bleeds)		
LMWH vs UFH							
Perez de Llano et al[257]/2003	Enoxaparin at 1 mg/kg SC bid	Enoxaparin: 29/29	6 mo	Enoxaparin: 3/29 (10%)	Enoxaparin: 0/29 (0%);	Enoxaparin: 2/29 (8%)	Four patients withdrawn and two unavailable for follow-up; allocation group not reported
	UFH at 5,000 IU followed by infusion of approximately 35,000 IU/24 h	UFH: 21/21		UFH: 2/21 (10%) RR, 1.09 (95% CI, 0.20–5.94)	UFH: 0/21 (0%)	UFH: 0/21 (0%) RR, 3.67 (95% CI, 0.19–72.63)	
Simonneau et al[43]/ 1997	Tinzaparin: 175 IU/kg SC qd	LMWH: 304/304	90 d	LMWH: 5/304 (2%)	LMWH: 6/304 (2.0%);	LMWH: 12/304 (4%)	
	UFH: 50 IU/kg followed by infusion of 500 IU/kg/24 h	UFH: 308/308		UFH: 6/308 (2%) RR, 0.84 (95 CI, 0.26–2.74)	UFH: 8/308 (3%) RR, 0.76 (95% CI, 0.27–2.16)	UFH: 14/308 (5%) RR, 0.87 (95% CI, 0.41–1.85)	
Meyer et al[256]/1995	Dalteparin: 120 anti-Xa IU/kg SC bid	LMWH: 29/29	3 mo	LMWH: 0/29 (0%)	LMWH: 0/29 (0%)	LMWH: 1/29 (3%)	Dalteparin dose is higher than is currently recommended
	UFH: infusion of 500 IU/ kg/24 h (no bolus)	UFH: 31/31		UFH: 0/31 (0%)	UFH: 0/31 (0%)	UFH: 1/31 (3%) RR, 1.07 (95% CI, 0.07–16.31)	

Table 15—*Continued*

Author/yr	Interventions	Patients Analyzed, No./Total	Length of Follow-up	Recurrent DVT and PE, No./Total	Major Bleeding, No./Total	Total Mortality, No./Total	Comments
Thery et al[258]/1992	Group 1: UFH at 50 IU/kg followed by infusion of 600 IU/kg/24 h	Group 1: 33/33	14 d	Group 1: 0/33 (0%)	Group 1: 2/33 (6%);	Group 1: 1/33 (3)	Enrollment stopped because of bleeding in groups 3 and 4; doses in groups 1, 3, and 4 are higher than currently recommended
	Group 2: nadroparin at approximately 160 IU/kg SC bid	Group 2: 35/35		Group 2: 0/35 (0%);	Group 2: 0/35 (0%) RR, 0.19 (95% CI, 0.01–3.79)	Group 2: 1/35 (3) RR, 0.94 (95% CI, 0.06–14.47)	
	Group 3: nadroparin, approximately 240 IU/kg SC tid	Group 3: 26/26		Group 3: 0/26 (0%);	Group 3: 5/26 (19%) RR, 3.17 (95% CI, 0.67–15.06)	Group 3: 0/26 (0%) RR, 0.42 (95% CI, 0.02–9.90);	
	Group 4: nadroparin, approximately 360 IU/kg SC tid	Group 4: 0/7		Group 4: 0/7 (0%)	Group 4: 4/7 (57%) RR, 9.43 (95% CI, 2.13–41.78)	Group 4: 1/7 (14%) RR, 4.71 (95% CI, 0.33–66.67)	
Fondaparinux vs UFH							
Buller et al[60]/ 2003	Fondaparinux at 7.5 mg (50-100 kg) or 5.0 mg (< 50 kg), or 10.0 mg (> 100 kg) SC daily	1,103/1,103	3 mo	Int: 43/1,103 Contr: 56/1,110	Int: 14/1,103 Contr: 12/1,110	Int: 57/1,103 Contr: 48/1,110	Average dose of UFH was 26,100 U on the second day of treatment
	UFH by IV infusion adjusted to APTT	1,110/1,110		RR, 0.77 (95% CI, 0.52–1.14)	RR, 1.17 (95% CI, 0.55–2.53)	RR, 1.20 (95% CI, 0.82–1.74)	

*Int = intervention; contr = control. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 16—*Randomized Trials of Thrombolytic Therapy vs No Thrombolytic Therapy for Acute PE: Clinical Description and Results (Section 4.3)**

Author/yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Recurrent DVT and PE, No./Total (%)	Major Bleeding, No./Total (%)	Total Mortality, No./Total (%)	Comments
Streptokinase plus heparin vs heparin							
Tibbutt et al[277]/1974	Streptokinase at 600,000 U intrapulmonary followed by 100,000 U for 72 h Heparin at 5,000 U intrapulmonary, followed by 2,500 U for 72 h	Streptokinase: 11/13 (84.6%) Heparin: 12/17 (70.6%)	72 h	Streptokinase: 0/11 Heparin: 0/12	Streptokinase: 1/11:(9.1%) Heparin: 1/12 (8.3%) RR, 0.92 (95% CI, 0.06–12.95)	Streptokinase: 0/11 Heparin: 0/12	All hydrocortisone at 100 mg and at 60 h of treatment; warfarin initial dose 25 mg for 6 mo Seven patients failed to complete the treatment regimen and were excluded from the analysis Patients reporting major bleeding required a blood transfusion Some 6-mo follow-up data available
Ly et al[275]/1978	Streptokinase at 250,000 U followed by 100,000 U/h for 72 h Heparin at 15,000 U followed by 1,250 U/h for 7 d	Streptokinase: 14/14 Heparin: 11/11	10 d	Streptokinase: 1/14 (7.1%) Heparin: 2/11 (18.2%) RR, 2.55 (95% CI, 0.26–24.56)	Streptokinase: 4/14 (28.6%) Heparin: 2/11 (18.2%) RR, 0.64 (95% CI, 0.14–2.86)	Streptokinase: 1/14 (7.1%) Heparin: 2/11 (18.2%) RR, 2.55 (95% CI, 0.26–24.56)	Primary outcome was angiographic reperfusion 5 of the 25 patients received nonrandomized therapy
Dotter et al[271]/1979	Streptokinase at 250,000 U followed by 100,000 U/h for 18–72 h Heparin at 1,500 U per kg for 2–7 d	Streptokinase: 15/15 Heparin: 16/16	In-hospital	Streptokinase: 0/15 Heparin: 1/16 (6.3%) RR, 2.82 (95% CI, 0.12–64.39)	Streptokinase: 3/15 (20.0%) Heparin: 4/16 (25.0%) RR, 1.25 (95% CI, 0.33–4.68)	Streptokinase: 1/15 (6.7%) Heparin: 2/16 (12.5%) RR, 1.88 (95% CI, 0.19–18.60)	All: warfarin/VKA: Primary outcome was angiographic reperfusion (not clearly stated)
Jerjes-Sanchez et al[273]/1995	Streptokinase at 1,500,000 U over 1 h followed by a bolus of heparin 10,000 U plus constant infusion of 1,000 U/h; heparin at 10,000 U followed by 1,000 U/h	Heparin: 4/4 Streptokinase: 4/4	In-hospital	Streptokinase: 0/4 0%) Heparin: 4/4 (100%) RR. 9.00 (95% CI, 0.64–126.85)	Streptokinase: 0/4 (0%) Heparin: 0/4 (0%)	Streptokinase: 0/4 (0%) Heparin: 4/4 (100%) RR, 9.00 (95% CI, 0.64–126.85)	Primary outcome not stated; trial stopped early for benefit; all patients had cardiogenic shock at randomization; heparin-treated patients appear to have failed heparin therapy before randomization, whereas the streptokinase patients had not

Table 16—*Continued*

Author/yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Recurrent DVT and PE, No./Total (%)	Major Bleeding, No./Total (%)	Total Mortality, No./Total (%)	Comments
Urokinase vs heparin							
UPET Study Group[269,278]/1970	Urokinase: infusion of 2,000 CTA U/lb followed by 2,000 CTA U/lb/h Heparin: infusion of 75 U/lb followed by 10 U/lb/h	Urokinase, 82/82 Heparin: 78/78	2 wk	Urokinase: 12/82 (14.6%) Heparin: 15/78 (19.2%) RR, 1.31 (95% CI, 0.66–2.63)	Urokinase: 37/82 (45.1%) Heparin: 21/78 (26.9%) RR, 0.60 (95% CI, 0.39–0.92)	Urokinase: 6/82 (7.3%) Heparin: 7/78 (8.9%) RR, 1.23 (95% CI, 0.43–3.49)	All: heparin for a minimum of 5 d The major bleeding reported includes moderate plus severe bleeding Angiographic data follow-up data available up to 12 mo
Marini et al[276]/1988	High dose: urokinase at 3,300,000 U over 12 h Low-dose: urokinase at 800,000 U over 12 h daily for 3 d Heparin at 30,000 U/d for 7 d followed by oral anticoagulants	High dose: urokinase: 10/10 Low dose: urokinase: 10/10 Heparin: 10/10	7 d	High dose: urokinase: 0/10 Low dose: urokinase: 0/10 Heparin: 0/10	High dose: urokinase: 0/10 Low dose: urokinase: 0/10 Heparin: 0/10	High dose: urokinase: 0/10 Low dose: urokinase: 0/10 Heparin: 0/10	Primary outcome was lung scan perfusion Thrombolysis arms did not receive heparin All patients: oral Anticoagulants continued for 1 yr
rt-PA plus heparin vs heparin							
Dalla-Volta and Palla[270]/1992	rt-PA at 10 mg followed by 90 mg over 2 h Heparin at 10,000 U followed by 1,750 U/h for 7 to 10 d	rt-PA: 20/20 Heparin: 16/16	30 d	rt-PA: 1/20 (5.0%) Heparin: 0/16 RR, 2.43 (95% CI, 0.11–55.89)	rt-PA: 3/20 (15.0%) Heparin: 2/16 (12.5%) RR, 1.20 (95% CI, 0.23–6.34)	rt-PA: 2/20 (10.0%) Heparin: 0/16 RR, 4.05 (95% CI, 0.21–78.76)	Primary outcome was angiographic reperfusion
Goldhaber et al[391]/1993	rt-PA at 100 mg over 2 h followed by heparin at 1,000 U/h Heparin at 5,000 U followed by 1,000 U/h	rt-PA: 46/46 Heparin: 55/55	In-hospital 14–21 d	rt-PA: 0/46; Heparin: 5/55 (9.1%) RR, 0.11 (95% CI, 0.01–1.91)	rt-PA: 3/46 (6.5%) Heparin: 1/55 (1.8%) RR, 3.59 (95% CI, 0.39–33.33)	rt-PA: 0/46 Heparin: 2/55 3.6%) RR, 0.24 (95% CI, 0.01–4.84)	Primary outcome was echocardiographic right ventricular function
Konstantinides et al[279]/2002	rt-PA at 100 mg, followed by alteplase at 90 mg over 2 h plus heparin at 1,000 U/h Heparin at 5,000 U followed by 1.000 U/h plus placebo	rt-PA: 118/118 Heparin plus placebo: 138/138	30 d	rt-PA: 4/118 (3.4%) Heparin plus placebo: 4/138 (2.9%) RR, 1.17 (95% CI, 0.30–4.57)	rt-PA: 1/118 (0.8%) Heparin plus placebo: 5/138 (3.6%) RR, 0.23 (95% CI, 0.03–1.97)	rt-PA: 4/118 (3.4%) Heparin plus placebo: 3/138 (2.2%) RR, 1.56 (95% CI, 0.36–6.83)	Primary outcome was death or need for escalation of therapy (later decision could be made after unblinding)

Table 16—*Continued*

Author/yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Recurrent DVT and PE, No./Total (%)	Major Bleeding, No./Total (%)	Total Mortality, No./Total (%)	Comments
Levine et al[301]/1990	rt-PA at 0.6 mg/kg over 2 min	rt-PA: 33/33	10 d	rt-PA: 0/33	rt-PA: 0/33	rt-PA: 1/33 (3.0%)	Primary outcome was lung scan reperfusion
	Placebo plus heparin at 5,000 U followed by 30,000 U/d	Placebo: 25/25		Placebo: 0/25	Placebo: 0/25	Placebo: 0/25 RR, 2.29 (95% CI, 0.10–54.06)	
PIOPED Investigators[272]/1990	rt-PA at 40–80 mg at 1 mg/min	rt-PA: 9/9	7 d	rt-PA: 0/9	rt-PA: 1/9 (11.1%)	rt-PA: 0/9	Primary outcome not stated (serial angiographic and lung scans were assessed)
	Placebo plus heparin (doses determined by physician)	Placebo: 4/4		Placebo: 0/4	Placebo: 0/4 RR, 1.50 (95% CI, 0.07–30.59)	Placebo: 0/4	Heparin doses were determined by attending physician in both groups One death occurred 19 d after treatment

*CTA = Committee on Thrombolytic Agents. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

tricular enlargement on echocardiography. This trial will randomize approximately 1,000 patients to thrombolysis with a bolus regimen of tenecteplase plus heparin vs heparin alone.

In summary, there is good evidence that thrombolytic therapy accelerates resolution of PE and results in more rapid hemodynamic improvement. The evidence that thrombolytic therapy improves clinical outcome is less secure. In the absence of risk factors for bleeding, patients who are hemodynamically compromised are very likely to benefit, as are sick patients with major pulmonary arterial obstruction, although the evidence supporting the latter group is indirect.

Choice of Thrombolytic Therapy Regimen

Nine randomized trials[292–299] (total of 621 patients) have compared the rate of thrombus resolution achieved with various IV thrombolytic regimens. These regimens included urokinase administered over 2 h [295] or 12 h[292,298]; streptokinase given over 2 h[296], 12 h[297] or 24 h[292]; and recombinant tissue plasminogen activator (rt-PA) administered over 15 min[293,299] or 2 h.[42,293–299] An additional study[300] compared IV with catheter-directed pulmonary arterial administration of rt-PA (50 mg $>$ 2 h). The results of these studies suggest the following: (1) prolonged infusions of thrombolytic agents (*eg*, $\geq$ 12 h) are associated with higher rates of bleeding[292,294]; (2) 2-h infusions achieve more rapid clot lysis than 12- or 24- h infusions[294,297,298]; (3) when a high-concentration, 2-h infusion of thrombolysis is administered, there is no clear difference in the efficacy or safety of rt-PA vs streptokinase[296]; (4) the relative efficacy and safety of bolus rt-PA regimens (*eg*, approximately 50 mg in $\leq$ 15 min) compared with a 2-h infusion of 100 mg of rt-PA is uncertain[293,299,301]; and (5) infusion of rt-PA directly into a pulmonary artery as opposed to a peripheral vein does not accelerate thrombolysis but does cause more frequent bleeding at the catheter insertion site (there was no attempt to infuse rt-PA directly into, or to mechanically disrupt, the thrombus in this study from 1988).[300] When a lytic agent is appropriate for PE, current evidence supports that thrombolytic therapy should be infused into a peripheral vein over 2 h or less. rt-PA, at a dose of 100 mg over 2 h, is currently the most widely used and evaluated regimen. In patients with imminent or actual cardiac arrest, bolus infusion of thrombolytic therapy is indicated.

Initial Anticoagulant Therapy in Patients Treated With Thrombolytic Therapy

In the absence of a contraindication, anticoagulation with UFH, LMWH, or fondaparinux should not

be delayed until diagnostic testing for PE has been completed (see Section 4.1). IV UFH has been used in conjunction with thrombolytic therapy in the trials that have evaluated thrombolysis for PE (Table 16). Consequently, initial anticoagulation with IV UFH is appropriate if thrombolytic therapy is being considered. Different regimens of IV UFH have not been compared in randomized trials in patients with PE who are treated with thrombolytic therapy.

Before thrombolytic therapy is administered, IV UFH should be administered in full therapeutic doses (*eg*, bolus of 80 U/kg followed by 18U/kg/h initially [Sections 1.1 and 4.1]). During administration of thrombolytic therapy, it is acceptable to either continue, or suspend, the UFH infusion (these two practices have never been compared). During a 2-h infusion of 100 mg of tPA, US regulatory bodies recommend suspension of IV UFH, whereas IV UFH is continued during the tPA infusion in many other countries. After administration of thrombolytic therapy, IV UFH should be restarted or continued. In the United States, it is recommended that the APTT is checked immediately after completion of the tPA infusion and that, provided the APTT is not > 80 s, IV UFH is restarted without a bolus at the same rate of infusion as was being used before tPA was started. If UFH has not been suspended, the infusion is continued at the same rate with ongoing adjustment according to APTT results.

Recommendations

4.3.1. All PE patients should undergo rapid risk stratification (Grade 1C)**. For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk** (Grade 1B). **Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy** (Grade 2B)**. The decision to use thrombolytic therapy depends on the clinician's assessment of PE severity, prognosis, and risk of bleeding. For the majority of patients with PE, we recommend against using thrombolytic therapy** (Grade 1B)**.**

4.3.2. In patients with acute PE, when a thrombolytic agent is used, we recommend that treatment be administered via a peripheral vein rather than placing a pulmonary artery catheter to administer treatment (Grade 1B)**.**

4.3.3. In patients with acute PE, with administration of thrombolytic therapy, we recommend use of regimens with short infusion times (*eg*, a 2-h infusion) over those with prolonged infusion times (*eg*, a 24-h infusion) [Grade 1B]**.**

4.4 Catheter Extraction or Fragmentation for the Initial Treatment of PE

Interventional catheterization techniques for massive PE include mechanical fragmentation of thrombus with a standard pulmonary artery catheter, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy, or pigtail rotational catheter embolectomy.[302–305] Pharmacologic thrombolysis and mechanical interventions can be combined when bleeding risk is not high. The goal of catheter extraction of thrombus is to reduce pulmonary arterial resistance enough to reduce pulmonary artery hypertension, alleviating right ventricular dilatation and dysfunction, and rapidly increase cardiac output. Catheter embolectomy rarely results in extraction of massive pulmonary arterial thrombus. More often, clot fragments are suctioned through the catheter or displaced distally with modest angiographic improvement.

There are no randomized trials or prospective cohort studies that have evaluated interventional catheterization techniques for massive PE. Case series[302–305] that have included modest numbers of patients (*eg*, ≤ 50) suggest that these techniques can be lifesaving.

Recommendation

4.4.1. For most patients with PE, we recommend against use of interventional catheterization techniques (Grade 1C)**. In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest use of interventional catheterization techniques if appropriate expertise is available** (Grade 2C)**.**

4.5 Pulmonary Embolectomy for the Initial Treatment of PE

Emergency surgical embolectomy with cardiopulmonary bypass is another management strategy for with massive PE.[306–308] This operation is also suited for acute PE patients who require surgical excision of a right atrial thrombus or impending paradoxical arterial embolism, or closure of a patent foramen ovale. Surgical embolectomy can also be performed to rescue patients in whom thrombolysis has been unsuccessful. Outcomes are better when patients are referred before the onset of cardiogenic shock. At one hospital, 47 patients underwent surgical embolectomy in a 4-year period with a 96% survival rate.[306] The procedure is

best performed on a warm, beating heart, without aortic cross-clamping, cardioplegia, or fibrillatory arrest.

Recommendation

4.5.1. In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest that pulmonary embolectomy may be used if appropriate expertise is available (Grade 2C)**.**

4.6 Vena Caval Filters for the Initial Treatment of PE

As previously noted in section 1.13, vena caval filters can be used instead of initial anticoagulant therapy (*eg*, unacceptable risk of bleeding) or as an adjunct to anticoagulation in patients with acute VTE. As for acute DVT, no randomized trials or prospective cohort studies have evaluated IVC filters as sole therapy for acute PE (*ie*, without concurrent anticoagulation). As described in Section 1.13 and Table 6, the PREPIC study,[29,135] which evaluated IVC filters as an adjunct to anticoagulation in 400 high-risk patients with proximal DVT, showed that filters reduced PE, increased DVT, and did not change overall frequency of VTE (DVT and/or PE combined). The PREPIC study[29] included 145 patients (36% of total) with symptomatic PE and 52 patients (13% of total) with asymptomatic PE at enrolment in addition to proximal DVT. Multivariable analyses did not find an association between the presence of PE at entry and the frequency of PE at 2 years; however, such an association was present after 8 years of follow-up.[135]

There is uncertainty about the risk and benefits of inserting an IVC filter as an adjunct to anticoagulant and thrombolytic therapy in patients with massive PE. Among patients with hemodynamic compromise in the International Cooperative Pulmonary Embolism Registry, insertion of an IVC filter was associated with a reduction of early recurrent PE and death.[280] Epidemiologic data suggest that insertion of an IVC filter in patients who present with PE (with or without symptomatic DVT) is associated with about a doubling of the frequency of VTE during follow-up; most of this increase is due to a higher frequency of DVT (approximately 2.6-fold increase) rather than PE (approximately 1.3-fold increase).[137]

Recommendations

4.6.1. For patients with PE, we recommend against the routine use of a vena caval filter in addition to anticoagulants (Grade 1A)**.**

4.6.2. In patients with acute PE, if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an IVC filter (Grade 1C)**.**

4.6.3. For patients with acute PE who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if the risk of bleeding resolves (Grade 1C)**.**

5.0 Long-term Treatment of Acute PE

In the following sections, studies that were performed exclusively in patients with PE will be emphasized. In addition, subgroup analyses of PE patients enrolled in studies that included patients who only presented with symptoms of DVT will be presented. As the findings of studies with DVT patients are relevant to PE patients, and as the findings of studies performed exclusively in patients with PE have been consistent with studies that included DVT patients, the recommendations for long-term treatment of PE are the same as for DVT (see corresponding sections for treatment of DVT).

5.1 VKA for the Long-term Treatment of PE

There has been only one evaluation of duration of VKA therapy exclusively in patients with PE. After 3 months of initial treatment, patients with PE provoked by a temporary risk factor were randomized to stop or to receive 3 more months of therapy, and those with unprovoked PE were randomized to stop or to receive 6 more months of therapy (WODIT PE; Table 8). Consistent with studies that included patients who presented with DVT, extended VKA therapy was effective while treatment was being received. However, extending the duration of treatment beyond 3 months did not lower the rates of recurrence that were observed when anticoagulants were subsequently stopped.

5.2 LMWH for the Long-term Treatment of PE

Two small studies[309,310] from the same investigator group have compared long-term LMWH (enoxaparin, 1 mg/kg SC bid for approximately 14 days, followed by 1.5 mg/kg/d SC) with long-term VKA exclusively in patients who presented with PE. The combined results of these two studies are that there was a similar frequency of recurrent VTE (enoxaparin: 4/60; VKA: 1/40) and major bleeding (enoxaparin: 1/60; VKA: 2/40) with the two treatments.[309] Of the 12 other studies that compared LMWH with VKA therapy for long term treatment of VTE (see Section 2.3), only 2 studies[211,213]

included patients with PE; in these 2 studies, all patients had cancer and 295 patients had PE (36% of all enrolled patients; some PE may have been asymptomatic in one study[213]); subgroup analyses were not reported for the PE patients.

5.3 New Antithrombotic Agents for the Long-term Treatment of PE

Fondaparinux has not been evaluated as a long-term treatment for VTE. As previously noted (Section 2.5), ximelagatran has been shown to markedly reduce recurrent VTE (hazard ratio, 0.16) without increasing bleeding in patients with VTE who had completed 6 months of initial treatment with VKAs.[171] In this study, ximelagatran was noted to be equally effective in the subgroup of 447 patients with PE (35% of total) as in the patients with DVT alone.[171] As previously noted (Section 4.2), the long-acting pentasaccharide idraparinux was reported to be less effective than standard therapy with heparins and VKA for the first 3 to 6 months of treatment of PE.[62] After an initial 6 months of treatment with either idraparinux or warfarin (48% of patients initially presented with symptomatic PE), compared with placebo, 6 months of extended therapy with idraparinux markedly reduced recurrent VTE and increased bleeding.[223]

5.4 Treatment of Asymptomatic PE

Diagnosis of unexpected PE when contrast-enhanced CT is performed for other indications has become relatively common.[311–314] Usually (*eg*, approximately 80% of cases), CT has been performed to evaluate known cancer, and the prevalence of incidental PE is higher in inpatients that in outpatients (*eg*, approximately 4% vs 1% of CT scans).[311,314] When there is evidence of an unexpected PE, the first priority is to review the CT scans to determine if the findings are convincing for acute PE. Other recent CT scans may be available for comparison, or the current scan may also reveal DVT in the central deep veins (*eg*, subclavian, IVC, iliac). If there is any uncertainty about the presence of acute PE, additional diagnostic testing is required (*eg*, d-dimer, ultrasonography of the deep veins, dedicated CT pulmonary angiography). When PE is diagnosed unexpectedly in patients with cancer, the clinical history often reveals symptoms suggestive of PE.[312]

Recommendations

5.1.1. For patients with PE secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A)**.**

5.1.2. For patients with unprovoked PE, we recommend treatment with a VKA for at least 3 months (Grade 1A)**. We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked PE should be evaluated for the risk-benefit ratio of long-term therapy** (Grade 1C)**. For patients with a first unprovoked episode of VTE that is a PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment** (Grade 1A)**.** *Values and preferences:* This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A)**.**

5.1.3. For patients with PE and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A)**. For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved** (Grade 1C)**.**

5.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C)**.**

5.1.5. In patients with PE, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A)**. For patients with unprovoked PE who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of conventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (INR range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment** (Grade 1A)**. We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared with an INR range of 2.0 to 3.0** (Grade 1A)**.**

5.1.6. In patients who are unexpectedly found to have asymptomatic PE, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 1C)**.**

6.0 Chronic Thromboembolic Pulmonary Hypertension

CTPH occurs much more frequently after acute PE than had previously been believed. The old teaching was that CTPH had a prevalence of not more than 1 in 500 cases of acute PE; however, data from prospective cohort studies indicate

the frequency is approximately 3%.[315–317] After acute PE initiates CTPH, pulmonary vascular remodeling may cause severe pulmonary hypertension out of proportion to pulmonary vascular thrombosis.[318]

6.1 Pulmonary Thromboendarterectomy, VKA, and Vena Cava Filter for the Treatment of CTPH

Primary therapy for CTPH is pulmonary thromboendarterectomy, which, if successful, can reduce and sometimes cure pulmonary hypertension.[318] The operation requires a median sternotomy, institution of cardiopulmonary bypass, deep hypothermia with circulatory arrest periods, and exploration of both pulmonary arteries. Pulmonary thromboendarterectomy removes organized thrombus by establishing an endarterectomy plane in all involved vessels. At the most experienced centers, the mortality rate is $< 5\%$.[318] The most common postoperative problem is reperfusion pulmonary edema, generally managed with supportive care that requires several days of mechanical ventilation. When pulmonary thromboendarterectomy is successful, patients can usually resume normal daily activities and experience a greatly improved quality of life. Management usually includes insertion of a permanent vena cava filter before or during pulmonary endarterectomy and indefinite anticoagulant therapy with a target INR of 2.5.[319] No randomized trials of CTPH therapy have been undertaken. Patients with CTPH who are not candidates for pulmonary endarterectomy because of comorbid disease or surgically inaccessible lesions may be candidates for pulmonary artery angioplasty.[320]

Some patients with CTPH have predominantly distal (*ie*, subsegmental) vascular involvement. The pathophysiology of pulmonary microvascular disease remains uncertain but may involve release of mediators by endothelial cells or platelets, or plexiform lesions similar to idiopathic pulmonary hypertention.[321,322] It is possible that some of the medical therapies for idiopathic pulmonary hypertension might have a beneficial role in CTPH, especially in those patients who are not surgical candidates or who have a poor response to thrombendarterectomy due to distal microvascular disease. Novel therapies include prostacyclin analogs such as epoprostenol, beraprost, iloprost and treprostinil, endothelin receptor antagonists such as bosentan, and phosphodiesterase-5 inhibitors such as sildenafil.[322–324] A cohort study[325] of 47 patients with inoperable CTPH who were treated with bosentan therapy showed sustained functional and hemodynamic improvement with 96% survival after 1 year.

Recommendations

6.1.1. In selected patients with CTPH, such as those with central disease under the care of an experienced surgical/medical team, we recommend pulmonary thromboendarterectomy (Grade 1C)**.**

6.1.2. For all patients with CTPH, we recommend life-long treatment with a VKA targeted to an INR of 2.0 to 3.0 (Grade 1C)**.**

6.1.3. For patients with CTPH who undergo pulmonary thromboendarterectomy, we suggest the placement of a permanent vena caval filter before or at the time of the procedure (Grade 2C)**.**

6.1.4. For patients with inoperable CTPH, we suggest referral to a center with expertise in pulmonary hypertension so that patients can be evaluated for alternative treatments, such as vasodilator therapy or balloon pulmonary angioplasty (Grade 2C)**.**

7.0 Superficial Vein Thrombosis

7.1 Treatment of Infusion Thrombophlebitis

Peripheral vein infusion thrombophlebitis is estimated to occur in 25 to 35% of hospitalized patients who have peripheral IV catheters.[326] In a three-arm randomized trial[327] of 120 hospitalized patients with infusion thrombophlebitis, diclofenac emulsion gel used topically three times daily and oral diclofenac (75 mg bid) were superior to placebo in relieving local symptoms of thrombophlebitis at 48 h, with positive responses in 60% in both active treatment groups vs only 20% in the control group. Three other controlled trials have assessed the effects of various topical gels or creams compared with placebo for relief of symptoms or clinical resolution of SVT. The largest of these trials[328] randomized 126 inpatients with infusion thrombophlebitis to heparin sodium gel or placebo gel three times daily. At 7 days, phlebitis had resolved in 44% of the heparin group and 26% of the placebo group ($p = 0.03$). In a trial[329] that included 68 patients with spontaneous or infusion-related thrombophlebitis who were randomized to heparinoid cream, piroxicam gel, or placebo, there were no differences among treatment groups in symptoms or size of affected area at 14 days. Finally, a small trial[330] of 23 patients with infusion thrombophlebitis who were randomized to topical essaven gel (contains aescinate, phospholipids, heparin) or placebo found significant improvement in intensity of local symptoms in the group that received essaven. In this study, all patients were also treated with enoxaparin 0.1 mL/10 kg body weight daily (equivalent of 1 mg/kg) for 4 weeks (Table 17). No controlled trials

Table 17—*Infusion Thrombophlebitis Treatment: Clinical Description and Results (Section 7.1)

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Becherucci et al[327]/2000	Parallel RCT, single center	120 hospitalized patients with infusion thrombophlebitis	Topical diclofenac emulsion gel q8h for six doses (n = 40) Oral diclofenac at 75 mg bid for four doses (n = 40) Untreated controls (n = 40)	Intensity of local symptoms (flushing, swelling, warmth, pain)	48 h	Intensity of local symptoms: Topical diclofenac: 60% reduction Oral diclofenac: 60% reduction Control: 20% reduction (p = 0.0001 for both treatment groups vs control)
De Sanctis et al[330]/2001	Parallel RCT, single center	23 patients with confirmed infusion thrombophlebitis	Topical essaven gel (contains aescinate, phospholipids, heparin) once daily (n = 12) Placebo gel once daily (n = 11) Each administered for 4 wk, along with enoxaparin 1 mg/kg for 4 wk	Temperature of affected area Symptom score (based on local pain, disability, and swelling)	4 wk	Temperature at 4 wk: Essaven gel: 71% of baseline Placebo: 86% of baseline (p < 0.05) Symptom score at 4 wk: Essaven gel: 33% of baseline Placebo: 80% of baseline (p < 0.05)
Vilardell et al[328]/1999	Parallel RCT, single center	126 inpatients with superficial phlebitis secondary to indwelling catheter	Heparin sodium gel (1,000 IU/g); Placebo gel; Each applied tid until resolution of phlebitis or 7 d maximum	Resolution of phlebitis	7 d	Resolution of phlebitis: Heparin gel: 27/61 (44.3%) Placebo: 17/65 (26.1%) RR, 1.69 (95% CI, 1.03–2.78; p = 0.03) Note: large No. of withdrawals due to hospital discharge counted as "non-resolution"
Bergqvist et al[329]/1990	Parallel RCT, single center	68 patients (30 inpatients with infusion thrombophlebitis and 38 outpatients with spontaneous thrombophlebitis)	Topical piroxicam gel (0.5%; n = 22), heparinoid cream (n = 22) or placebo (n = 24) applied bid for 14 d or until symptoms disappeared	Intensity of local symptoms Size of thrombophlebitic area Pain intensity by VAS	Approximately 14 d	Intensity of local symptoms: Piroxicam gel: 50% of day 0; Heparinoid cream: 60% of day 0 Control: 45% of day 0 Size of involved area: Piroxicam gel: 5.4% of day 0 Heparinoid cream: 7.8% of day 0 Control: 4.6% of day 0 Pain intensity: Piroxicam gel: 8.8% of day 0; Heparinoid cream: 2.9% of day 0 Control: 5.2% of day 0 (p = not significant for all comparisons)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Study design: RCT, cohort.
‡Drugs: NSAIDs, topical treatments, vs placebo, no treatment, each other, or different durations or regimens of the same agent.
§Symptomatic relief, resolution of phlebitis.

have evaluated systemic anticoagulants for the treatment of infusion thrombophlebitis.

Recommendation

7.1.1. For patients with symptomatic infusion thrombophlebitis as a complication of IV infusion, we suggest oral diclofenac or another nonsteroidal antiinflammatory drug (NSAID) [Grade 2B]**, topical diclofenac gel** (Grade 2B)**, or heparin gel** (Grade 2B) **until resolution of symptoms or for up to 2 weeks. We recommend against the use of systemic anticoagulation** (Grade 1C)**.**

7.2 Treatment of SVT

SVT has been less well studied than DVT but is estimated to occur more often.[331,332] It commonly affects the lower limbs, often involves a varicose vein, is associated with chronic venous insufficiency, malignancy, thrombophilia, pregnancy or exogenous estrogens, obesity, sclerotherapy and a history of VTE, or it may be unprovoked.[331–333]

Although traditionally considered a benign disease, a number of studies[331,332] indicate that the consequences of SVT may be more serious and have led to trials of more aggressive treatment with the goals of reducing symptoms, extension, recurrence, and progression to VTE (Table 18). The treatment of superficial vein thrombosis has been the subject of a recent Cochrane Collaboration systematic review.[334]

Short-Duration Heparin, LMWH, and NSAIDs

In a placebo-controlled trial,[335] 462 patients with SVT were randomly allocated to receive 8 to 12 days of enoxaparin in two dosages (40 mg and 1.5 mg/kg SC daily, tenoxicam 20 mg po daily, or placebo). During the treatment period and at 3-month follow-up, rates of SVT extension or recurrence were 29.5% and 33.0%, respectively, in the placebo group, significantly higher than that of the other three treatment groups (enoxaparin 40 mg, 8.3% and 14.5%; enoxaparin 1.5 mg/kg, 5.7% and 15.1%; tenoxicam, 13.1% and 15.2%). Rates of DVT tended to be lower in the treatment groups vs the placebo group during the initial treatment period, but this trend was lost by 3 months, predominantly due to the occurrence of VTE in the treatment groups during the first 3 weeks after treatment was stopped, suggesting that the initial duration of therapy was inadequate.

In an open-label randomized trial[336] of 117 patients, 6-day courses of calcium nadroparin administered SC daily at doses of 6,150 anti-Xa IU or 31.5 anti-Xa IU/kg were superior to naproxen (500 mg once daily) for relief of symptoms and signs of SVT, but there was no difference in rates of SVT extension at the end of treatment or at 8 weeks.

Longer Courses of Heparin or LMWH

A blinded randomized trial[337] compared a 30-day course of low- vs high-dose SC nadroparin in 164 patients with SVT. During 3 months of follow-up, there were five cases of SVT extension in the low-dose group (all occurred on treatment), compared with two cases in the high-dose group (one occurred on treatment). There were two symptomatic DVTs in the low-dose group vs three DVTs (two symptomatic) and one symptomatic PE (occurred on treatment) in the high-dose group. Lack of a control group precludes assessment of whether either of the treatments was more effective than no treatment; for example, the rate of VTE at 3 months in the high dose group (4.8%) was similar to the 3-month rate of VTE in the placebo group (4.5%) of the previously described STENOX trial.[335]

Sixty patients with acute thrombosis of the great saphenous vein were randomized to receive a 4-week course of SC UFH in moderately high unmonitored doses (12,500 IU bid for 1 week, followed by 10,000 IU bid) or prophylactic doses (5,000 IU bid).[338] At 6 months, 6 patients (20%) in the low-dose heparin group had VTE (three symptomatic events), of which four episodes occurred during treatment, compared with 1 patient (3.3%) in the high-dose heparin group, who had symptomatic DVT after treatment was completed.

One trial[339] found that warfarin was superior to control and had similar effectiveness to low-dose UFH and LMWH with regard to rate of SVT extension at 3 months; however, no information was provided on dose or duration of anticoagulants. A number of other small trials have compared topical[340] or alternate anticoagulants (*eg*, dermatan sulfate)[341] for variable time periods to treat SVT (Table 18). No trials have evaluated the role of fondaparinux in the management of SVT.

Surgical vs Medical Therapy

A nonblinded randomized trial[339] with six treatment arms that included approximately 70 patients per group showed that compression alone or in addition to flush ligation of the saphenous vein were inferior to complete vein stripping or treatment with UFH, LMWH, or warfarin (doses and durations of treatment were not specified) for the end point of SVT extension at 3 months. A second trial[342] compared saphenofemoral ligation, performed under local anesthesia, with enoxaparin 1 mg/kg bid for 1 week, and then daily for 3 weeks. During 6-month follow-up, VTE occurred in two patients (6.7%) in the surgery group (both PE) vs none in the enoxaparin group, while SVT occurred in

one patient (3.3%) in the surgery group and three patients (10%) in the enoxaparin group. Two patients in the surgical group had wound infections, and the cost of surgical treatment was more than three times higher that of medical treatment. Finally, a review of six studies (includes a study[339] described above, and five small case series) comparing surgical therapy to anticoagulation for SVT showed similar rates of SVT progression but higher rates of VTE and complications with surgical therapy.[343]

Recommendation

7.2.1. For patients with spontaneous superficial vein thrombosis, we suggest prophylactic or intermediate doses of LMWH (Grade 2B) **or intermediate doses of UFH** (Grade 2B) **for at least 4 weeks. We suggest that as an alternative to 4 weeks of LMWH or UFH, VKA (target INR, 2.5; range, 2.0 to 3.0) can be overlapped with 5 days of UFH and LMWH and continued for 4 weeks** (Grade 2C)**. We suggest that oral NSAIDs should not be used in addition to anticoagulation** (Grade 2B)**. We recommend medical treatment with anticoagulants over surgical treatment** (Grade 1B)**.**

Remark: It is likely that less extensive superficial vein thrombosis (*ie*, where the affected venous segment is short in length or further from the saphenofemoral junction) does not require treatment with anticoagulants. It is reasonable to use oral or topical NSAIDs for symptom control in such cases.

8.0 Acute UEDVT

Although most episodes of DVT occur in the lower limbs, it is estimated that 1 to 4% of cases involve the upper extremities. UEDVT can be classified into two etiologic groups: primary (includes unprovoked with or without thrombophilia, effort related, and thoracic outlet syndrome) and secondary (provoked by central venous catheters, pacemakers, or cancer); secondary UEDVT accounts for 75 to 80% of all cases.[344–346]

UEDVT may involve the subclavian, axillary or brachial veins. Clinical manifestations include edema, dilated collateral veins over the arm, neck, or chest, and limb pain or discoloration. The disease may lead to complications, including pulmonary embolism (estimated to occur in up to one third of patients[346]), recurrent UEDVT (a prospective study[347] reported cumulative incidence rates of 2.0%, 4.2% and 7.7% after 1, 2, and 5 years, respectively) and PTS of the arm.[347,348] The treatment of patients with acute UEDVT may be divided into the initial treatment phase (with anticoagulants, thrombolytic therapy, catheter/surgical techniques, or filter placement) and long-term treatment (or secondary prophylaxis) with anticoagulants to prevent recurrent VTE.

8.1 IV UFH or LMWH for the Initial Treatment of UEDVT

It is generally accepted that, as for patients with lower-limb DVT, patients with UEDVT require treatment with anticoagulants to prevent thrombus extension and PE (Table 19). To date, no RCTs have evaluated UFH, LMWH, or other anticoagulants for the initial treatment of UEDVT. Several small prospective cohort studies have reported low rates of recurrent DVT, PE, and major bleeds using treatment regimens for UEDVT similar to those for patients with lower-limb DVT (Table 19). In a prospective two-center cohort study,[349] 46 outpatients with UEDVT were treated with SC LMWH followed by warfarin. At 3 months, there was one recurrence, one major bleed, and no episodes of PE. In 36 inpatients with UEDVT, LMWH twice daily for up to 7 days followed by warfarin for an average of 5 months (target INR, 2.0 to 2.5) led to significant early symptom relief and no recurrent DVT or PE at 1 year.[350] Rates of VTE recurrence were similarly low in a cohort of 53 patients who received UFH or LMWH for the initial treatment of UEDVT followed by warfarin for 3 months,[347] and in 74 cancer patients with central venous catheter-associated UEDVT, in whom treatment with LMWH for 5 to 7 days followed by warfarin for 3 months appeared to prevent catheter failure and was not associated with any recurrent VTE[351] (Table 19).

Recommendation

8.1.1. For patients with acute UEDVT, we recommend initial treatment with therapeutic doses of LMWH, UFH, or fondaparinux as described for leg DVT (see Section 1) [Grade 1C]**.**

8.2 Thrombolytic Therapy for the Initial Treatment of UEDVT

No randomized controlled studies have evaluated the efficacy and safety of thrombolytic therapy compared with standard anticoagulation for the initial treatment of patients with UEDVT (Table 20). A number of retrospective and small prospective studies[92,352–358] that included 6 to 118 patients have evaluated streptokinase, urokinase, or rT-PA administered with varying doses, methods of administration (IV, catheter directed), and infusion durations. Three of these studies[352,356,357] included control groups that received anticoagula-

Table 18—*Superficial Vein Thrombosis Treatment: Clinical Description and Results (Section 7.2)**

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
STENOX Study Group[335]/ 2003	Parallel RCT, multicenter	436 patients with ultrasound-confirmed acute symptomatic SVT (≥ 5 cm length) of lower extremity	Enoxaparin at 40 mg/d SC Enoxaparin at 1.5 mg/kg/d SC Tenoxicam at 20 mg/d po Placebo once daily All administered for 8–12 d All patients prescribed elastic bandages or compression stockings for at least 15 d	Day 12 (end of treatment): screening ultrasound or symptomatic recurrence: VTE SVT recurrence/extension to saphenofemoral junction 3 mo VTE SVT recurrence/extension Major bleed Death	3 mo	VTE day 12: Placebo: 4/112 (3.6%); PE, 0 Enoxaparin, 40 mg: 1/110 (0.9%); PE, 0; RR, 0.25 (95% CI, 0.03–2.24) Enoxaparin at 1.5 mg/kg: 1/106 (0.9%); PE, 0; RR, 0.26 (95% CI, 0.03–2.33) Tenoxicam: 2/99 (2.0%); PE, 1; RR, 0.57 (95% CI, 0.11–3.02) p = not significant for all comparisons of active treatment vs placebo SVT; recurrence/extension day 12: Placebo: 33/112 (29.5%) Enoxaparin at 40 mg: 9/110 (8.3%) RR, 0.28 (95% CI, 0.14–0.55) Enoxaparin at 1.5 mg/kg: 6/106 (5.7%) RR, 0.19 (95% CI, 0.08–0.44) Tenoxicam: 13/99 (13.1%) RR, 0.45 (95% CI, 0.25–0.80) VTE at 3 mo: Placebo: 5/112 (4.5%); PE, 0 Enoxaparin at 40 mg: 6/110 (5.7%) PE, 2; RR, 1.22 (95% CI, 0.38–3.89) Enoxaparin at 1.5 mg/kg: 4/106 (3.9%); PE, 0; RR, 0.85; 95% CI, 0.23–3.06 Tenoxicam: 4/99 (4.3%); PE, 1; RR, 0.91 (95% CI, 0.25–3.28) p = not significant for all comparisons of active treatment vs placebo SVT; recurrence/extension at 3 mo: Placebo: 37/112 (33.0%) Enoxaparin at 40 mg: 16/110 (14.5%); RR, 0.44 (95% CI, 0.26–0.74) Enoxaparin at 1.5 mg/kg: 16/106 (15.1%); RR, 0.46 (95% CI, 0.27- 0.77) Tenoxicam: 15/99 (15.2%); RR, 0.46 (95% CI, 0.27- 0.78) Major bleed: 0 Death: 0

Table 18—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Titon et al[336]/1994	Parallel RCT, multicenter	117 patients with ultrasound-confirmed SVT of lower extremities	Nadroparin fixed dose, 6,150 anti-Xa IU/d Nadroparin 31.5 anti-Xa IU/kg/d SC Naproxen 500 mg/d po Treatments given for 6 d All patients wore compression stockings for 7 d	Echographic extension of thrombus at day 7 and at 8 wk Changes in symptoms and clinical signs (warmth, flushing, edema, pain on palpation) DVT PE Major bleed	8 weeks	Day 7 extension of thrombus: Fixed-dose nadroparin: 1/38 (2.6%) Weight-based nadroparin: 2/40 (5%); RR, 1.90 (95% CI, 0.18–20.1) Naproxen: 1/39 (2.6%); RR, 0.97 (95% CI, 0.06–15.02); P = not significant 8 wks: extension of thrombus or new SVT Fixed dose nadroparin: 2/36 (5.6%) Weight-based nadroparin: 0/40 (0%); RR 0.18 (95% CI), 0.01–3.64) Naproxen: 0/39 (0%); RR, 0.19 (95% CI, 0.01–3.73) No DVT, PE, or major bleed in any group Intensity of symptoms/signs: overall improvement in score from day 0 to day 7: Fixed –dose nadroparin: 79.1% improved Weight-based nadroparin: 63.0% improved Naproxen: 46.4% improved ($p < 0.01$ in favor of nadroparin groups vs naproxen; this difference was maintained at 8 wk
Prandoni et al[337] for Vesalio Investigators Group/2005	Parallel RCT, multicenter	164 patients with ultrasound-confirmed acute SVT of the greater saphenous vein	High-dose, weight-adjusted nadroparin (190 antiXa IU/kg for 10 d followed by 95 antiXa IU/kg for 20 d) Low-dose nadroparin (2,850 anti-Xa IU) for 30 d; no placebo group; NSAIDS and aspirin use discouraged	Composite outcome of asymptomatic or symptomatic SVT extension, asymptomatic or symptomatic DVT, symptomatic PE at 3 mo Improvement in clinical symptoms and signs at 1 mo Major bleed Death	3 mo	3 mo follow-up: SVT: High dose: 2/83 (2.4%; 1 occurred while receiving treatment) Low dose: 5/81 (6.2%; all occurred while receiving treatment) RR, 2.56 (95% CI, 0.51–12.83) VTE: High dose: 4/83 (4.8%; 3 symptomatic events; 1 [PE] occurred while receiving treatment) Low dose: 2/81 (2.5%; both symptomatic DVT) RR, 0.51 (95% CI, 0.10–2.72) Rate of improvement in clinical symptoms and signs similar both groups Major bleed: 0 Death: 0

Table 18—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Marchiori et al[338]/ 2002	Parallel RCT, single center	60 patients with ultrasound-confirmed first acute SVT of greater saphenous vein	Low-dose UFH (5,000 IU SC bid for 4 wk) High-dose UFH (12,500 IU for 1 wk, then 10,000 IU for 3 wk) Use of concomitant systemic or local antiinflammatory drugs permitted, but use not described	VTE Extension/recurrence of thrombosis Major bleed Heparin-induced thrombocytopenia Death	6 mo	VTE during treatment period: Low dose: 4/30 (13.3%; 3 asymptomatic DVT, 1 PE) High dose: 0/30 (0%); RR, 0.11 (95% CI, 0.01–1.98; p = not significant) Extension/recurrence SVT during treatment period Low dose: 7/30 (23.3%) High dose: 3/30 (10%); RR, 0.40 (95% CI, 0.11–1.40; p = not significant) Overall VTE during follow-up period: Low dose: 6/30 (20%) High dose: 1/30 (3.3%), RR, 0.17 (95% CI, 0.02–1.30; p = not significant) Overall extension/recurrence SVT during follow-up period: Low dose: 11/30 (36.7%) High dose: 8/30 (26.7%) RR, 0.73 (95% CI, 0.34–1.55; p = not significant) No major bleed, heparin-induced thrombocytopenia, or death in any group
Belcaro et al[339]/ 1999	Parallel RCT, multicenter	562 patients with ultrasound-confirmed SVT and large varicose veins or venous incompetence	Group A: elastic compression stockings alone Group B: elastic compression stockings and simple flush ligation Group C: elastic compression stockings and complete stripping and perforator ligation Group D: elastic compression stockings and low-dose SC heparin Group E: elastic compression stockings and LMWH Group F: elastic compression stockings and VKA Doses and duration of anticoagulants not specified	Extension of SVT at 3 mo Extension of SVT at 6 mo New DVT at 3 mo	6 mo	Extension of thrombus at 3 mo: Group A: 32/78 (41%) Group B: 11/78 (14.1%); RR, 0.34 (95% CI, 0.19–0.63) Group C: 0/70; RR, 0.02 (95% CI, 0.00–0.27) Group D: 4/71 (5.6%); RR, 0.14 (95% CI, 0.05–0.37) Group E: 4/76 (5.2%); RR, 0.13 (95% CI, 0.05–0.35) Group F: 5/71 (7.0%); RR, 0.17 (95% CI, 0.07–0.42; p < 0.05 for groups C, D, E, and F vs groups A or B Extension at 6 mo: Group A: 13/78 (16.7%) Group B: 6/78 (7.7%); RR, 0.46 (95% CI, 0.18–1.15) Group C: 1/70 (1.4%); RR, 0.09 (95% CI, 0.01–0.64) Group D: 2/71 (2.8%); RR, 0.17 (95% CI, 0.04–0.72) Group E: 1/76 (1.3%); RR, 0.08(95% CI, 0.01–0.59) Group F: 5/71 (7%); RR, 0.42 (95% CI, 0.16–1.13 P value not stated New DVT at 3 mo: Group A: 6/78 (7.7%) Group B: 2/78 (2.5%); RR, 0.33 (95% CI, 0.07–1.60) Group C: 2/70 (2.8%); RR. 0.37 (95% CI, 0.08–1.78) Group D: 0/71 (0%); RR, 0.08 (95% CI, 0.0–1.47) Group E: 0/76 (0%); RR, 0.08 (95% CI, 0.0–1.38) Group F: 0/71 (0%); RR, 0.08 (95% CI, 0.0–1.47) P = not significant

Table 18—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Lozano and Almazan[342]/ 2003	Parallel RCT, single center	60 patients with ultrasound-confirmed above-knee internal saphenous SVT	Saphenofemoral disconnection under local anesthesia with short-term use of a compression bandage Outpatient enoxaparin at 1 mg/kg bid for 1 wk and then once daily for 3 wk No placebo/control group All patients were instructed to wear elastic compression stockings and used acetaminophen for pain	Recurrence/extension of SVT VTE Complications of surgery Major bleed Death Costs	6 mo	Recurrent SVT: Surgical group: 1/30 (3.3%) Enoxaparin group: 3/30 (10%) RR, 3.0 (95% CI, 0.33–27.24) VTE: Surgical group: 2/30 (6.7%; both symptomatic PE) Enoxaparin group: 0/30 (0%) RR, 0.20; 95% CI, 0.01–4.0 Wound infections: Surgical group: 2/30 (6.7%) Major bleeding: 0 Death: 0 Cost of treatment: Surgical group: $1,400 per patient; mean 1.6 d in hospital Enoxaparin group: $300 per patient; 0 d in hospital
Sullivan et al[343]/ 2001	Systematic review of six studies (includes Belcaro[339] above and five small case series)	Patients with objectively confirmed above-knee SVT	Ligation of greater saphenous vein at saphenofemoral junction, with or without vein stripping (n = 246) Anticoagulation (IV heparin followed by VKA for 6 wk-6 mo; n = 88)	SVT progression DVT PE Surgical complications Bleeding complications	Surgical group: 4–6 mo Medical group: 6 d to 14 mo	SVT progression: Surgical group: 18/148 (12%) Medical group: 10/71 (14%) RR, 0.16 (95% CI, 0.56–2.38) DVT Surgical group: 7/204 (3.4%) Medical group: 2/88 (2.2%) RR, 0.66 (95% CI, 0.14–3.13) PE Surgical group: 2/98 (2.0%) Medical group: 0/17 (0%) RR, 1.10 (95% CI, 0.06–21.98) Surgical complications: 6/78 (7.7%; hematoma, seroma, infection) Bleeding complications: 0/17 (0%)

Table 18—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Gorski et al[340]/ 2005	Parallel RCT, multicenter	46 patients with ultrasound-confirmed SVT	Topical liposomal heparin spray gel (four sprays of 458 IU tid) Enoxaparin at 40 mg SC qd Treatment for 7–14 d	Pain by VAS (0–10 scale) Area of erythema Subjective efficacy assessment by investigator and patient Duplex assessment for thrombus regression day 21 DVT Adverse events Death	21 d	Data extrapolated from graphs and figures in paper by reviewer Pain by VAS day 21 Topical heparin, 0 LMWH, 0 Improvement noted at each time point; no pain at 21 d, no significant difference between groups Area of erythema: Improvement noted at each time point; no erythema at 21 d, no significant difference between groups Subjective efficacy assessed Majority of patients (> 75%) reported good or very good treatment efficacy; no signigicant difference between groups Thrombus regression Topical heparin: 10/21 (47.6%) LMWH: 9/23 (39.1%) RR, 0.82 (95% CI, 0.42–1.62) DVT Topical heparin: 3/21 (14.3%) LMWH heparin: 1/23 (4.3%) RR, 0.30 (95% CI, 0.03–2.70) Adverse events Allergic reaction in one patient in enoxaparin group Death: 0
Andreozzi et al[341]/1996	Parallel RCT, multicenter	56 patients with SVT of the lower limbs	Group A: dermatan sulfate at 100 mg SQ qd Group B: dermatan sulfate at 100 mg SQ bid Group C: dermatan sulfate at 200 mg IM qd Treatment for 30 d	Pain Increase in functional ability Local edema	30 d	Data extrapolated from graphs and figures in paper by reviewer Resolution of pain, day 30: Group A: 47% Group B: 83% Group C: 79% (p value not stated) Increase in ability to perform normal daily activities: day 30 Group A: 44% Group B: 67% Group C: 84% ($p < 0.05$; groups B and C vs group A) Local edema: day 30: Progressive improvement in all three groups; no significant differences between groups

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Study design: RCT, cohort 2.
‡Drugs: VKA, UFH, LMWH, NSAIDs, aspirin, topical treatments, surgery vs placebo, no treatment, each other or different durations or regimens of the same agent.
§Outcomes: extension of thrombus, symptomatic relief, DVT and PE, major bleeding, surgical complications, death.

tion alone. In some studies, a few patients additionally had venous angioplasty[354] or surgical decompression[352,354,357] (Table 20).

In the largest of the studies,[357] 118 consecutive patients with UEDVT were assessed retrospectively. At a median of 40 months of follow-up, venous patency on ultrasound was noted in 65% of patients who had been treated with IV urokinase compared with 20% of patients treated with standard anticoagulants; however, the rates of recurrent VTE were similar in the two groups and the lysis group had a 15.2% rate of bleeding, compared with no bleeds in the anticoagulant group, a difference that was highly statistically significant. In the largest of the prospective studies,[353] among 35 patients with primary UEDVT treated with CDT followed by warfarin for a mean of 5 months, the rate of ipsilateral UEDVT recurrence at 54 months of follow-up was substantial at 23%.

To summarize the heterogeneous, low-to-moderate quality data available, some studies[352,356,357] report good-to-excellent success of thrombolytic therapy in terms of early and late venous patency. However, for important clinical end points such as PE, recurrent VTE, bleeding, and PTS, it is not known if initial thrombolytic therapy is, on balance, superior or inferior to anticoagulant therapy, or whether one thrombolytic approach is better or worse than another, as no prospective, controlled comparisons have been performed.

Recommendations

8.2.1. For most patients with acute UEDVT, we recommend against the routine use of systemic or catheter-directed thrombolytic therapy (Grade 1C)**.**

8.2.2. In selected patients with acute UEDVT (*eg*, those with a low risk of bleeding and severe symptoms of recent onset), we suggest that CDT may be used for initial treatment if appropriate expertise and resources are available (Grade 2C)**.**

8.3 Catheter Extraction, Surgical Thrombectomy, Transluminal Angioplasty, Stent Placement, Staged Approach of Lysis Followed by Interventional or Surgical Procedure, SVC Filter Insertion, for the Initial Treatment of UEDVT.

A number of reviews[359,360] have advocated staged, multidisciplinary approaches to the management of primary UEDVT that involve thrombolysis and angioplasty or stent placement, followed by early or late surgical decompression of the thoracic outlet. However, data on the efficacy and safety of these approaches are limited and derived from small, uncontrolled, prospective[361–363] or retrospective[364–372] case series, most single-center (Table 21). In studies where results were reported separately for surgical and nonsurgical approaches, surgery with or without lysis tended to achieved higher late rates of vein patency and lower rates of PTS than lysis alone.[361,367] Among studies that only reported results for surgical treatment, rates of PTS ranged from 15 to 50%,[366,368,370,373] which are similar to rates reported after medical therapy alone.[347,348] Most studies did not provide data on surgical complications; however, one small prospective study[362] reported a 26% rate of serious postoperative complications.

SVC filters have been used in small series of patients with contraindications to or failure of anticoagulant therapy.[363,364] In a prospective study[363] of 41 patients with UEDVT who had SVC filters placed, the rates of PE and PTS during long-term follow-up were 2.4% and 0%, respectively. In a retrospective series[364] of 72 patients with SVC filters, there were no episodes of PE or SVC thrombosis during long-term follow-up.

Recommendations

8.3.1. For most patients with acute UEDVT, we recommend against the routine use of catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, or SVC filter placement (Grade 1C)**.**

8.3.2. In selected patients with acute UEDVT (*eg*, those with primary UEDVT and failure of anticoagulant or thrombolytic treatment who have severe persistent symptoms), we suggest that catheter extraction, surgical thrombectomy, transluminal angioplasty, or a staged approach of lysis followed by a vascular interventional or surgical procedure may be used if appropriate expertise and resources are available (all Grade 2C)**.**

8.3.3. In selected patients with acute UEDVT (*eg*, those in whom anticoagulant treatment is contraindicated and there is clear evidence of DVT progression or clinically significant PE), we suggest placement of an SVC filter (Grade 2C)**.**

8.4 Anticoagulants for the Long-term Treatment of UEDVT

There are no randomized studies of duration or intensity of long-term anticoagulation for the prevention of recurrent VTE in patients with UEDVT (Table

Table 19—*Initial Treatment of Acute UEDVT With IV UFH or LMWH: Clinical Description and Results (Section 8.1)

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Savage et al[349]/ 1999	Prospective cohort, two center	46 outpatients with UEDVT (includes 16 patients with central venous catheter)	Dalteparin daily for 5–7 d (200 IU/kg) and VKA with target INR of 2.0–3.0 Duration of VKA not provided	Symptomatic recurrence/ extension of DVT PE Major bleed Death	3 mo	Recurrence/extension DVT: 1/46 (2%) PE: 0/46 Major bleed: 1/46 (2%; on VKA) Death: 7/46 (15%; none from PE or bleed)
Karabay et al[350]/ 2003	Prospective cohort, single center	36 inpatients with UEDVT (includes 13 with central venous catheter)	Nadroparin SC bid, 86 aXa IU/kg for up to 7 d, then VKA (started on day 3; target INR, 2–2.5) for mean of 4.7 mo	Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death	1 yr	Significant symptom relief: day 7: 32/36 (89%) Lysis: day 10 ≥ 35%: 16/36 (45%) < 35%: 17/36 (47%) none: 3/36 (8%) Recurrent DVT: 0/36 PE: 0/36 Death: 9/36 (25%); none due to PE or bleed
Prandoni et al[229]/ 2004	Prospective cohort, number of centers not stated	53 patients with first UEDVT (included 6 with central venous catheter)	Therapeutic dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death	Median, 48 mo	Results not presented according to initial treatment with UFH vs LMWH Recurrent VTE: 3/53 (5.7%; 2 arm, 1 leg); cumulative incidence 1 yr, 2 yr, and 5 yr: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%); due to cancer, PE, congestive heart failure (numbers not provided)
Kovacs et al[351]/ 2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had central venous catheter)	Dalteparin daily for 5–7 d (200 IU/kg) and VKA to achieve target INR of 2.0–3.0	Recurrent VTE PE Major bleed Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0/74 PE: 0/74 Major bleed: 3/74 (4%) Death: 7/74 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0/74

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Prospective cohort studies.
‡Drugs: IV UFH or LMWH followed by oral anticoagulants.
§Recurrent DVT and PE, major bleeding, total mortality, early symptom relief.

22). There is general agreement that, as for patients with lower-extremity DVT, patients with symptomatic acute DVT of the upper extremity require long-term treatment with anticoagulants following initial treatment, and that a similar process as for lower-extremity DVT should be used to determine the optimal duration of anticoagulation.[374–377] However, there is little evidence to support indefinite anticoagulant therapy for a first unprovoked UEDVT.

In prospective cohort studies[346,349–351,378] of the treatment of UEDVT, patients received VKA (target INR, 2.5; range, 2.0 to 3.0) for periods of 3 to 6 months or longer. Similar regimens were reported in retrospective studies.[373,379–383] Rates of recurrent VTE, bleeding, PTS, and death reported during long-term follow-up in these studies are shown in Table 22. No data are available regarding the long-term use of LMWH monotherapy or newer anticoagulants, such as fondaparinux, for the long-term treatment of UEDVT.

Table 20—*Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Clinical Description and Results (Section 8.2)**

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
AbuRahma et al[352]/ 1996	Retrospective case series, single center	19 patients with UEDVT (13 primary, 6 central venous catheter related)	Adjusted IV heparin then VKA for 3–12 mo (n = 9) Urokinase at 4,500 U/kg load, then 4,500 U/kg/h for 24–48 h or streptokinase 250,000U then 100,000U/h for 48 h plus IV heparin plus VKA (n = 10) Three patients also had first rib resection	Bleed with initial treatment Vein patency on ultrasound at final follow-up Clinical resolution at final follow-up	Mean, 36 mo	Bleed: 0/19 Vein patent: Anticoagulation group: 2/9 (22.2%) Lysis group: 8/10 (80%) p = 0.018 Complete clinical resolution: Anticoagulation group: 2/9 (22.2%) Lysis group: 8/10 (80%)
Pegis et al[355]/1997	Prospective case series, single center	6 patients with effort-induced UEDVT and thoracic outlet syndrome	Catheter-directed urokinase infusion (2,500 U/kg bolus, then 2,500 U/kg/h) and heparin (100 U/kg q12h) during a mean of 64 h	Immediate clot lysis (complete, partial, or no lysis) Bleed Able to resume normal level of activity	31 mo (mean)	Complete lysis: 3/6 (50%) Partial lysis: 2/6 (33%) No lysis: 1/6 (17%) Bleed: 0/6 Able to resume usual activity: 5/6 (83%) Patient with no lysis was the one not able to resume activity
Schindler et al[358]/ 1999	Retrospective case series, single center	18 cancer patients undergoing regional thrombolysis for central venous catheter-related UEDVT during high-dose chemotherapy	Urokinase IV infusion at a dose of 75,000–150,000 U/h for 24–96 h, then adjusted IV heparin for 5–7 d and VKA (target INR, 2–3) for at least 3 mo	VTE recurrence Bleed during lysis	Unspecified	VTE recurrence (all UEDVT): 4/18 (22.2%) [day 13, 16, 48, 54], all with subtherapeutic INR Bleed: 4/18 (22.2%) minor; 1/18 (5.6%) major
Petrakis et al[356]/ 2000	Retrospective case series, single center	20 patients with 1° (n = 11) and 2° (n = 9) UEDVT	Anticoagulant therapy (adjusted IV heparin for 7 d, VKA to achieve prothrombin time 1.5–2 × control for 6–12 mo; n = 11) Thrombolysis (urokinase at 4,500 U/kg loading dose, then 4,500 U/kg/h, or streptokinase at 250,000 U load, then 100,00U/h for 24–48 h, followed by IV heparin for 7 d and VKA for 3 mo (n = 9)	Vein patency at follow-up Clinical improvement in symptoms	Anticoagulation group: 82 mo (mean) Lysis group: 52 mo (mean)	Venous patency: anticoagulation: 1/11 (9%) Lysis: 5/9 (56%) [p = 0.040] Clinical improvement: anticoagulation: 4/11 (36%) Lysis: 8/9 (89%) [p = 0.028]
Horne et al[92]/2000	Prospective cohort, single center	18 patients with axillary or subclavian DVT	Catheter-directed rt-PA (2 mg/cm of thrombus to maximum of 20 mg), then VKA for 3 mo	Immediate patency Establishment of antegrade flow Bleeding events	6 mo	Immediate patency: 10/18 (56%); antegrade flow: 11/18 (61%); bleeds (all minor): 5/18 (28%)
Lokanathan et al[354]/ 2001	Retrospective case series, single center	28 patients with first episode of primary UEDVT (0 centra; venous catheters)	Urokinase bolus (range, 10,000-1,000,000 U) plus continuous infusion (50,000–240,000 U/h), followed by IV heparin then VKA for 3 mo 12 patients had angioplasty; 2 patients had thoracic outlet decompression	VTE recurrence PE Bleed PTS symptoms	2.9 yr (mean)	VTE recurrence: 3/21 (14%) PE: 1/21 (5%) Bleed: 0 PTS: none: 6/21 (29%) Mild: 13/21 (62%) Moderate: 2/21 (10%)

Table 20—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Sabeti et al[357]/2002	Retrospective cohort study, single center	118 consecutive inpatients with UEDVT	Adjusted IV heparin or LMWH 100 IU/kg bid plus oral VKA for 6 mo (INR, 2–3) [n = 62] Urokinase at 150,00 IU/h for 24 h plus oral VKA for 6 mo (INR, 2–3) [n = 33] 3 patients also had first rib resection	Vein patency on ultrasound (assessed in 83 patients) Recurrent VTE Bleed PTS	Median, 40 mo	Venous patency rate: significantly higher in lysis group than anticoagulation group (p = 0.01 log rank test); data not provided Recurrent VTE: Anticoagulation group: 5/62 Lysis group: 2/33, p = 0.9 Major bleed: Anticoagulation group: 0/62; Lysis group: 5/33 p < 0.0001 PTS: Anticoagulation group: 6/62; Lysis group: 3/33 p = 0.3
Lee et al[353]/2006	Prospective case series, single center	35 patients with primary UEDVT who had complete resolution of acute symptoms with CDT (n = 29) or IV heparin (n = 6)	Oral VKA for mean of 5.2 mo	Recurrent DVT	54 mo	Ipsilateral recurrent DVT: 8/35 (23%)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Retrospective and prospective cohort studies.
‡Drugs: thrombolytic therapy, compared with different types of lytic therapy or with anticoagulants.
§Outcomes: Recurrent DVT and PE, vein patency, major bleeding, total mortality, and PTS of the arm.

Table 21—*Initial Treatment of Acute UEDVT With Catheter Extraction, Surgical Thrombectomy, Transluminal Angioplasty, Stent Placement, Staged Approach to Lysis Followed by Intervention or Surgical Procedure, or SVC Filter Insertion: Clinical Description and Results (Section 8.3)

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Machleder[361]/ 1993	Prospective case series, single center	50 patients with primary UEDVT	Staged multidisciplinary approach Systemic or catheter-directed lysis with urokinase or streptokinase, followed by IV heparin and VKA for 3 mo, with subsequent surgical treatment (transaxillary first rib resection) in cases where an underlying compressive abnormality of vein remained or obstruction of venous collaterals with arm abduction was present 35 patients (70%) underwent transaxillary first rib resection	Bleed PTS symptoms	3.1 yr (mean)	Bleed: 1/50 (occurred on VKA) PTS symptoms: In those who had surgery: None: 25/35 (72%) Minimal: 5/35 (14%) Persistent: 5/35 (14%) In those who did not have surgery: None: 6/15 (40%) Minimal: 4/15 (27%) Persistent: 5/15 (33%)
Malcynski et al[367]/1993	Retrospective case series, single center	12 patients with primary UEDVT	Staged multidisciplinary approach Catheter-directed lysis (urokinase or streptokinase), then IV heparin plus VKA (3–6 mo) [n = 9] Surgical decompression (first rib resection or scalenectomy; n = 8; 5 of these also treated with lysis)	Bleed Vein patency PTS	Mean, 3 yr	Bleed: 1/12 (8.3%) [minor] Vein patency: Lysis: (25%) Lysis plus surgery: 5/5 (100%) Surgery alone: 3/3 (100%) PTS: Lysis alone: 3/4 (75%) Lysis plus surgery: 0/5 (0%) Surgery alone: 0/3 (0%)
Sanders and Cooper[369]/ 1995	Retrospective, single center	12 patients with acute or chronic UEDVT or nonthrombotic subclavian vein obstruction	Various surgical interventions including first rib resection, thrombectomy, venous bypass, vein patch angioplasty, thrombolysis All patients received VKA for 3–6 mo	PTS (pain, swelling)	26 mo (mean)	PTS: 6/12 (50%)
Meier et al[368]/ 1996	Retrospective, single center	11 patients with primary UEDVT	Thrombolysis with catheter-directed urokinase (250,000–500,000 U bolus) followed by infusion of 60,000–180,000 U/h (n = 11), venous stent (Wallstent) placement in some patients (n = 8); all had IV heparin and VKA for 3 mo; five patients subsequently had first rib resection	Recurrent VTE Stent complications PTS symptoms	12 mo	Recurrent arm DVT on venogram at 8–12 wk: 2/11 (18%) Stent fracture: 2/11 (18%) PTS: 3/11 (27%)
Sheeran et al[370]/ 1997	Retrospective case series, single center	14 patients with primary UEDVT	Staged multidisciplinary approach Catheter-directed urokinase (240/000 U/h for 4 h then 120,000 U/h, followed by IV heparin and VKA for 3 mo (prothrombin time 1.5–2 × control) Most patients also underwent transluminal angioplasty (n = 5) and first rib resection (n = 8)	Bleed PTS	24 mo	Bleed: 0 PTS: 2/14 (14.3%)

Table 21—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Lee et al[366]/ 1998	Retrospective case series, single center	11 patients with UEDVT from thoracic inlet obstructive disease	Catheter-directed lysis (urokinase) followed by adjusted IV heparin within 5 d of lysis, surgical decompression, venous bypass or angioplasty, followed by VKA for 3–6 mo	PTS (residual symptoms, limited function)	24 mo (mean)	PTS: 2/11 (18.2%)
Yilmaz et al[372]/ 2000	Retrospective case series, single center	24 patients with spontaneous effort thrombosis of the subclavian vein	Staged multidisciplinary approach Streptokinase at 10,000 U loading dose then 10,000 U/h until clot lysis then UFH (20,000 U/h) followed by VKA for 3 mo 6–12 wks later, 19 patients had first rib resection	Immediate outcomes (n = 24) Clot; lysis PE Bleed Long-term symptoms (n = 13)	40 mo (mean)	Clot lysis: 23/24 (95.8%) PE: 1/24 (4%) Bleed (minor): 4/24 (16.7%) Persistent symptom: 2/13 (15%) [all refused rib resection]
Feugier et al[365]/ 2001	Retrospective case series, single center	10 athletes with exertional UEDVT	Staged multidisciplinary approach Catheter-directed urokinase (2,500 IU/kg/h) for 24–72 h, followed by heparin and VKA (n = 6), LMWH and VKA alone (n = 4); duration of VKA not provided All patients subsequently had surgical treatment 9 d–9 mo later	Pain Ability to resume sports activities Edema Death	45 mo (mean)	Pain: 0/10 (0%) Resumption of activities: 10/10 (100%; within mean of 71 d) Edema: 3/10 (30%) Death: 0/10 (0%) [results not provided by initial treatment group]
Urschel and Patel[371]/2003	Retrospective case series	406 patients with primary UEDVT, including 22 referred for stent thrombosis	Catheter-directed lysis (urokinase at 4,400 U/kg bolus then 4,400 U/h or tPA at 2 mg/h for 8 h, then 1 mg/h until clot lysis, followed by IV heparin, then first rib resection)	PE Death Symptoms of PTS	Stent group: 3.5 yr; Surgery group: 7 yr	PE: 0 Death: 0 PTS: Initial stent group: 5/22 (23%) Surgery-only group: 4/384 (1%)
Schneider et al[362]/2004	Prospective, two-center study	23 patients with acute subclavian vein thrombosis	Thrombolysis (n = 21) followed by immediate decompression surgery (n = 7) or delayed surgical decompression after VKA for 0.5–7 mo (n = 14); anticoagulation alone (n = 2) Transluminal angioplasty also performed in 16 patients	Surgical complications Subclavian vein patency at follow-up Residual pain and swelling Death	Mean, 10 mo	Surgical complications: Wound hematoma requiring operative exploration: 3 (13%) Phrenic nerve dysfunction: 1 (4%); Postoperative subclavian rethrombosis: 2 (8%) Subclavian vein patency at follow-up: 22/23 (96%) Residual pain and swelling: 1/23 (4%) Death: 0/23

Table 21—*Continued*

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Spence et al[363]/ 1999	Prospective cohort, single center	41 patients with UEDVT with failure of or contraindication to anticoagulation (central venous catheter in 36 patients)	Placement of Greenfield (33 patients), Simon nitinol (5 patients), Vena Tech (2 patients), or Bird's Nest (1 patient) filters	PE PTS Death	Median, 12 wk	PE: 1/41 (2.4%) at 44 mo in a patient with acute leg DVT; PTS: 0/41 Death (survival analysis): 59% at 12 mo (none due to PE)
Ascher et al[364]/ 2000	Retrospective case series, single center	72 patients with UEDVT (20 with central venous catheter) in whom anticoagulation was contraindicated (n = 67) or had failed (n = 5).	Greenfield SVC filter	PE SVC thrombosis Filter; complications Death	Mean, 7.8 mo	PE: 0 SVC thrombosis: 0 Complications: one filter incorrectly discharged into innominate vein Death: 38/72 (53%; none due to VTE clinically; no autopsies)

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Retrospective and prospective cohort studies.
‡Catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, SVC filter.
§Recurrent DVT and PE, major bleeding, operative complications, total mortality, and PTS of the arm.

Recommendations

8.4.1. For patients with acute UEDVT, we recommend treatment with a VKA for ≥ 3 months (Grade 1C)**.**

Remark: A similar process as for lower-extremity DVT (see Section 2) should be used to determine the optimal duration of anticoagulation.

8.4.2. For most patients with UEDVT in association with an indwelling central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C)**.**

8.4.3. For patients who have UEDVT in association with an indwelling central venous catheter that is removed, we do not recommend that the duration of long-term anticoagulant treatment be shortened to < 3 months (Grade 2C)**.**

8.5 Prevention of PTS of the Arm

PTS of the arm occurs in 15 to 25% of patients after treated UEDVT.[347,348] Upper-extremity PTS is a potentially disabling condition that adversely affect QOL, particularly if the dominant arm is involved.[384] To date, no controlled studies have evaluated the effectiveness of elastic bandages, compression sleeves, or venoactive drugs to prevent PTS after UEDVT.

Recommendation

8.5.1. For patients at risk for PTS after UEDVT, we do not suggest routine use of elastic compression or venoactive medications (Grade 2C)**.**

8.6 Treatment of PTS of the Arm

Symptoms of PTS of the arm include swelling, heaviness, and limb fatigue with exertion.[347,384] No controlled studies have evaluated the effectiveness of elastic bandages, compression sleeves (as are used for lymphedema), or venoactive drugs to treat PTS after UEDVT. Anecdotal evidence suggests that patients with persistent arm swelling and pain may derive symptomatic relief from elastic bandages or compression sleeves. As these are unlikely to cause harm, they could be tried.

Recommendation

8.6.1. In patients with UEDVT who have persistent edema and pain, we suggest elastic bandages or elastic compression sleeves to reduce symptoms of PTS of the upper extremity (Grade 2C)**.**

Table 22—*Long-term Treatment of Acute UEDVT: Clinical Description and Results (Section 8.4)**

Author/yr	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Lindblad et al[382]/ 1988	Retrospective case series, multicenter	120 patients with confirmed UEDVT (includes 29 with central venous catheter)	Heparin then VKA (n = 59), heparin alone (n = 32), no treatment (n = 5), VKA (n = 5), streptokinase (n = 5), or other (n = 4) Drug, doses, duration of anticoagulation not provided	PE PTS	8 yr(mean)	PE: 4/120 (3%; 3 fatal) PTS pain or discomfort: Mild: 29/120 (24%) Moderate: 5/120 (4%) Severe: 0 (Results not provided by treatment group)
Burihan et al[379]/ 1993	Retrospective case series, single center	52 patients with confirmed UEDVT (includes 15 with central venous catheter)	IV heparin then VKA (n = 43), SC heparin (n = 7), venous thrombectomy (n = 1), or SVC-right atrial bypass (n = 1) Drug doses not provided; duration of anticoagulation, 6 mo	PE Death PTS	6 mo	PE: 2/52 (4%) Death: 9/52 (17%) PTS: Symptom free: 21/52 (40%) Minimal edema: 11/52 (21%) Symptomatic edema: 7/52 (13%) [Results not provided by treatment group]
Hingorani et al[380]/ 1997	Retrospective cohort study, single center	170 patients with UEDVT (97 with central venous catheter)	Adjusted IV heparin then VKA for 3–6 mo (target INR, 2–3; n = 87) SVC filter (n = 23) Thrombolysis plus operative decompression of thoracic outlet syndrome (n = 2) No anticoagulant therapy (n = 58)	Recurrent VTE Death PTS (significant swelling)	Mean, 13 mo	Recurrent VTE: 2/170 (1.2%) Death; 1-mo mortality: 25/170 (15%) 3-mo mortality: 58/170 (34%) [No deaths from PE] PTS: 7 (4%) [Results not provided by treatment group]
Marie et al[373]/ 1998	Retrospective case series, single center	49 patients with confirmed UEDVT (includes 3 with central venous catheter)	Heparin therapy (LMWH, n = 36; UFH, n = 11); VKA (n = 44), surgical thrombectomy plus venous ligation (n = 1) Duration of VKA, 3–6 mo	Symptomatic VTE; recurrence PE PTS (residual limb edema, pain or heaviness); major bleed	6 mo	VTE recurrence: 1/49 (2.2%) PE: 6/49 (12.2%) PTS: 19/49 (38.8%) Major bleed: 0 (Results not provided by treatment group)
Savage et al[349]/ 1999	Prospective cohort, two center	46 outpatients with confirmed UEDVT (includes 16 with central venous catheter)	Dalteparin daily for 5–7 d (200 IU/kg) and VKA to achieve target INR of 2.0–3.0 for 3 mo Duration of VKA not provided	Symptomatic recurrence/extension of DVT PE Major bleed Death	3 mo	Recurrence/extension: 1/46 (2%) PE: 0 Major bleed: 1/46 (2%; on VKA) Death: 7/46 (15%; none from PE or bleed)

Table 22—*Continued*

Author	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Marinella et al[383]/ 2000	Retrospective case series, single center	90 patients with confirmed UEDVT (includes 65 with central venous catheter)	Heparin (n = 65), VKA (n = 53), catheter removal (in 39/65 patients with central venous catheter) Drug doses, duration of anticoagulation not provided	Death	Not specified	Death: 11/90 (12%) [Results not provided by treatment group]
Massoure et al[392]/ 2000	Retrospective case series, single center	40 patients with confirmed UEDVT (22 with central venous catheter)	LMWH (n = 27), UFH (n = 13), catheter-directed lysis (n = 4), VKA (n = 26; mean duration not specified)	PE Major bleed PTS Death	9 mo (mean)	PE: 2/40 (5%) Major bleed: 2/40 (5%) PTS: 14/40 (35%; severe in 2/40 [5%]) Death: 16/40 (40%)
Hingorani et al[381]/ 2001	Retrospective chart review, single center	165 patients with confirmed UEDVT: 144 with UEDVT alone (includes 90 with central venous catheter), and 21 with both UEDVT and lower-extremity DVT (includes 14 with central venous catheter)	UEDVT alone: systemic anticoagulation (n = 94), no anticoagulation (n = 31), SVC filter (n = 16), aspirin (n = 3) UEDVT and lower-extremity DVT: systemic anticoagulation (n = 17); SVC plus IVC filter (n = 2); no anticoagulation (n = 1), aspirin (n = 1) Drug doses, duration of anticoagulation not provided	PE at time of UEDVT diagnosis Death within 2 mo of UEDVT diagnosis	2 mo	PE at time of UEDVT diagnosis: UEDVT alone: 16/144 (11%) UEDVT plus lower-extremity DVT: 2/21 (9.5%; p = 0.59) All-cause death within 2 mo of diagnosis: UEDVT alone: 38/144 (26%) UEDVT plus lower-extremity DVT: 11/21 (52%) [< 0.02] Death from PE not reported (Results not provided by treatment group)
Karabay et al[350]/ 2003	Prospective cohort, single center	36 inpatients with confirmed UEDVT (includes 13 with central venous catheter)	Nadroparin SC bid, 86 aXa IU/kg for up to 7 d, then VKA (started on day 3; target INR, 2–2.5) for mean of 4.7 mo	Symptom relief; lysis of thrombus on ultrasound Recurrent DVT PE Death PTS	1 yr	Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%) < 35%: 17/36;(47%) None: 3/36 (8%) Recurrent DVT: 0 PE: 0 Death: 9/36 (25%), none due to PE or bleed PTS: 0
Martinelli et al[378]/ 2004	Case-control study with prospective follow-up of cases, single center	98 patients with primary UEDVT (none with central venous catheter)	VKA for mean 6 mo (n = 77), heparin SQ (n = 14), or antiplatelet agents (n = 7) for ≤ 3 mo	Recurrent VTE after anticoagulants stopped	Median, 5.1 yr	Recurrent VTE: 12/98 (12%) overall (all UEDVT) Annual incidence of recurrent VTE: 2.4% (95% CI, 1.2–4.0% Results not provided by treatment group)

Table 22—*Continued*

Author	Type of Study†	Participants	Intervention‡	Outcomes§	Follow-up	Results
Prandoni et al[347]/ 2004	Prospective cohort, number of centers not stated	53 patients with confirmed first UEDVT (included 6 with central venous catheter)	Therapeutic dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death PTS	Median, 48 mo	Results not presented according to initial treatment with UFH vs LMWH; Recurrent VTE: 3/53 (5.7%; 2 arm, 1 leg); cumulative incidence at 1 yr, 2 yr, and 5 yr: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%); due to cancer, PE, congestive heart failure (breakdown not provided) PTS: 13/53 24.5%); 2-yr cumulative incidence: 27.3%
Kahn et al[384]/2005	Retrospective cohort, single center	24 patients with confirmed UEDVT (includes 11 with central venous catheter)	Heparin (median of 9 d, then VKA (median, 5 mo; n = 23), LMWH monotherapy (n = 1)	PTS	Median, 13 mo	PTS: 11/24 (46%)
Persson et al[393]/ 2006	Retrospective case series, single center	31 patients with confirmed primary UEDVT (none with central venous catheter)	LMWH followed by VKA for 3–6 mo	Recurrent VTE PTS	5 yr	Recurrent VTE: 0 PTS: 9/31 (29%; none severe)
Kovacs et al[351]/ 2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had central venous catheter)	Dalteparin (200 IU/kg) daily for 5–7 d and VKA to achieve target INR of 2.0–3.0	Recurrent VTE PE Major bleed Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0 PE: 0 Major bleed: 3 (4%) Death: 7 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Retrospective and prospective cohort studies (includes studies in Table 8.1).
‡VKA, UFH, LMWH vs placebo, control, or each other.
§Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm.

Appendix: Summary

Table 23—*Streptokinase Plus Heparin vs Control (Heparin)*

Quality Assessment								Summary of Findings				
								No. of Patients/Total Patients (%)		Effect		
Studies, No.	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Streptokinase Plus Heparin	Control (Heparin)	RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
4*	RCT	Some limitations†	No important inconsistency	No directness	Some imprecision‡	No reporting bias	No strong association‡	1/44 (2.27)	7/43 (16.2%)	0.25 (0.06–1.15)§	Not significant	Moderate
Major bleeding												
4*	RCT	Some limitations	No important inconsistency	No directness	Some imprecision‡	No reporting bias	No strong association	8/44 (18.18)	7/43 (16.2)	1.076 (0.43–2.72)‖	Not significant	Moderate
Total mortality												
4*	RCT	Some limitations	No important inconsistency	No directness	Some imprecision‡	No reporting bias	No strong association	2/44 (4.55)	4/43 (9.30)	0.46 (0.09–2.29)¶	Not significant	Moderate

*Includes Tibbutt D, 1974; Ly B, 1978; Dotter C, 1979; and Jerjes-Sanchez C. 1995.

†See methods table.

‡95% CI includes no effects.

§Based on metaanalysis of three studies: Tibbutt D, 1974 reports no cases of DVT in either the treatment (0 of 11 patients) or control group (0 of 12 patients) and was not included in the metaanalysis.

‖Based on metaanalysis of three studies: Jerjes-Sanchez C, 1995 reports no cases of major bleeding in either the treatment (0 of 4 patients) or control group (0 of 4 patients) and was not included in the metaanalysis

¶Based on metaanalysis of three studies: Tibbutt D, 1974 and Jerjes-Sanchez C, 1995 report no deaths in either the treatment or control group and were excluded from the metaanalysis.

Table 24—*Urokinase vs Control (Heparin)*

Quality Assessment								Summary of Findings				
								No. of Patients/Total (%)		Effect		
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Urokinase	Control (Heparin)	RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
2*	RCT	Some limitations†	No important inconsistency	No problems	Some imprecision‡	No reporting bias	No strong association	12/98 (12.24)	15/88 (17.05)	0.76 (0.38–1.52)§	Not significant	Moderate
Major bleeding												
2*	RCT	Some limitations	No important inconsistency	No problems	No problems	No reporting bias	No strong association	37/92 (40.22)	21/88 (23.86)	1.68 (1.08–2.59)§	Not significant	Moderate
Total mortality												
2*	RCT	Some limitations	No important inconsistency	No problems	Some imprecision	No reporting bias	No strong association	6/92 (6.52)	7/88 (7.95)	0.82 (0.29–2.32)§	Not significant	Moderate

*Includes UPET study group 1970; Marini C 1988.
†See methods table.
‡95% CI contains no effect.
§Based on one study: Marini C, 1988 was excluded because it reports no cases in either treatment or control groups.

Table 25—*rt-PA Plus Heparin vs Control (Heparin)*

Quality Assessment								Summary of Findings				
								No of Patients		Effect		
Studies, No.	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	rt-PA Plus Heparin	Control (Heparin)	RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
1*	RCT	Some limitations†	No important inconsistency	No problems	Some imprecision‡	No reporting bias	No strong association	0/46 5/55 (9.09)	0.108 (0.01–1.91)	Not significant	Moderate	
Major bleeding												
1*	RCT	Some limitations	No important inconsistency	No problems	Some imprecision	No reporting bias	No strong association	3/46 (6.52)	1/55 (1.82)	3.59 (0.39–33.33)	Not significant	Moderate
Total mortality												
1*	RCT	Some limitations	No important inconsistency	No problems	Some imprecision	No reporting bias	No strong association	0/46 2/53 (3.64)	0.24 (0.01–4.84)	Not significant	Moderate	

*Goldhaber S, 1993.
†No evidence of blinding; see methods table.
‡95% CI shows no effect.

Table 26—*rt-PA Plus Heparin vs Control (Heparin Plus Placebo)*

Quality Assessment								Summary of Findings				
								No. of Patients/Total (%)		Effect		
Studies, No.	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	rt-PA Plus Heparin	Control (Heparin Plus Placebo)	RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
1*	RCT	No serious limitations	No important inconsistency	No directness	Some imprecision†	No reporting bias	No strong association	4/118 (3.39)	4/138 (2.9)	1.17 (0.30–4.58)	Not significant	Moderate
Major bleeding												
1*	RCT	No serious limitations	No important inconsistency	No directness	Some imprecision	No reporting bias	No strong association	4/118 (3.39)	4/138 (2.90)	0.23 (0.03–1.97)	Not significant	Moderate
Total mortality												
1*	RCT	No serious limitations	No important inconsistency	No directness	Some imprecision	No reporting bias	No strong association	4/118 (3.39)	3/138 (2.17)	1.56 (0.36–6.83)	Not significant	Moderate

*Konstantinides S, 2002.
†95% CI contains no effect.

Table 27—*rt-PA and Heparin vs Control (Heparin)*

Quality Assessment								Summary of Findings				
								No. of Patients/Total (%)		Effect		
No. of studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	rt-PA Plus Heparin	Control (Heparin)	RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
1*	RCT	Some limitations†	No important inconsistency	No directness	Some imprecision‡	No reporting bias	No strong association	1/20 (5.00)	0/16 2.43 (0.11–55.89)	Not significant	Moderate	
Major bleeding												
1*	RCT	Some limitations	No important inconsistency	No directness	Some imprecision	No reporting bias	No strong association	3/20 (15.0%)	2/16 (12.5o)	1.20 (0.23–6.34)	Not significant	Moderate
Total mortality												
1*	RCT	Some limitations	No important inconsistency	No directness	Some imprecision	No reporting bias	No strong association	2/20 (10.00)	0/16	4.05 (0.21–78.76)	Not significant	Moderate

*Dalla-Volta S, 1992.
†No evidence on blinding; see methods table.
‡95% CI contains no effect.

Table 28—*rt-PA vs Control (Placebo)*

Studies, No.	Design	Quality Assessment: Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Summary of Findings: No. of Patients/Total (%) rt-PA	Control (Placebo)	Effect: RR (95% CI) or Weighted Mean Difference	Events Prevented per 1,000 Treated	Quality
Recurrent DVT and PE												
2*	RCT	No serious limitations	No important inconsistency	No problems	Not applicable	No reporting bias	Not applicable	0/42	0/29	Not applicable	Not significant	Moderate
Major bleeding												
2*	RCT	No serious limitations	No important inconsistency	No problems	Some imprecision†	No reporting bias	No strong association	1/42 (2.38)	0/29 1.50 (0.07–30.59)‡	Not significant	Moderate	
Total mortality												
2*	RCT	No serious limitations	No important inconsistency	No problems	Some imprecision	No reporting bias	No strong association	1/42 (2.38)	0/29	2.29 (0.10, 54.05)§	Not significant	Moderate

*Includes Levine M, 1990; and PIOPED Investigators, 1990.
†95% CI contains no effect.
‡Based on one study: Levine M, 1990 was excluded because it reports no cases in either treatment or control groups.
§Based on one study: PIOPED Investigators 1990 was excluded because it reports no cases in either treatment or control groups.

References

1 Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1960; 1:1309–1312
2 Alpert JS, Smith R, Carlson J, et al. Mortality in patients treated for pulmonary embolism. JAMA 1976; 236:1477–1480
3 Kanis JA. Heparin in the treatment of pulmonary thromboembolism. Thrombos Diath Haemorrh 1974; 32:519
4 Kernohan RJ, Todd C. Heparin therapy in thromboembolisc disease. Lancet 2007; 1:621–623
5 Brandjes DPM, Heijboer H, Buller HR, et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992; 327:1485–1489
6 Gallus AS, Jackaman J, Tillett J, et al. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. Lancet 1986; 2:1293–1296
7 Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990; 322:1260–1264
8 Ansell J, Hirsh J, Poller L, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133(suppl):160S–198S
9 Crowther MA, Ginsberg JS, Kearon C, et al. A randomized trial comparing 5 mg and 10 mg warfarin loading doses. Arch Intern Med 1999; 159:46–48
10 Harrison L, Johnston M, Massicotte MP, et al. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997; 126:133–136
11 Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. Ann Intern Med 2003; 138:714–719
12 Garcia D, Regan S, Crowther M, et al. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. Chest 2005; 127:2049–2056
13 Levine MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. Chest 2001; 119(suppl):108S–121S
14 Basu D, Gallus AS, 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; 287:324–327
15 Cruickshank MK, Levine MN, Hirsh J, et al. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med 1991; 151:333–337
16 Raschke RA, Gollihare B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. Arch Intern Med 1996; 156:1645–1649
17 Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. Ann Intern Med 1993; 119:874–881
18 Anand S, Ginsberg JS, Kearon C, et al. The relation between the activated partial thromboplastin time response and recurrence in patients with venous thrombosis treated with continuous intravenous heparin. Arch Intern Med 1996; 156:1677–1681
19 Anand SS, Bates S, Ginsberg JS, et al. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin time results. Arch Intern Med 1999; 159:2029–2032
20 Hull RD, Raskob G, Brant RF, et al. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. Arch Intern Med 1997; 157:2317–2321

21 Hull RD, Raskob GE, Brant RF, et al. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med 1997; 157:2562–2568
22 Levine MN, Hirsh J, Gent M, et al. A randomized trial comparing the activated thromboplastin time with the heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 1994; 154:49–56
23 Hommes DW, Bura A, Mazzolai L, et al. Subcutaneous heparin compared with continuous intravenous heparin administration in the initial treatment of deep vein thrombosis. Ann Intern Med 1992; 116:279–284
24 Prandoni P, Carnovali M, Marchiori A. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. Arch Intern Med 2004; 164:1077–1083
25 Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 2006; 296:935–942
26 Lim W, Dentali F, Eikelboom JW, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med 2006; 144:673–684
27 Bates SM, Greer IA, Papinger I, et al. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy; evidence-based guidelines. Chest 2004; 126(suppl):627S–644S
28 Breddin HK, Hach-Wunderle V, Nakov R, et al. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. N Engl J Med 2001; 344:626–631
29 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998; 338:409–415
30 Duroux P. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis: a collaborative European multicentre study. Thromb Haemost 1991; 65:251–256
31 Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 1996; 76:195–199
32 Harenberg J, Schmidt JA, Koppenhagen K, et al. Fixed-dose, body weight-independent subcutaneous LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis: EASTERN Investigators. Thromb Haemost 2000; 83:652–656
33 Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326:975–982
34 Kakkar V, Gebska M, Kadziola Z, et al. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost 2003; 89:674–680
35 Kirchmaier CM, Wolf H, Schafer H, et al. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis: Certoparin Study Group. Int Angiol 1998; 17:135–145
36 Koopman MMW, Prandoni P, Piovella F, 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. N Engl J Med 1996; 334:682–687
37 Levine M, Gent M, Hirsh 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; 334:677–681
38 Lindmarker P, Holmstrom M, Granqvist S, et al. Comparison of once-daily subcutaneous fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thrombosis and Haemostasis 1994; 72:186–190
39 Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001; 134:191–202
40 Prandoni P, Lensing AWA, Buller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992; 339:441–445
41 Riess H, Koppenhagen K, Tolle A, et al. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. Thromb Haemost 2003; 90:252–259
42 Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993; 153:1541–1546
43 Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997; 337:663–669
44 The Columbus Investigators. Low molecular weight heparin is an effective and safe treatment for deep-vein thrombosis and pulmonary embolism. N Engl J Med 1997; 337:657–662
45 Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160:181–188
46 Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130:800–809
47 van Dongen CJJ, van der Belt AGM, Prins MH, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2004
48 Belcaro G, Nicolaides AN, Cesarone MR, 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; 50:781–787
49 Faivre R, Neuhart E, Kieffer Y, et al. Subcutaneous administration of a low-molecular-weight-heparin (CY 222) compared with subcutaneous administration of standard heparin in patients with acute deep vein thrombosis [abstract]. Thromb Haemost 1987; 58:1
50 Lopaciuk S, Meissner AJ, Filipecki S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thromb Haemost 1992; 68:14–18
51 Charbonnier BA, Flessinger JN, Banga JD, et al. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. Thromb Haemost 1998; 79:897–901
52 Holmstrom M, Berglund S, Granquist S, et al. Fragmin once or twice daily subcutaneously in the treatment of deep

venous thrombosis of the leg. Thromb Res 1992; 67:49–55
53 Partsch H, Kechavarz B, Mostbeck A, et al. Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once-or twice-daily low-molecular-weight heparin. J Vasc Surg 1996; 24:774–782
54 Siegbahn A, Hassan S, Boberg J, et al. Subcutaneous treatment of deep venous thrombosis with low molecular weight heparin: a dose finding study with LMWH-Novo. Thromb Res 1989; 55:767–778
55 Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost 2001; 86:980–984
56 Boccalon H, Elias A, Chale JJ, et al. 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; 160:1769–1773
57 Wells PS, Anderson DR, Rodger MA, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med 2005; 165:733–738
58 Faivre R, Neuhart Y, Kieffer Y, et al. A new treatment of deep venous thrombosis: low molecular weight heparin fractions; randomized study. Presse Med 1988; 17:197–200
59 Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med 2004; 140:867–873
60 Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695–1702
61 Fiessinger JN, Huisman MV, Davidson BL, et al. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. JAMA 2005; 293:681–689
62 Buller HR, Cohen AT, Davidson B, et al. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007; 237:1094–1104
63 Bergan JJ, Schmid-Schonbein GW, Smith PD, et al. Chronic venous disease. N Engl J Med 2006; 355:488–498
64 Cho JS, Martelli E, Mozes G, et al. Effects of thrombolysis and venous thrombectomy on valvular competence, thrombogenicity, venous wall morphology, and function. J Vasc Surg 1998; 28:787–799
65 Johnson BF, Manzo RA, Bergelin RO, et al. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. J Vasc Surg 1995; 21:307–312
66 Killewich LA, Bedford GR, Beach KW, et al. Spontaneous lysis of deep venous thrombi: rate and outcome. J Vasc Surg 1989; 9:89–97
67 Markel A, Manzo RA, Bergelin RO, et al. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. J Vasc Surg 1992; 15:377–382
68 Meissner MH, Manzo RA, Bergelin RO, et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. J Vasc Surg 1993; 18:596–605
69 Nicolaides AN, Schull K, Fernandes E, et al. Ambulatory venous pressure: new information: investigation of vascular disorders. New York, NY: Churchill Livingstone, 1981; 488–494
70 Rhodes JM, Cho JS, Gloviczki P, et al. Thrombolysis for experimental deep venous thrombosis maintains valvular competence and vasoreactivity. J Vasc Surg 2000; 31:1193–1205
71 Shull KC, Nicolaides AN, Fernandes e Fernandes J, et al. Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. Arch Surg 1979; 114:1304–1306
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; 24:209–214
73 Plate G, Einarsson E, Ohlin P, et al. Thrombectomy with temporary arteriovenous fistula: the treatment of choice in acute iliofemoral venous thrombosis. J Vasc Surg 1984; 1:867–876
74 Meissner MH, Mewissen M. Early outcome after catheter-directed thrombolysis for acute deep venous thrombosis: follow-up of a national multicenter registry. J Vasc Surg 2008 (in press)
75 Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 1999; 211:39–49
76 Bjarnason H, Kruse JR, Asinger DA, et al. Iliofemoral deep venous thrombosis: safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. J Vasc Interv Radiol 1997; 8:405–418
77 Comerota AJ, Aldridge SC, Cohen G, et al. A strategy of aggressive regional therapy for acute iliofemoral venous thrombosis with contemporary venous thrombectomy or catheter-directed thrombolysis. J Vasc Surg 1994; 20:244–254
78 Comerota AJ, Kagan SA. Catheter-directed thrombolysis for the treatment of acute iliofemoral deep venous thrombosis. Phlebology 2000; 15:149–155
79 Comerota AJ, Throm RC, Mathias SD, et al. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg 2000; 32:130–137
80 Juhan CM, Alimi YS, Barthelemy PJ, et al. Late results of iliofemoral venous thrombectomy. J Vasc Surg 1997; 25:417–422
81 Laiho MK, Oinonen A, Sugano N, et al. Preservation of venous valve function after catheter-directed and systemic thrombolysis for deep venous thrombosis Eur J Vasc Endovasc Surg 2004; 28:391–396
82 Plate G, Akesson H, Einarsson E, et al. Long-term results of venous thrombectomy combined with a temporary arteriovenous fistula. Eur J Vasc Surg 1990; 4:483–489
83 Plate G, Eklof B, Norgren L, et al. Venous thrombectomy for iliofemoral vein thrombosis: 10-year results of a prospective randomised study. Eur J Vasc Endovasc Surg 1997; 14:367–374
84 Akesson H, Brudin L, Dahlstrom JA, et al. Venous function assessed during a 5 year period after acute ilio-femoral venous thrombosis treated with anticoagulation. Eur J Vasc Surg 1990; 4:43–48
85 Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004; 239:118–126
86 O'Donnell TF, Browse NL, Burnand KG, et al. The socioeconomic effects of an iliofemoral venous thrombosis. J Surg Res 1977; 22:483–488
87 Strandness DE Jr, Langlois Y, Cramer M, et al. Long-term sequelae of acute venous thrombosis. JAMA 1983; 250:1289–1292
88 Berridge DC, Gregson RH, Hopkinson BR, et al. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. Br J Surg 1991; 78:988–995
89 AbuRahma AF, Perkins SE, Wulu JT, et al. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. Ann Surg 2001; 233:752–760
90 Castaneda F, Li R, Young K, et al. Catheter-directed thrombolysis in deep venous thrombosis with use of reteplase: immediate results and complications from a pilot

study. J Vasc Interv Radiol 2002; 13:577–580
91 Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. J Vasc Interv Radiol 2005; 15:347–352
92 Horne MK, III, Mayo DJ, Cannon RO III, et al. Intraclot recombinant tissue plasminogen activator in the treatment of deep venous thrombosis of the lower and upper extremities. Am J Med 2000; 108:251–255
93 Jackson LS, Wang XJ, Dudrick SJ, et al. Catheter-directed thrombolysis and/or thrombectomy with selective endovascular stenting as alternatives to systemic anticoagulation for treatment of acute deep vein thrombosis. Am J Surgery 2005; 190:864–868
94 Kasirajan K, Gray B, Ouriel K. Percutaneous AngioJet thrombectomy in the management of extensive deep venous thrombosis. J Vasc Interv Radiol 2001; 12:179–185
95 Kim HS, Patra A, Paxton BE, et al. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. J Vasc Interv Radiol 2006; 17:1099–1104
96 Lin PH, Zhou W, Dardik A, et al. Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. Am J Surg 2006; 192:782–788
97 Ogawa T, Hoshino S, Midorikawa H, et al. Intermittent pneumatic compression of the foot and calf improves the outcome of catheter-directed thrombolysis using low-dose urokinase in patients with acute proximal venous thrombosis of the leg. J Vasc Surg 2005; 42:940–944
98 Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. Radiology 1994; 191:487–494
99 Semba CP, Dake MD. Catheter-directed thrombolysis for iliofemoral venous thrombosis. SeminVasc Surg 1996; 9:26–33
100 Sillesen H, Just S, Jorgensen M, et al. Catheter-directed thrombolysis for treatment of ilio-femoral deep venous thrombosis is durable, preserves venous valve function and may prevent chronic venous insufficiency. Eur J Vasc Endovasc Surg 2005; 30:556–562
101 Vedantham S, Vesely TM, Parti N, et al. Lower extremity venous thrombolysis with adjunctive mechanical thrombectomy. J Vasc Interv Radiol 2002; 13:1001–1008
102 Verhaeghe R, Stockx L, Lacroix H, et al. Catheter-directed lysis of iliofemoral vein thrombosis with use of rt-PA. Eur Radiol 1997; 7:996–1001
103 Arnesen H, Heilo A, Jakobsen E, et al. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. Acta Med Scand 1978; 203:457–463
104 Arnesen H, Hoiseth A, Ly B. Streptokinase or heparin in the treatment of deep vein thrombosis: follow-up results of a prospective study. Acta Med Scand 1982; 211:65–68
105 Browse NL, Thomas ML, Pim HP. Streptokinase and deep vein thrombosis. Br Med J 1968; 3:717–720
106 Duckert F, Muller G, Nyman D, et al. Treatment of deep vein thrombosis with streptokinase. Br Med J 1975; 1:479–481
107 Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. Br J Surg 1979; 66:838–843
108 Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis Am J Med 1990; 88:235–240
109 Kakkar VV, Flanc C, Howe CT, et al. Treatment of deep vein thrombosis: a trial of heparin, streptokinase, and arvin. Br Med J 1969; 1:806–810
110 Kiil J, Carvalho A, Sakso P, et al. Urokinase or heparin in the management of patients with deep vein thrombosis? Acta Chir Scand 1981; 147:529–532
111 Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89:1018–1029
112 Porter JM, Seaman AJ, Common HH, et al. Comparison of heparin and streptokinase in the treatment of venous thrombosis. Am Surg 1975; 41:511–519
113 Robertson BR, Nilsson IM, Nylander G. Value of streptokinase and heparin in treatment of acute deep venous thrombosis: a coded investigation. Acta Chir Scand 1968; 134:203–208
114 Schulman S, Granqvist S, Juhlin-Dannfelt A, et al. Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase. Acta Med Scand 1986; 219:349–357
115 Schweizer J, Elix H, Altmann E, et al. Comparative results of thrombolysis treatment with rt-PA and urokinase: a pilot study. VASA 1998; 27:167–171
116 Schweizer J, Kirch W, Koch R, et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. J Am Coll Cardiol 2000; 36:1336–1343
117 Tsapogas MJ, Peabody RA, Wu KT, et al. Controlled study of thrombolytic therapy in deep vein thrombosis. Surgery 1973; 74:973–984
118 Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis: results of a randomized trial. Chest 1990; 97(suppl):172S–175S
119 Verhaeghe R, Besse P, Bounameaux H, et al. Multicenter pilot study of the efficacy and safety of systemic rt-PA administration in the treatment of deep vein thrombosis of the lower extremities and/or pelvis. Thromb Res 1989; 55:5–11
120 Watz R, Savidge GF. Rapid thrombolysis and preservation of valvular venous function in high deep vein thrombosis: a comparative study between streptokinase and heparin therapy. Acta Med Scand 1979; 205:293–298
121 Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev 2004; CD002783
122 Delomez M, Beregi JP, Willoteaux S, et al. Mechanical thrombectomy in patients with deep venous thrombosis. Cardiovasc Intervent Radiol 2001; 24:42–48
123 Kinney TB, Valji K, Rose SC, et al. Pulmonary embolism from pulse-spray pharmacomechanical thrombolysis of clotted hemodialysis grafts: urokinase versus heparinized saline. J Vasc Interv Radiol 2000; 11:1143–1152
124 Comerota AJ, Gale SS. Technique of contemporary iliofemoral and infrainguinal venous thrombectomy. J Vasc Surg 2006; 43:185–191
125 Karp RB, Wylie EJ. Recurrent thrombosis after iliofemoral venous thrombectomy. Surg Forum 1966; 17:147
126 Lansing AM, Davis WM. Five-year follow-up study of iliofemoral venous thrombectomy. Ann Surg 1968; 168:620–628
127 Einarsson E, Albrechtsson U, Eklof B. Thrombectomy and temporary AV-fistula in iliofemoral vein thrombosis: technical considerations and early results. Int Angiol 1986; 5:65–72
128 Einarsson E, Albrechtsson U, Eklof B, et al. Follow-up evaluation of venous morphologic factors and function after thrombectomy and temporary arteriovenous fistula in thrombosis of iliofemoral vein. Surg Gynecol Obstet 1986; 163:111–116
129 Juhan C, Cornillon B, Tobiana F, et al. Patency after iliofemoral and iliocaval venous thrombectomy. Ann Vasc Surg 1987; 1:529–533
130 Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. Surgery 1979; 85:31–43
131 Meissner AJ, Huszcza S. Surgical strategy for management of deep venous thrombosis of the lower extremities. World J Surg 1996; 20:1149–1155
132 Neglen P, al-Hassan HK, Endrys J, et al. Iliofemoral venous

thrombectomy followed by percutaneous closure of the temporary arteriovenous fistula. Surgery 1991; 110:493–499
133 Schwarzbach MH, Schumacher H, Bockler D, et al. Surgical thrombectomy followed by intraoperative endovascular reconstruction for symptomatic ilio-femoral venous thrombosis Eur J Vasc Endovasc Surg 2005; 29:58–66
134 Torngren S, Swedenborg J. Thrombectomy and temporary arterio-venous fistula for ilio-femoral venous thrombosis. Int Angiol 1988; 7:14–18
135 Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 2005; 112:416–422
136 Streiff MB. Vena caval filters: a comprehensive review. Blood 2000; 95:3669–3677
137 White RH, Zhou H, Kim J, et al. A population-based study of the effectiveness of IVC filter use among patients with venous thromboembolism. Arch Intern Med 2000; 160:2033–2041
138 Aschwanden M, Labs KH, Engel H, et al. Acute deep vein thrombosis: early mobilization does not increase the frequency of pulmonary embolism. Thromb Haemost 2001; 85:42–46
139 Blattler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. Int Angiol 2003; 22:393–400
140 Junger M, Diehm C, Storiko H, et al. Mobilization versus immobilization in the treatment of acute proximal deep venous thrombosis: a prospective, randomized, open, multicentre trial. Curr Med Res Opin 2006; 22:593–602
141 Partsch H, Blattler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg 2000; 32:861–869
142 Schellong SM, Schwarz T, Kropp J, et al. Bed rest in deep vein thrombosis and the incidence of scintigraphic pulmonary embolism. Thromb Haemost 1999; 82(suppl 1):127–129
143 Partsch H. Therapy of deep vein thrombosis with low molecular weight heparin, leg compression and immediate ambulation. VASA 2001; 30:195–204
144 Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol 2004; 23:206–212
145 Trujillo-Santos J, Perea-Milla E, Jimenez-Puente A, et al. Bed rest or ambulation in the initial treatment of patients with acute deep vein thrombosis or pulmonary embolism: findings from the RIETE registry. Chest 2005; 127:1631–1636
146 Lagerstedt CI, Olsson CG, Fagher BO, et al. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985; 515–518
147 Hull R, Delmore T, Genton E, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. The N Engl J Med 1979; 301:855–858
148 Levine MN, Hirsh J, Gent M, 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; 74:606–611
149 Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Lancet 1992; 340:873–876
150 Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med 1997; 336:393–398
151 Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458–462
152 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
153 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
154 Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. N Engl J Med 2001; 345:165–169
155 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; 334:674–680
156 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; 340:901–907
157 Kearon C, Ginsberg JS, Anderson DR, et al. 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; 2:743–749
158 Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631–639
159 Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006; 355:1780–1789
160 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; 103:2453–2460
161 Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for prevention of recurrent venous thromboembolism. N Engl J Med 2003; 348:1425–1434
162 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; 332:1661–1665
163 Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 2000; 160:761–768
164 Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep vein thrombosis or pulmonary embolism. Thromb Haemost 2002; 88:407–414
165 Palareti G, Legnani C, Cosmi B, et al. Risk of venous thromboembolism recurrence: high negative predictive value of d-dimer performed after oral anticoagulation is stopped. Thromb Haemost 2002; 87:7–12
166 Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125:1–7
167 Pini M, Aiello S, Manotti C, et al. Low molecular weight heparin versus warfarin the prevention of recurrence after deep vein thrombosis. Thromb Haemost 1994; 72:191–197
168 Baglin T, Luddington R, Brown K, et al. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003; 362:523–526
169 Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 2005; 293:2352–2361
170 Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 2000; 160:769–774
171 Schulman S, Wahlander K, Lundstrîm T, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349:1713–1721

172 Eichinger S, Minar E, Hirschl M, et al. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost 1999; 81:14–17
173 Eichinger S, Pabinger I, Stumpflen A, et al. The risk of recurrent venous thromboembolism in patients with and without Factor V Leiden. Thromb Haemost 1997; 77:624–628
174 Ho WK, Hankey GJ, Quinlan DJ, et al. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med 2006; 166: 729–736
175 Lindmarker P, Schulman S, Sten-Linder M, et al. The risk of recurrent venous thromboembolism in carriers and noncarriers of the G1691A Allele in the coagulation factor V gene and the G20210A Allele in the prothrombin gene. Thromb Haemost 1999; 81:684–689
176 Miles JS, Miletich JP, Goldhaber SZ, et al. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol 2001; 37:215–218
177 Palareti G, Legnani C, Cosmi B, et al. Predictive value of d-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation 2003; 108:313–318
178 Ridker PM, Miletich JP, Stampfer MJ, et al. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation 1995; 92:2800–2802
179 Schulman S, Lindmarker P, Holmstrom M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. J Thromb Haemost 2006; 4:734–742
180 Simioni P, Prandoni P, Lensing AW, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood 2000; 96:3329–3333
181 Schulman S, Lockner D, Juhlin-Dannfelt A. The duration of oral anticoagulation after deep vein thrombosis. Acta Med Scand 1985; 217:547–552
182 Schulman S. Unresolved issues in anticoagulant therapy. J Thromb Haemost 2003; 1:1464–1470
183 Holmgren K, Andersson G, Fagrell B, et al. One-month versus six-month therapy with oral anticoagulants after symptomatic deep vein thrombosis. Acta Med Scand 1985; 218:279–284
184 Ost D, Tepper J, Mihara H, et al. Duration of anticoagulation following venous thromboembolism: a meta-analysis. JAMA 2005; 294:706–715
185 Kearon C. Natural history of venous thromboembolism. Circulation 2003; 107:I-22–I30
186 Locadia M, Bossuyt P, Stalmeier P, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost 2004; 92:1336–1341
187 Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. JAMA 2003; 290:1071–1074
188 Shrivastava S, Ridker PM, Glynn RJ, et al. D-dimer, factor VIII coagulant activity, low-intensity warfarin and the risk of recurrent venous thromboembolism. J Thromb Haemost 2006; 4:1208–1214
189 Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Am J Med 1998; 104:332–338
190 McRae S, Tran H, Schulman S, et al. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet 2006; 368:371–378
191 White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. Ann Intern Med 1998; 128:737–740
192 Cosmi B, Legnani C, Cini M, et al. D-dimer levels in combination with residual venous obstruction and the risk of recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis. Thromb Haemost 2005; 94:969–974
193 Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. Haematologica 2002; 87: 515–522
194 Prandoni P, Lensing AW, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002; 137:955–960
195 Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133(suppl):257S–298S
196 Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin: a randomized, controlled trial. Ann Intern Med 2000; 133:687–695
197 Beyth RJ, Quinn LM, Landefeld S. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998; 105:91–99
198 Dentali F, Douketis JD, Lim W, et al. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med 2007; 167:117–124
199 Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006; 151:713–719
200 Kuijer PMM, Hutten BA, Prins MH, et al. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999; 159:457–460
201 Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Lancet 1996; 348:423–428
202 Pengo V, Legnani C, Noventa F, et al. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding: a Multicenter Inception Cohort Study. Thromb Haemost 2001; 85:418–422
203 Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome. N Engl J Med 2003; 349:1133–1138
204 Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost 2005; 3:848–853
205 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; 307:1676–1681
206 Hull R, Delmore T, Carter C, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med 1982; 306: 189–194
207 Bynum LJ, Wilson JE. Low-dose heparin therapy in the long-term management of venous thromboembolism. Am J Med 1979; 67:553–556
208 Monreal M, Lafoz E, Olive A, et al. Comparison of subcu-

taneous unfractionated heparin with a low molecular weight heparin (fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71:7–11
209 Das SK, Cohen AT, Edmondson RA, et al. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World J Surg 1996; 20:521–527
210 Hamann H. Rezidivprophylaxe nach phlebothrombose-orale antikoagulation oder niedermolelulares heparin subkutan. Vasomed 1998; 10:133–136
211 Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–153
212 Gonzalez-Fajardo JA, Arreba E, Castrodeza J, 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; 30:283–292
213 Meyer G, Marjanovic Z, Valcke J, 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; 162:1729–1735
214 Veiga F, Escriba A, Maluenda MP, 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; 84:559–564
215 Lopaciuk S, Bielska-Falda H, Noszczyk W, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thromb Haemost 1999; 81:26–31
216 Lopez-Beret P, Orgaz A, Fontcuberta J, 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
217 Hull R, Pineo G, Mah A, et al. Long-term low molecular weight heparin treatment versus oral anticoagulant therapy for proximal deep vein thrombosis. Blood 2000; 96:449a
218 Hull RD, Pineo GF, Brant RF, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. Am J Med 2007; 120:72–82
219 Iorio A, Guercini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. J Thromb Haemost 2003; 1:1906–1913
220 van der Heijden JF, Hutten BA, Buller HR, et al. Vitamin K antagonists or low molecular weight heparin for the long term treatment of symptomatic venous thromboembolism (Cochrane Review). The Cochrane Library 2002; Issue 4 Oxford, UK: Update Software
221 Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 2006; 119:1062–1072
222 Weitz J, Hirsh J, Samama MM. New antithrombotic drugs: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133(suppl):234S–256S
223 Buller HR, Cohen AT, Davidson B, et al. Extended prophylaxis of venous thromboembolism with idraparinux. N Engl J Med 2007; 357:1105–1112
224 Robinson KS, Anderson DR, Gross M, et al. Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: the Post-Arthoplasty Screening Study; a randomized, controlled trial. Ann Intern Med 1997; 127:439–445
225 Vaitkus PT, Leizorovicz A, Cohen AT, et al. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. Thromb Haemost 2005; 93:76–79
226 Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev 2002; 16:155–165
227 Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349:759–762
228 Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001; 161:2105–2109
229 Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004; 141:249–256
230 Kolbach DN, Sandbrink MW, Hamulyak K, et al. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2004; CD004174
231 Kahn SR, Shbaklo H, Shapiro S, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. BMC Cardiovasc Dis 2007; 7:21
232 Ginsberg JS, Magier D, Mackinnon B, et al. Intermittent compression units for severe post-phlebitic syndrome: a randomized crossover study. Can Med Assoc J 1999; 160: 1303–1306
233 Smith PC, Sarin S, Hasty J, et al. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. Surgery 1990; 108:871–875
234 Kumar S, Samraj K, Nirujogi V, et al. Intermittent pneumatic compression as an adjuvant therapy in venous ulcer disease. J Tissue Viability 2002; 12:42–44,46,48
235 Kolari PJ, Pekanmaki K, Pohjola RT. Transcutaneous oxygen tension in patients with post-thrombotic leg ulcers: treatment with intermittent pneumatic compression. Cardiovasc Res 1988; 22:138–141
236 Barwell J, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004; 363:1854–1859
237 Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007; 335:83
238 Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plast Reconstr Surg 1994; 93:829–833
239 Martin M. PHLECO: a multicenter study of the fate of 1647 hospital patients treated conservatively without fibrinolysis and surgery. Clin Investig 1993; 71:471–477
240 Arenas R, Atoche C. Postthrombotic leg ulcers: safety and efficacy of treatment with pentoxifylline (double-blind study in 30 patients). Dermatologia Revista Mexicana 1988; 32:34–38
241 Barbarino C. Pentoxifylline in the treatment of venous leg ulcers. Curr Med Res Opin 1992; 12:547–551
242 Colgan MP, Dormandy J, Jones P, et al. The efficacy of Trental in the tratment of venous ulceration. Phlebologie 1989: 1154
243 Dale JJ, Ruckley CV, Harper DR, et al. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. BMJ 1999; 319:875–878
244 Falanga V, Fujitani RM, Diaz C, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. Wound Repair Regen 1999; 7:208–213
245 Herdy WDC, Thomas JB, Souza SR, et al. Efficacy of

pentoxifylline in the healing of venous leg ulcers: a clinical comparative study. Arquivos Brasileiros de Medicina 1997; 71:157–161
246 Schurman W, Eberhardt R. The efficacy of pentoxifylline added to topical and compression therapy in patients with varicose and postthrombotic leg ulcers. Therapiewoche 1986; 36:2343–2345
247 Weitgasser H. The use of pentoxifylline (Trental 400) in the treatment of leg ulcers: results of a double-blind trial. Pharmatherapeutica 1983; 2:143–151
248 Nikolovska S, Pavlova L, Petrova N, et al. Pentoxifylline: efficient in the treatment of venous ulcers in the absence of compression? Acta Dermatovenerol Croat 2002; 10:9–13
249 Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs 2003; 63:71–100
250 Shoab SS, Porter J, Scurr JH, et al. Endothelial activation response to oral micronised flavonoid therapy in patients with chronic venous disease: a prospective study. Eur J Vasc Endovasc Surg 1999; 17:313–318
251 Garner RC, Garner JV, Gregory S, et al. Comparison of the absorption of micronized (Daflon 500 mg) and nonmicronized 14C-diosmin tablets after oral administration to healthy volunteers by accelerator mass spectrometry and liquid scintillation counting. J Pharm Sci 2002; 91:32–40
252 Coleridge-Smith P, Lok C, Ramelet AA. Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. Eur J Vasc Endovasc Surg 2005; 30:198–208
253 Coccheri S, Scondotto G, Agnelli G, et al. Randomised, double blind, multicentre, placebo controlled study of sulodexide in the treatment of venous leg ulcers. Thromb Haemost 2002; 87:947–952
254 Campbell IA, Yeoh J, Medlicott S. Duration of hospital stay in patients with pulmonary venous thromboembolism: a randomized comparison of unfractionated heparinversus low molecular weight heparin [abstract]. Thorax 1998; 53:254
255 Kuijer PM, Gallus AS, Cade J, et al. Randomized comparison of LMWH versus standard heparin in the initial treatment of pulmonary embolism [abstract]. Thromb Haemost 1995; 73:974
256 Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995; 74:1432–1435
257 Perez de Llano LA, Baloira VA, Veres RA, et al. Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism. Arch Bronconeumol 2003; 39:341–345
258 Thery C, Simonneau G, Meyer G, et al. Randomized trial of subcutaneous low-molecular-weight heparin CY 216 (Fraxiparine) compared with intravenous unfractionated heparin in the curative treatment of submassive pulmonary embolism. Circulation 1992; 85:1380–1389
259 Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med 2004; 140:175–183
260 Beer JH, Burger M, Gretener S, et al. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. J Thromb Haemost 2003; 1:186–187
261 Kovacs MJ, Anderson D, Morrow B, et al. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost 2000; 83:209–211
262 Wells PS, Kovacs M, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin. Arch Intern Med 1998; 158:1809–1812
263 Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. Thromb Haemost 2000; 84:548–552
264 Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172:1041–1046
265 Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007; 132:24–30
266 Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. Arch Intern Med 2002; 162:2537–2541
267 Dong B, Jirong Y, Wang Q, et al. Thrombolytic treatment for pulmonary embolism. Cochrane Database Syst Rev 2006; 2; cD004437
268 Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004; 110:744–749
269 Urokinase Pulmonary Embolism Trial: a national co-operative study. Circulation 1973; 47(suppl II):1
270 Dalla-Volta S, Palla A. PAIMS 2-alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism: plasminogen Activator Italian Multicenter Study 2. J Am Coll Cardiol 1992; 20:520–526
271 Dotter CT, Seamon AJ, Rosch J, et al. Streptokinase and heparin in the treatment of pulmonary embolism: a randomized comparison. Vasc Surg 1979; 13 42–52
272 PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism. Chest 1990; 97: 528–533
273 Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streprokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. J Thromb Thrombol 1995; 2:227–229
274 Lopaciuk S, Meissner AJ, Ciesielski L, et al. Subcutaneous sodium heparin versus intravenous sodium heparin in the treatment of deep vein thrombosis: proceedings of the 6th International Meeting of the Danubian League Against Thrombosis and Haemorrhagic Disorders. Vienna, Austria: 1989; 389–393
275 Ly B, Arnesen H, Eie H, et al. A controlled clinical trial of streptokinse and heparin in the treatment of major pulmonary embolism. Acta Med Scand 1978; 203:465–470
276 Marini C, Di Ricco G, Rossi G, et al. Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: a randomized clinical trial. Respiration 1988; 54:162–173
277 Tibbutt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. BMJ 1974; 1:343–347
278 Urokinase Pulmonary Embolism Trial Study Group. Urokinase pulmonary embolism trial: phase I results. JAMA 1970; 214:2163–2172
279 Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002; 347:1143–1150
280 Kucher N, Rossi E, De Rosa M, et al. Massive pulmonary embolism. Circulation 2006; 113:577–582
281 Goldhaber SZ, Visni L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386–1389

282 Douketis JD, Leeuwenkamp O, Grobara P, et al. The incidence and prognostic significance of elevated cardiac troponins in patients with submassive pulmonary embolism. J Thromb Haemost 2005; 3:508–513
283 Giannitsis E, Katus HA. Risk stratification in pulmonary embolism based on biomarkers and echocardiography. Circulation 2005; 112:1520–1521
284 Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002; 106: 1263–1268
285 Scridon T, Scridon C, Skali H, et al. Prognostic significance of troponin elevation and right ventricular enlargement in acute pulmonary embolism. Am J Cardiol 2005; 96:303–305
286 Becattini C, Vedovati M, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007; 116:427–433
287 Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med 2002; 136:691–700
288 Schoepf UJ, Kucher N, Kipfmueller F, et al. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation 2004; 110:3276–3280
289 Ten Wolde M, Sohne M, Quak E, et al. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. Arch Intern Med 2004; 164:1685–1689
290 Fiumara K, Kucher N, Fanikos J, et al. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol 2006; 97:127–129
291 Kanter DS, Mikkola KM, Patel SR, et al. Thrombolytic therapy for pulmonary embolism: frequency of intracranial hemorrhage and associated risk factors. Chest 1997; 111: 1241–1245
292 Urokinase-streptokinase embolism trial: phase 2 result. JAMA 1974; 229:1606–1613
293 Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis: an international multicenter randomized trial; The Bolus Alteplase Pulmonary Embolism Group. Chest 1994; 106:718–724
294 Goldhaber SZ, Kessler CM, Heit J, et al. A randomized controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. Lancet 1988; 2:293–298
295 Goldhaber SZ, Kessler CM, Heit JA, et al. Recombinant tissue-type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: a randomized controlled multicenter trial. J Am Coll Cardiol 1992; 20:24–30
296 Meneveau N, Schiele F, Metz D, et al. Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. J Am Coll Cardiol 1998; 31:1057–1063
297 Meneveau N, Schiele F, Vuillemenot A, et al. Streptokinase vs alteplase in massive pulmonary embolism: a randomized trial assessing right heart haemodynamics and pulmonary vascular obstruction. Eur Heart J 1997; 18:1141–1148
298 Meyer G, Sors H, Charbonnier B, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. J Am Coll Cardiol 1992; 19:239–245
299 Sors H, Pacouret G, Azarian R, et al. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism: a randomized controlled multicenter trial. Chest 1994; 106:712–717
300 Verstraete M, Miller GAH, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988; 77:353–360
301 Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 1990; 98:1473–1479
302 de Gregorio M, Gimeno M, Alfonso R, et al. Mechanical fragmentation and intrapulmonary fibrinolysis in the treatment of massive pulmonary embolism hemodynamic repercussions. Arch Bronconeumol 2001; 37:58–64
303 Fava M, Loyola S, Flores P, et al. Mechanical fragmentation and pharmacologic thrombolysis in massive pulmonary embolism. J Vasc Interv Radiol 1997; 8:261–266
304 Schmitz-Rode T, Janssens U, Duda SH, et al. Massive pulmonary embolism: percutaneous emergency treatment by pigtail rotation catheter. J Am Coll Cardiol 2000; 36:375–380
305 Schmitz-Rode T, Janssens U, Schild HH, et al. Fragmentation of massive pulmonary embolism using a pigtail rotation catheter. Chest 1998; 114:1427–1436
306 Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005; 129: 1018–1023
307 Meneveau N, Seronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006; 129:1043–1050
308 Sukhija R, Aronow WS, Lee J, et al. Association of right ventricular dysfunction with in-hospital mortality in patients with acute pulmonary embolism and reduction in mortality in patients with right ventricular dysfunction by pulmonary embolectomy. Am J Cardiol 2005; 95:695–696
309 Beckman JA, Dunn K, Sasahara AA, et al. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. Thromb Haemost 2003; 89:953–958
310 Kucher N, Quiroz R, McKean S, et al. Extended enoxaparin monotherapy for acute symptomatic pulmonary embolism. Vasc Med 2005; 10:251–256
311 Gosselin MV, Rubin GD, Leung AN, et al. Unsuspected pulmonary embolism: prospective detection on routine helical CT scans. Radiology 1998; 208:209–215
312 O'Connell CL, Boswell WD, Duddalwar V, et al. Unsuspected pulmonary emboli in cancer patients: clinical correlates and relevance. J Clin Oncol 2006; 24:4928–4932
313 Sebastian AJ, Paddon AJ. Clinically unsuspected pulmonary embolism–an important secondary finding in oncology CT. Clin Radiol 2006; 61:81–85
314 Storto ML, Di Credico A, Guido F, et al. Incidental detection of pulmonary emboli on routine MDCT of the chest. AJR Am J Roentgenol 2005; 184:264–267
315 Becattini C, Agnelli G, Pesavento R, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest 2006; 130:172–175
316 Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004; 350:2257–2264
317 Ribeiro A, Lindmarker P, Johnsson H, et al. Pulmonary embolism: one year follow-up with echocardiography doppler and five-year survival analysis. Circulation 1999; 99: 1325–1330
318 Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003; 76:1457–1462
319 Fedullo PF, Auger WR, Kerr KM, et al. Chronic thrombo-

embolic pulmonary hypertension. N Engl J Med 2001; 345:1465–1472
320 Feinstein JA, Goldhaber SZ, Lock JE, et al. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001; 103:10–13
321 Galie N, Kim NH. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006; 3:571–576
322 Hoeper MM, Mayer E, Simonneau G, et al. Chronic thromboembolic pulmonary hypertension. Circulation 2006; 113:2011–2020
323 Bresser P, Pepke-Zaba J, Jais X, et al. Medical therapies for chronic thromboembolic pulmonary hypertension: an evolving treatment paradigm. Proc Am Thorac Soc 2006; 3:594–600
324 Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. J Thromb Haemost 2007; 5:483–489
325 Hughes RJ, Jais X, Bonderman D, et al. The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. Eur Respir J 2006; 28:138–143
326 Tagalakis V, Kahn SR, Libman M, et al. The epidemiology of peripheral vein infusion thrombophlebitis: a critical review. Am J Med 2002; 113:146–151
327 Becherucci A, Bagilet D, Marenghini J, et al. Effect of topical and oral diclofenac on superficial thrombophlebitis caused by intravenous infusion. Med Clin (Barc) 2000; 114:371–373
328 Vilardell M, Sabat D, Arnaiz JA, et al. Topical heparin for the treatment of acute superficial phlebitis secondary to indwelling intravenous catheter: a double-blind, randomized, placebo-controlled trial. Eur J Clin Pharmacol 1999; 54:917–921
329 Bergqvist D, Brunkwall J, Jensen N, et al. Treatment of superficial thrombophlebitis: a comparative trial between placebo, Hirudoid cream and piroxicam gel. Ann Chir Gynaecol 1990; 79:92–96
330 De Sanctis MT, Cesarone MR, Incandela L, et al. Treatment of superficial vein thrombophlebitis of the arm with Essaven gel: a placebo-controlled, randomized study. Angiology 2001; 52(suppl 3):S63–S67
331 Decousus H, Epinat M, Guillot K, et al. Superficial vein thrombosis: risk factors, diagnosis, and treatment. Curr Opin Pulm Med 2003; 9:393–397
332 Wichers IM, Di Nisio M, Buller HR, et al. Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism: a systematic review. Haematologica 2005; 90:672–677
333 Quenet S, Laporte S, Decousus H, et al. Factors predictive of venous thrombotic complications in patients with isolated superficial vein thrombosis. J Vasc Surg 2003; 38:944–949
334 Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev 2007; CD004982
335 Superficial Thrombophlebitis Treated by Enoxaparin Study Group. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a nonsteroidal anti-inflammatory agent, and placebo in the treatment of superficial vein thrombosis. Arch Intern Med 2003; 163:1657–1663
336 Titon JP, Auger D, Grange P, et al. Therapeutic management of superficial venous thrombosis with calcium nadroparin: dosage testing and comparison with a non-steroidal anti-inflammatory agent. Ann Cardiol Angeiol (Paris) 1994; 43:160–166
337 Prandoni P, Tormene D, Pesavento R. High vs. low doses of low-molecular-weight heparin for the treatment of superficial vein thrombosis of the legs: a double-blind, randomized trial. J Thromb Haemost 2005; 3:1152–1157
338 Marchiori A, Verlato F, Sabbion P, et al. High versus low doses of unfractionated heparin for the treatment of superficial thrombophlebitis of the leg: a prospective, controlled, randomized study. Haematologica 2002; 87:523–527
339 Belcaro G, Nicolaides AN, Errichi BM, et al. Superficial thrombophlebitis of the legs: a randomized, controlled, follow-up study. Angiology 1999; 50:523–529
340 Gorski G, Szopinski P, Michalak J, et al. Liposomal heparin spray: a new formula in adjunctive treatment of superficial venous thrombosis. Angiology 2005; 56:9–17
341 Andreozzi GM, Signorelli S, Di Pino L, et al. Tolerability and clinical efficacy of desmin in the treatment of superficial thrombovaricophlebitis. Angiology 1996; 47:887–894
342 Lozano FS, Almazan A. Low-molecular-weight heparin versus saphenofemoral disconnection for the treatment of above-knee greater saphenous thrombophlebitis: a prospective study. Vasc Endovascular Surg 2003; 37:415–420
343 Sullivan V, Denk PM, Sonnad SS, et al. Ligation versus anticoagulation: treatment of above-knee superficial thrombophlebitis not involving the deep venous system. J Am Coll Surg 2001; 193:556–562
344 Becker DM, Philbrick JT, Walker FB. Axillary and subclavian venous thrombosis: prognosis and treatment. Arch Intern Med 1991; 151:1934–1943
345 Joffe HV, Kucher N, Tapson VF, et al. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation 2004; 110:1605–1611
346 Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis: risk factors, diagnosis, and complications. Arch Intern Med 1997; 157:57–62
347 Prandoni P, Bernardi E, Marchiori A, et al. The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. BMJ 2004; 329:484–485
348 Elman ER, Kahn SR. The post-thrombotic syndrome after upper extremity deep venous thrombosis: a systematic review. Thromb Res 2006; 117:609–614
349 Savage KJ, Wells PS, Schulz V, et al. Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost 1999; 82:1008–1010
350 Karabay O, Yetkin U, Onol H. Upper extremity deep vein thrombosis: clinical and treatment characteristics. J Int Med Res 2004; 32:429–435
351 Kovacs MJ, Kahn SR, Rodger M, et al. A pilot study of central venous catheter survival in cancer patients using low molecular weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost 2007; 5:1650–1653
352 AbuRahma AF, Short YS, White JF III, et al. Treatment alternatives for axillary-subclavian vein thrombosis: long-term follow-up. Cardiovasc Surg 1996; 4:783–787
353 Lee JT, Karwowski JK, Harris EJ, et al. Long-term thrombotic recurrence after nonoperative management of Paget-Schroetter syndrome. J Vasc Surg 2006; 43:1236–1243
354 Lokanathan R, Salvian AJ, Chen JC, et al. Outcome after thrombolysis and selective thoracic outlet decompression for primary axillary vein thrombosis. J Vasc Surg 2001; 33:783–788
355 Pegis JD, Papon X, Pasco A, et al. *In situ* thrombolysis in the treatment of venous thrombosis of effort in the arm. J Mal Vasc 1997; 22:187–192
356 Petrakis IE, Katsamouris A, Kafassis E, et al. Two different therapeutic modalities in the treatment of the upper extremity deep vein thrombosis: preliminary investigation with 20 case reports. Int J Angiol 2000; 9:46–50
357 Sabeti S, Schillinger M, Mlekusch W, et al. Treatment of

subclavian-axillary vein thrombosis: long-term outcome of anticoagulation versus systemic thrombolysis. Thromb Res 2002; 108:279–285
358 Schindler J, Bona RD, Chen HH, et al. Regional thrombolysis with urokinase for central venous catheter-related thrombosis in patients undergoing high-dose chemotherapy with autologous blood stem cell rescue. Clin Appl Thromb Haemost 1999; 5:25–29
359 Caparrelli DJ, Freischlag J. A unified approach to axillosubclavian venous thrombosis in a single hospital admission. Semin Vasc Surg 2005; 18:153–157
360 Thomas IH, Zierler BK. An integrative review of outcomes in patients with acute primary upper extremity deep venous thrombosis following no treatment or treatment with anticoagulation, thrombolysis, or surgical algorithms. Vasc Endovascular Surg 2005; 39:163–174
361 Machleder HI. Evaluation of a new treatment strategy for Paget-Schroetter syndrome: spontaneous thrombosis of the axillary-subclavian vein. J Vasc Surg 1993; 17:305–315
362 Schneider DB, Dimuzio PJ, Martin ND, et al. Combination treatment of venous thoracic outlet syndrome: open surgical decompression and intraoperative angioplasty. J Vasc Surg 2004; 40:599–603
363 Spence LD, Gironta MG, Malde HM, et al. Acute upper extremity deep venous thrombosis: safety and effectiveness of superior vena caval filters. Radiology 1999; 210:53–58
364 Ascher E, Hingorani A, Tsemekhin B, et al. Lessons learned from a 6-year clinical experience with superior vena cava Greenfield filters. J Vasc Surg 2000; 32:881–887
365 Feugier P, Aleksic I, Salari R, et al. Long-term results of venous revascularization for Paget-Schroetter syndrome in athletes. Ann Vasc Surg 2001; 15:212–218
366 Lee MC, Grassi CJ, Belkin M, et al. Early operative intervention after thrombolytic therapy for primary subclavian vein thrombosis: an effective treatment approach. J Vasc Surg 1998; 27:1101–1107
367 Malcynski J, O'Donnell TF Jr, Mackey WC, et al. Long-term results of treatment for axillary subclavian vein thrombosis. Can J Surg 1993; 36:365–371
368 Meier GH, Pollak JS, Rosenblatt M, et al. Initial experience with venous stents in exertional axillary-subclavian vein thrombosis. J Vasc Surg 1996; 24:974–981
369 Sanders RJ, Cooper MA. Surgical management of subclavian vein obstruction, including six cases of subclavian vein bypass. Surgery 1995; 118:856–863
370 Sheeran SR, Hallisey MJ, Murphy TP, et al. Local thrombolytic therapy as part of a multidisciplinary approach to acute axillosubclavian vein thrombosis (Paget-Schroetter syndrome). J Vasc Interv Radiol 1997; 8:253–260
371 Urschel HC Jr, Patel AN. Paget-Schroetter syndrome therapy: failure of intravenous stents. Ann Thorac Surg 2003; 75:1693–1696
372 Yilmaz EN, Vahl AC, Heek van NT, et al. Long-term results of local thrombolysis followed by first rib resection: an encouraging clinical experience in treatment of subclavian vein thrombosis. Vasc Surg 2000; 34:17–23
373 Marie I, Levesque H, Cailleux N, et al. Deep venous thrombosis of the upper limbs: apropos of 49 cases [in French]. Rev Med Interne 1998; 19:399–408
374 Baarslag HJ, Koopman MM, Reekers JA, et al. Diagnosis and management of deep vein thrombosis of the upper extremity: a review. Eur Radiol 2004; 14:1263–1274
375 Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):401S–428S
376 Elliott G. Upper-extremity deep vein thrombosis. Lancet 1997; 349:1188–1189
377 Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. Circulation 2002; 106:1874–1880
378 Martinelli I, Battaglioli T, Bucciarelli P, et al. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. Circulation 2004; 110:566–570
379 Burihan E, de Figueiredo LF, Francisco JJ, et al. Upper-extremity deep venous thrombosis: analysis of 52 cases. Cardiovasc Surg 1993; 1:19–22
380 Hingorani A, Ascher E, Lorenson E, et al. Upper extremity deep venous thrombosis and its impact on morbidity and mortality rates in a hospital-based population. J Vasc Surg 1997; 26:853–860
381 Hingorani A, Ascher E, Ward M, et al. Combined upper and lower extremity deep venous thrombosis. Cardiovasc Surg 2001; 9:472–477
382 Lindblad B, Tengborn L, Bergqvist D. Deep vein thrombosis of the axillary-subclavian veins: epidemiologic data, effects of different types of treatment and late sequelae. Eur J Vasc Surg 1988; 2:161–165
383 Marinella MA, Kathula SK, Markert RJ. Spectrum of upper-extremity deep venous thrombosis in a community teaching hospital. Heart Lung 2000; 29:113–117
384 Kahn SR, Elman EA, Bornais C, et al. Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. Thromb Haemost 2005; 93:499–502
385 Apollonio A, Angeletti R. Conservative treatment of venous leg ulcers (pentoxifylline vs defibrotide) [in Italian]. Giornale Italiano di Angiologia 1992; 12:151–156
386 Belcaro G, Cesarone MR, Nicolaides AN, et al. Treatment of venous ulcers with pentoxifylline: a 6-month randomized, double-blind, placebo controlled trial. Angiology 2002; 53(suppl 1):S45–S47
387 De Sanctis MT, Belcaro G, Cesarone MR, et al. Treatment of venous ulcers with pentoxifylline: a 12-month, double-blind, placebo controlled trial. Microcirculation and healing. Angiology 2002; 53(suppl 1):S49–S51
388 Guilhou JJ, Fevrier F, Debure C, et al. Benefit of a 2-month treatment with a micronized, purified flavonoidic fraction on venous ulcer healing: a randomized, double-blind, controlled versus placebo trial. Int J Microcirc Clin Exp 1997; 17(suppl 1):21–26
389 Glinski W, Chodynicka B, Roszkiewicz J, et al. Effectiveness of a micronized purified flavonoid fraction (MPFF) in the healing process of lower limb ulcers: an open multicentre study, controlled and randomized [in Italian]. Minerva Cardioangiol 2001; 49:107–114
390 Roztocil K, Stvrtinova V, Strejcek J. Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. Int Angiol 2003; 22:24–31
391 Goldhaber SZ, Haire WD, Feldstein ML, et al. Aleptase versus heparin in acute pulmonary embolism: randomized trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507–511
392 Massoure PL, Constans J, Caudry M, et al. Upper extremity deep venous thrombosis: 40 hospitalized patients [in French]. J Mal Vasc 2000; 25:250–255
393 Persson LM, Arnhjort T, Larfars G, et al. Hemodynamic and morphologic evaluation of sequelae of primary upper extremity deep venous thromboses treated with anticoagulation. J Vasc Surg 2006; 43:1230–1235