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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Anthony J. Comerota, MD; Paolo Prandoni, MD, PhD; Henri Bounameaux, MD; Samuel Z. Goldhaber, MD, FCCP; Michael E. Nelson, MD, FCCP; Philip S. Wells, MD; Michael K. Gould, MD, FCCP; Francesco Dentali, MD; Mark Crowther, MD; and Susan R. Kahn, MD

Background: **This article addresses the treatment of VTE disease.**
Methods: **We generated strong (Grade 1) and weak (Grade 2) recommendations based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.**
Results: **For acute DVT or pulmonary embolism (PE), we recommend initial parenteral anticoagulant therapy (Grade 1B) or anticoagulation with rivaroxaban. We suggest low-molecular-weight heparin (LMWH) or fondaparinux over IV unfractionated heparin (Grade 2C) or subcutaneous unfractionated heparin (Grade 2B). We suggest thrombolytic therapy for PE with hypotension (Grade 2C). For proximal DVT or PE, we recommend treatment of 3 months over shorter periods (Grade 1B). For a first proximal DVT or PE that is provoked by surgery or by a nonsurgical transient risk factor, we recommend 3 months of therapy (Grade 1B; Grade 2B if provoked by a nonsurgical risk factor and low or moderate bleeding risk); that is unprovoked, we suggest extended therapy if bleeding risk is low or moderate (Grade 2B) and recommend 3 months of therapy if bleeding risk is high (Grade 1B); and that is associated with active cancer, we recommend extended therapy (Grade 1B; Grade 2B if high bleeding risk) and suggest LMWH over vitamin K antagonists (Grade 2B). We suggest vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2B). We suggest compression stockings to prevent the postthrombotic syndrome (Grade 2B). For extensive superficial vein thrombosis, we suggest prophylactic-dose fondaparinux or LMWH over no anticoagulation (Grade 2B), and suggest fondaparinux over LMWH (Grade 2C).**
Conclusion: **Strong recommendations apply to most patients, whereas weak recommendations are sensitive to differences among patients, including their preferences.**

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Abbreviations: CALISTO = Comparison of ARIXTRA in Lower Limb Superficial Thrombophlebitis With Placebo; CDT = catheter-directed thrombolysis; CTPH = chronic thromboembolic pulmonary hypertension; HR = hazard ratio; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; PREPIC = Prevention du Risque d'Embolie Pulmonaire par Interruption Cave; PTS = postthrombotic (phlebitic) syndrome; RR = risk ratio; rt-PA = recombinant tissue plasminogen activator; SC = subcutaneous; SVT = superficial vein thrombosis; tPA = tissue plasminogen activator; UEDVT = upper-extremity DVT; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1. In patients with acute DVT of the leg treated with vitamin K antagonist (VKA) therapy, we

recommend initial treatment with parenteral anticoagulation (low-molecular-weight heparin [LMWH], fondaparinux, IV unfractionated heparin [UFH], or subcutaneous [SC] UFH) over no such initial treatment (Grade 1B)**.**

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C)**.**

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C)**.**

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)**.**

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B)**; we suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C)**; we recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B)**.**

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B)**.**

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH.

LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH**.**

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Affiliations: From the Departments of Medicine and Clinical Epidemiology and Biostatistics (Dr Kearon), Michael De Groote School of Medicine, McMaster University, Hamilton, ON, Canada; Departments of Medicine, Family Medicine, and Social and Preventive Medicine (Dr Akl), State University of New York at Buffalo, Buffalo, NY; Department of Surgery (Dr Comerota), Jobst Vascular Center, Toledo, OH; Department of Cardiothoracic and Vascular Sciences (Dr Prandoni), University of Padua, Padua, Italy; Department of Medical Specialties (Dr Bounameaux), University Hospitals of Geneva, Geneva, Switzerland; Department of Medicine (Dr Goldhaber), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Medicine (Dr Nelson), Shawnee Mission Medical Center, Shawnee Mission, KS; Department of Medicine (Dr Wells), University of Ottawa, Ottawa, ON, Canada; Departments of Medicine and Preventive Medicine (Dr Gould), Keck School of Medicine, University of Southern California, Los Angeles, CA; Department of Medicine (Dr Dentali), University of Insubria, Varese, Italy; Department of Medicine (Dr Crowther), Michael De Groote School of Medicine, McMaster University, Hamilton, ON, Canada; and Departments of Medicine and Clinical Epidemiology and Biostatistics (Dr Kahn), McGill University, Montreal, QC, Canada.
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Correspondence to: Elie A. Akl, MD, MPH, PhD, Department of Medicine, State University of New York at Buffalo, ECMC-CC 142, 462 Grider St, Buffalo, NY 14215; e-mail: elieakl@buffalo.edu

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2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Remarks: The recommendation is conditional on the adequacy of home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy, are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C).

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B).

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we suggest the use of compression therapy in these patients.

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **or (iii) extended therapy** (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **and (iii) extended therapy if there is a high bleeding risk** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B).

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical

transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) **and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B) **or extended therapy** (Grade 1B regardless of bleeding risk)**.**

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B)**. After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.**

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)**.**

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)**.**

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) **and recommend 3 months of anticoagulant treatment in those with a high bleeding risk** (Grade 1B)**.**

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B)**, and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B)**.**

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B)**.**

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants (see section 2.3).

In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2B)**.**

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs.

LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA.

Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4. In patients with DVT of the leg who receive extended therapy, we suggest treatment with the

same anticoagulant chosen for the first 3 months (Grade 2C)**.**

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B)**.**

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful.

Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C)**.**

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B)**.**

4.3. In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C)**.**

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B)**.**

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH.

LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.

In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B)**.**

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C)**.**

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against

systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).

5.6.2.2. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **or (iii) extended therapy** (Grade 1B regardless of bleeding risk).

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **and (iii) extended therapy if there is a high bleeding risk** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B).

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). **After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.**

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), **and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B).

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B).

6.4. In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), **and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs.

Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendation in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C)**.**

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B)**.**

7.1.1. In patients with chronic thromboembolic pulmonary hypertension (CTPH), we recommend extended anticoagulation over stopping therapy (Grade 1B)**.**

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C)**.**

8.1.1. In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B)**.**

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)**.**

9.1.1. In patients with acute upper-extremity DVT (UEDVT) that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B)**.**

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B)**.**

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C)**.**

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B)**.**

9.3.1. In most patients with UEDVT that is associated with a 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)**.**

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B)**.**

Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B)**, and we suggest this in patients with cancer** (Grade 2C)**.**

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C)**, and we suggest this in patients with no cancer** (Grade 2C)**.**

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B)**.**

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C)**.**

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C)**.**

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C)**.**

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B)**.**

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C)**.**

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

This article provides recommendations for the use of antithrombotic agents as well as the use of devices or surgical techniques in the treatment of patients with DVT and pulmonary embolism (PE), which are collectively referred to as VTE. We also provide recommendations for patients with (1) postthrombotic syndrome (PTS), (2) chronic thromboembolic pulmonary hypertension (CTPH), (3) incidentally diagnosed (asymptomatic) DVT or PE, (4) acute upper-extremity DVT (UEDVT), (5) superficial vein thrombosis (SVT), (6) splanchnic vein thrombosis, and (7) hepatic vein thrombosis.

Table 1 describes the populations, interventions, comparators, and outcomes (ie, PICO elements) for the questions addressed in this article and the design of the studies used to address them. Refer to Garcia et al,[1] Ageno et al,[2] and Holbrook et al[3] in these guidelines for recommendations on the management of parenteral anticoagulation (dosing and monitoring) and oral anticoagulation (dosing and monitoring). Refer to Bates et al[4] and Monagle et al[5] in these guidelines for recommendations for pregnancy and neonates and children. The current article builds on previous versions of these guidelines and, most recently, the eighth edition.[6]

1.0 Methods

1.1 Presentation as DVT or PE

In addressing DVT, we first review studies that included (1) only patients who presented with symptomatic DVT or (2) patients who presented with DVT or PE (ie, meeting the broader criterion of VTE). For the PE components, we review studies (and subgroups within studies) that required patients to have presented with symptomatic PE (who may also have had symptoms of DVT). For this reason and because more patients with VTE present with symptoms of DVT alone than with symptoms of PE (including those who also have symptoms of DVT), the DVT section deals with a larger body of evidence than the PE section.

In the evaluation of anticoagulant therapy, there are a number of justifications for inclusion of patients who present with DVT and PE in the same study, and for extrapolating evidence obtained in patients with one presentation of VTE (eg, DVT) to the other presentation (eg, PE). First, a majority of patients with symptomatic DVT also have PE (symptomatic or asymptomatic), and a majority of those with symptomatic PE also have DVT (symptomatic or asymptomatic).[7,8] Second, 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 those with only PE. Third, the risk of recurrence appears to be similar after PE and after proximal DVT.[7,9] Consequently, the results of all studies of VTE have been considered when formulating recommendations for short- and long-term anticoagulation of proximal DVT and PE (Fig 1), and these recommendations are essentially the same for proximal DVT or PE.

There are, however, some important differences between patients who present with PE and those who present with DVT that justify separate consideration of some aspects of the treatment of 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[9]; this difference may justify more aggressive initial treatment of PE (eg, thrombolytic therapy, insertion of an inferior vena cava (IVC) filter, more intensive anticoagulant therapy) compared with DVT. Second, recurrent episodes of VTE are about three times as likely to be

Table 1—*Structured Clinical Questions*

Issue (Informal Question)	Structured PICO Question: Population	Intervention	Comparators	Outcome	Methodology
	Patient with acute DVT of the leg (2.0-3.0)				
Initial anticoagulant (2.1)	Patients with acute DVT of the leg	Anticoagulation	No anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Whether to treat while awaiting the results of the diagnostic work-up (2.2.1- 2.2.3)	Patients with suspected acute DVT of the leg awaiting the results of diagnostic tests	Anticoagulation	No anticoagulation	PE, major bleeding, and mortality	RCTs and cohort studies
Whether to treat isolated distal thrombosis (2.3.1-2.3.4)	Patient with acute isolated distal DVT of the leg	Anticoagulation	No anticoagulation	DVT extension, PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Timing of initiation of VKA relative to the initiation of parenteral anticoagulation (2.4)	Patients with acute DVT of the leg	Early initiation of VKA	Delayed initiation of VKA	DVT extension, PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Duration of initial anticoagulation (2.4)	Patients with acute DVT of the leg	Longer duration	Shorter duration	DVT extension, PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Choice and route of initial anticoagulant (2.5.1, 2.5.2, 2.6)	Patients with acute DVT of the leg	UFH IV or SQ	LMWH, fondaparinux, rivaroxaban	DVT extension, PE, major bleeding, mortality, QOL, and PTS	RCTs
Setting of initial anticoagulation (2.7)	Patients with acute DVT of the leg	In-hospital treatment	At-home treatment	DVT extension, PE, major bleeding, mortality, QOL, and PTS	RCTs
Role of thrombolytic and mechanical interventions (2.9-2.12)	Patients with acute proximal DVT of the leg	Catheter directed thrombolysis Systemic thrombolytic therapy Operative venous thrombectomy	No active thrombus removal or another method of thrombus removal	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, shorter ICU and hospital stays, and acute complications	RCTs and cohort studies
Role of IVC filters in addition to anticoagulation (2.13.1)	Patients with acute DVT of the leg started on anticoagulation	IVC filter	No IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, and complications of procedure	RCTs
Role of IVC filters when anticoagulation is contraindicated (2.13.2)	Patients with acute DVT of the leg and a contraindication to anticoagulation	IVC filter	No IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, and complications of procedure	RCTs and cohort studies
Role of anticoagulation in patients who initially received an IVC filter when contraindication to anticoagulation resolves (2.13.3)	Patients with acute DVT of the leg who initially received an IVC filter, now contraindication to anticoagulation resolved	Anticoagulation in addition to IVC filter	No anticoagulation in addition to IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, and complications of procedure	RCTs and cohort studies
Role of early ambulation (2.14)	Patients with acute DVT of the leg started on anticoagulant treatment	Early ambulation	Initial bed rest	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, and complications of procedure	RCTs and cohort studies

(Continued)

Table 1—*Continued*

Issue (Informal Question)	Structured PICO Question: Population	Intervention	Comparators	Outcome	Methodology
Long-term anticoagulation therapy (3.0)	Patients with acute VTE of the leg	Long-term anticoagulation therapy	No long-term anticoagulation therapy	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Duration of long-term anticoagulation (3.1.1- 3.1.5)	Patients with an acute DVT of the leg	Longer duration	Shorter duration	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Intensity of VKA (3.2)	Patients with acute DVT of the leg	INR 2-3	Higher or lower INR ranges	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Choice of long-term anticoagulant (3.3.1, 3.3.2, 3.4)	Patients with acute DVT of the leg.	LMWH, dabigatran, rivaroxaban	VKA	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Whether to treat an incidentally diagnosed asymptomatic acute DVT of the leg (3.5)	Patients with incidentally diagnosed asymptomatic DVT of the leg	Anticoagulation	No anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
	Patients with PTS of the leg				
Role of compression stocking in preventing PTS (4.1)	Patients with acute DVT of the leg started on anticoagulant treatment	Compression stockings	No compression stockings	QOL, PTS, and recurrent DVT	RCTs
Role of compression stocking in PTS (4.2.1)	Patients with PTS of the leg	Compression stockings	No compression stockings	QOL, symptomatic relief, ulceration	RCTs and cohort studies
Role of intermittent pneumatic compression in PTS (4.2.2)	Patients with PTS of the leg	Intermittent pneumatic compression	No intermittent pneumatic compression	QOL, symptomatic relief, ulceration	RCTs and cohort studies
Role of venoactive medications in PTS (4.3)	Patients with PTS of the leg	Venoactive medications	No venoactive medications	QOL, PTS, and recurrent DVT	RCTs and cohort studies
	Patient with acute PE				
Initial anticoagulant (5.1)	Patients with acute PE	Anticoagulation	No initial anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Whether to treat while awaiting the results of the diagnostic work-up (5.2.1-5.2.3)	Patients with suspected acute PE awaiting the results of the diagnostic tests	Anticoagulation	No anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Timing of initiation of VKA relative to the initiation of parenteral anticoagulation (5.3)	Patients with acute PE	Early initiation of VKA	Delayed initiation of VKA	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Duration of initial anticoagulation (5.3)	Patients with acute PE	Longer duration	Shorter duration	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies

(Continued)

Table 1—*Continued*

Issue (Informal Question)	Structured PICO Question				Methodology
	Population	Intervention	Comparators	Outcome	
Choice and route of initial anticoagulant (5.4.1, 5.4.2)	Patients with acute DVT of the leg	UFH IV or SQ	LMWH, fondaparinux, and rivaroxaban	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Setting of initial anticoagulation (5.5)	Patients with acute PE	In-hospital treatment	At-home treatment	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Thrombolytic therapy in patients with acute PE (5.6.1.1, 5.6.1.2, 5.6.1.3)	Patients with acute PE	Thrombolytic therapy	No thrombolytic therapy	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Infusion time for thrombolytic therapy (5.6.2.1)	Patients with acute PE requiring thrombolytic therapy	Longer infusion time	Shorter infusion time	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Venous access for thrombolytic therapy (5.6.2.2)	Patients with acute PE requiring thrombolytic therapy	Peripheral vein	Pulmonary catheter	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of catheter-assisted thrombus removal (5.7)	Patients with acute PE	Use of catheter-assisted thrombus removal	No use of catheter-assisted thrombus removal	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of surgical pulmonary embolectomy (5.8)	Patients with acute PE	Surgical pulmonary embolectomy	No surgical pulmonary embolectomy	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of IVC filter in addition to anticoagulation in patients with acute PE (5.9.1)	Patients with acute PE started on anticoagulation	IVC filter	No IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of IVC filters when anticoagulation is contraindicated (5.9.2)	Patients with acute PE and a contraindication to anticoagulation	IVC filter	No IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of anticoagulation in patients who initially received an IVC filter when contraindication to anticoagulation resolves (5.9.3)	Patients with acute PE who initially received an IVC filter, now contraindication to anticoagulation resolved	Anticoagulation in addition to IVC filter	No anticoagulation in addition to IVC filter	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Duration of long-term anticoagulation in patients with acute PE (6.1-6.4)	Patients with acute PE	Longer duration	Shorter duration	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Intensity of VKA (6.5)	Patients with acute PE	INR 2-3	Higher or lower INR range	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Choice of long-term anticoagulant (6.6, 6.7, 6.8)	Patients with acute PE	LMWH, dabigatran, rivaroxaban	VKA	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs
Whether to treat an incidentally diagnosed asymptomatic acute PE (6.9)	Patients with incidentally diagnosed asymptomatic PE	Anticoagulation	No anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohorts

(Continued)

Table 1—*Continued*

Issue (Informal Question)	Structured PICO Question: Population	Intervention	Comparators	Outcome	Methodology
		Patient with CTPH			
Role of oral anticoagulation in CTPH (7.1.1)	Patients with CTPH	Oral anticoagulation	No oral anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of pulmonary thromboendarterectomy in CTPH (7.1.2)	Patients with CTPH	Pulmonary thromboendarterectomy	No pulmonary thromboendarterectomy	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
		Patient with SVT			
Role of anticoagulation in SVT (8.1.1, 8.1.2)	Patients with SVT	Anticoagulation	No anticoagulation or other anticoagulant	DVT and PE, major bleeding, mortality, QOL, symptomatic relief, and PTS	RCTs and cohort studies
		Patient with acute UEDVT			
Acute anticoagulation (9.1.1, 9.1.2)	Patients with UEDVT	Parenteral anticoagulation	No anticoagulation	Recurrent DVT and PE, major bleeding, mortality, QOL, and PTS	RCTs and cohort studies
Role of thrombolytic therapy (9.2.1, 9.2.2)	Patients with UEDVT	Systemic thrombolytic therapy	No systemic thrombolytic therapy	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, shorter ICU and hospital stays, and acute complications	RCTs and cohort studies
Whether indwelling central venous catheter should be removed (9.3.1)	Patients with UEDVT and indwelling central venous catheter	Removal of indwelling central venous catheter	No removal of indwelling central venous catheter	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, shorter ICU and hospital stays, and acute complications	RCTs and cohort studies
Duration of long-term anticoagulation (9.3.2-9.3.5)	Patients with UEDVT and indwelling central venous catheter	Longer duration	Shorter duration	Recurrent DVT and PE, major bleeding, mortality, QOL, PTS, shorter ICU and hospital stays, and acute complications	RCTs and cohort studies
Prevention of PTS of the arm (9.4)	Patients with UEDVT	Compression sleeves or venoactive medications	No compression sleeves or venoactive medications	QOL, PTS, and recurrent DVT	RCTs and cohort studies
Treatment of PTS of the arm (9.5.1, 9.5.2)	Patients with PTS of the arm	Compression sleeves or venoactive medications	No compression sleeves or venoactive medications	QOL, symptomatic relief, and ulceration	RCTs and cohort studies
		Patient with thrombosis in unusual sites			
Role of anticoagulation in splanchnic vein thrombosis (10.1, 10.2)	Patients with splanchnic vein thrombosis	Anticoagulation	No anticoagulation	Mortality, bowel ischemia, major bleeding, QOL, and symptomatic relief	RCTs and cohort studies
Role of anticoagulation in hepatic vein thrombosis (11.1, 11.2)	Patients with hepatic vein thrombosis	Anticoagulation	No anticoagulation	Mortality, liver failure, PE, major bleeding, QOL, and symptomatic relief	RCTs and cohort studies

CTPH = chronic thromboembolic pulmonary hypertension; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin, PE = pulmonary embolism; PICO = population, intervention, comparator, outcome; PTS = postthrombotic syndrome, QOL = quality of life; RCT = randomized controlled trial; SVT = superficial vein thrombosis; UEDVT = upper-extremity DVT; UFH = unfractionated heparin, VKA = vitamin K antagonist.

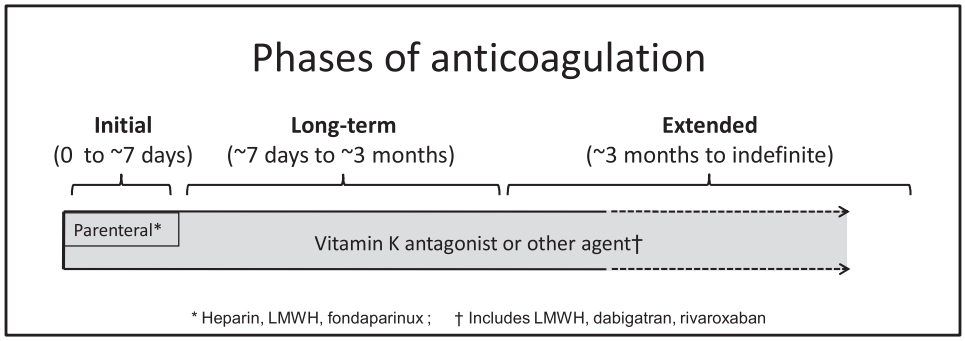

FIGURE 1. Phases of anticoagulation. LMWH = low-molecular-weight heparin.

PE after an initial PE than after an initial DVT (ie, about 60% after a PE vs 20% after a DVT)[7,9,10]; 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. These differences are most important for recommendations about the use of thrombus removal procedures (eg, thrombolytic therapy) in patients who present with DVT and PE.

1.2 Outcomes Assessed

The outcomes important to patients we considered for most recommendations are recurrent VTE, major bleeding, and all-cause mortality. These outcomes are categorized in two different ways in the evidence profiles. Whenever data were available, fatal episodes of recurrent VTE and bleeding were included in the mortality outcome, and nonfatal episodes of recurrent VTE and bleeding were reported separately in their own categories to avoid reporting an outcome more than once in an evidence profile. However, many original reports and published meta-analyses did not report fatal and nonfatal events separately. In this situation, we have reported the outcome categories of mortality, recurrent VTE, and major bleeding, with fatal episodes of VTE and bleeding included in both mortality and two specific outcomes (ie, fatal episodes of VTE and bleeding are included in two outcomes of the evidence profile).

With both ways of reporting outcomes, we tried to specifically identify deaths from recurrent VTEs and major bleeds. As part of the assessment of the benefits and harms of a therapy, we generally assume that ~5% of recurrent episodes of VTE are fatal[11,12] and that ~10% of major bleeds are fatal,[12-14] and if we deviated from these estimates, we noted the reasons for so doing. We did not consider surrogate outcomes (eg, vein patency) when there were adequate data addressing the corresponding outcome of importance to patients (eg, PTS).

When developing evidence profiles, we tried to obtain the baseline risk of outcomes (eg, risk of recurrent VTE or major bleeding) from observational studies because these estimates are most likely to reflect real-life incidence. In many cases, however, we used data from randomized trials because observational data were lacking or were of low quality. Methodologic issues specific to duration of anticoagulation are addressed in the section 3.1 under the subsection on general consideration in weighing the benefits and risks of different durations of anticoagulant therapy.

1.3 Patient Values and Preferences

In developing our recommendations, we took into account average patient values for each outcome and preferences for different types of antithrombotic therapy. As described in MacLean et al[15] and Guyatt et al[16] in these guidelines, these values and preferences for the most part were obtained from ratings that all panelists for these guidelines provided in response to standardized descriptions of different outcomes and treatments, supplemented with the findings of a systematic review of the literature on this topic.[15] However, we also took into account that values and preferences vary markedly among individual patients and that often there is appreciable uncertainty about the average patient values we used.

On average, we assumed that patients attach equal value (or dislike [disutility]) to nonfatal thromboembolic and major bleeding events. Concern that the panelist rating exercise that attached a similar disutility to vitamin K antagonist (VKA) therapy (frequent blood testing and telephone or clinic visits, attention to changes in other medications) and long-term low-molecular-weight-heparin (LMWH) therapy (daily subcutaneous [SC] injection, injection site bruising or nodules) may have been misguided led us to request a review of this issue at the final meeting of all panelists. Our judgment that, on average, patients would prefer VKA therapy to long-term LMWH therapy was confirmed at that meeting.

1.4 Influence of Bleeding Risk and Cost

Usually, we did not assess how an individual patient's risk of bleeding would influence each recommendation because (1) we considered that most recommendations would be unlikely to change based on differences in risk of bleeding (eg, anticoagulation vs no anticoagulation for acute VTE, comparison of anticoagulant regimens), (2) there are few data assessing outcomes in patients with different risks of bleeding, and (3) there is a lack of well-validated tools for stratifying risk of bleeding in patients with VTE. However, for a small number of the recommendations in which the risk of bleeding is very influential (eg, use of extended-duration anticoagulation), we stratified recommendations based on this risk (Table 2). Unless otherwise stated, the cost (eg, to the patient, a third-party payer, or society) associated with different treatments did not influence our recommendations. In most situations of uncertain benefit of a treatment, particularly if it was potentially harmful, we took the position of *primum non nocere* (first do no harm) and made a weak recommendation against the treatment.

2.0 TREATMENT OF ACUTE DVT

2.1 Initial Anticoagulation of Acute DVT of the Leg

The first and only randomized trial that compared anticoagulant therapy with no anticoagulant therapy in patients with symptomatic DVT or PE was published in 1960 by Barritt and Jordan.[50] Trial results suggested that 1.5 days of heparin and 14 days of

Table 2—*[Section 2.3, 3] Risk Factors for Bleeding With Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk Categories*

Risk Factors[a]			
Age > 65 y[17-25]			
Age > 75 y[17-21,23,25-34]			
Previous bleeding[18,24,25,30,33-36]			
Cancer[20,24,30,37]			
Metastatic cancer[36,38,]			
Renal failure[18,24,25,28,30,33]			
Liver failure[19,21,27,28]			
Thrombocytopenia[27,36]			
Previous stroke[18,25,27,39]			
Diabetes[18,19,28,32,34]			
Anemia[18,21,27,30,34]			
Antiplatelet therapy[19,27,28,34,40]			
Poor anticoagulant control[22,28,35]			
Comorbidity and reduced functional capacity[24,28,36]			
Recent surgery[21,41,b]			
Frequent falls[27]			
Alcohol abuse[24,25,27,34]			
	Estimated Absolute Risk of Major Bleeding, %		
Categorization of Risk of Bleeding[c]	Low Risk[d] (0 Risk Factors)	Moderate Risk[d] (1 Risk Factor)	High Risk[d] (≥ 2 Risk Factors)
Anticoagulation 0-3 mo[e]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[e]	3.2	12.8[f]
Anticoagulation after first 3 mo[g]			
Baseline risk (%/y)	0.3[h]	0.6	≥ 2.5
Increased risk (%/y)	0.5	1.0	≥ 4.0
Total risk (%/y)	0.8[i]	1.6[i]	≥ 6.5

See Table 1 legend for expansion of abbreviations.

[a]The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor (eg, location and extent of metastatic disease, platelet count), (2) temporal relationships (eg, interval from surgery or a previous bleeding episode),[29] and (3) how effectively a previous cause of bleeding was corrected (eg, upper-GI bleeding).

[b]Important for parenteral anticoagulation (eg, first 10 d) but less important for long-term or extended anticoagulation.

[c]Although there is evidence that risk of bleeding increases with the prevalence of risk factors,[20,21,25,27,30,33,34,36,42,43] this categorization scheme has not been validated. Furthermore, a single risk factor, when severe, will result in a high risk of bleeding (eg, major surgery within the past 2 d, severe thrombocytopenia).

[d]Compared with low-risk patients, moderate-risk patients are assumed to have a twofold risk and high-risk patients an eightfold risk of major bleeding.[18,20,21,27,28,30,36,44]

[e]The 1.6% corresponds to the average of major bleeding with initial UFH or LMWH therapy followed by VKA therapy (Table S6 Evidence Profile: LMWH vs IV UFH for initial anticoagulation of acute VTE). We estimated baseline risk by assuming a 2.6 relative risk of major bleeding with anticoagulation (footnote g in this table).

[f]Consistent with frequency of major bleeding observed by Hull et al[41] in high-risk patients.

[g]We estimate that anticoagulation is associated with a 2.6-fold increase in major bleeding based on comparison of extended anticoagulation with no extended anticoagulation (Table S27 Evidence Profile: extended anticoagulation vs no extended anticoagulation for different groups of patients with VTE and without cancer). The relative risk of major bleeding during the first 3 mo of therapy may be greater that during extended VKA therapy because (1) the intensity of anticoagulation with initial parenteral therapy may be greater than with VKA therapy; (2) anticoagulant control will be less stable during the first 3 mo; and (3) predispositions to anticoagulant-induced bleeding may be uncovered during the first 3 mo of therapy.[22,30,35] However, studies of patients with acute coronary syndromes do not suggest a ≥ 2.6 relative risk of major bleeding with parenteral anticoagulation (eg, UFH or LMWH) compared with control.[45,46]

[h]Our estimated baseline risk of major bleeding for low-risk patients (and adjusted up for moderate- and high-risk groups as per footnote d in this table).

[i]Consistent with frequency of major bleeding during prospective studies of extended anticoagulation for VTE[22,44,47,48,49] (and Table S27 Evidence Profile: extended anticoagulation vs no extended anticoagulation for different groups of patients with VTE and without cancer and Table S24).

VKA therapy markedly reduced recurrent PE (0/16 vs 10/19) and appeared to reduce mortality (1/16 vs 5/19) in patients with acute PE. In the early 1990s, a single randomized trial established the need for an initial course of heparin in addition to VKA as compared with starting treatment with VKA therapy alone[51] (Table 3, Table S1). (Tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement. See the "Acknowledgments" for more information.) The need for an initial course of heparin is also supported by the observation that there are high rates of recurrent VTE during 3 months of follow-up in patients

Table 3—*[Section 2.1] Summary of Findings: Parenteral Anticoagulation vs No Parenteral Anticoagulation in Acute VTE*[a,51]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated absolute effects: Risk With No Parenteral Anticoagulation	Anticipated absolute effects: Risk Difference With Parenteral Anticoagulation (95% CI)
Mortality	120 (1 study), 6 mo	Moderate[b,c] due to imprecision	RR 0.5 (0.05-5.37)	33 per 1,000	16 fewer per 1,000 (from 31 fewer to 144 more)
VTE symptomatic extension or recurrence	120 (1 study), 6 mo	Moderate[b,d] due to imprecision	RR 0.33 (0.11-0.98)	200 per 1,000	134 fewer per 1,000 (from 4 fewer to 178 fewer)
Major bleeding	120 (1 study), 6 mo	Moderate[b,c] due to imprecision	RR 0.67 (0.12-3.85)	50 per 1,000	16 fewer per 1,000 (from 44 fewer to 142 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio.

[a]Both groups treated with acenocoumarol.

[b]Study described as double blinded; outcome adjudicators blinded. None of the study participants were lost to follow-up. Intention-to-treat analysis. Study was stopped early for benefit.

[c]CI includes values suggesting no effect as well as values suggesting either appreciable benefit or appreciable harm.

[d]Low number of events caused by the early stoppage of the trial.

with acute VTE treated with suboptimal heparin therapy.[1,3,52,53] We discuss whether isolated distal (calf) DVT should be sought and if isolated distal DVT is diagnosed, whether and how it should be treated in section 2.3.

Recommendation

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV unfractionated heparin [UFH], or SC UFH) over no such initial treatment (Grade 1B)**.**

2.2 Whether to Treat With Parenteral Anticoagulation While Awaiting the Results of Diagnostic Work-up for VTE

We identified no trial addressing this question. The decision regarding treatment while awaiting test results requires balancing (1) minimizing thrombotic complications in patients with VTE and (2) avoiding bleeding in those without VTE. Our recommendations are based on two principles. First, the higher the clinical suspicion for VTE (use of validated prediction models for probability of having DVT[54] or PE[55,56] can usefully inform this assessment,[57] the shorter the acceptable interval without treatment until results of diagnostic testing become available. Second, the higher the risk of bleeding, the longer the acceptable interval without treatment until results are available.

Our recommendations assume that patients do not have major risk factors for bleeding, such as recent surgery. The recommendations also take into account that starting anticoagulant therapy in patients who ultimately have DVT excluded is costly and is a burden to patients and the health-care system. Poor cardiopulmonary reserve may also encourage the use of anticoagulant therapy while awaiting diagnostic testing. If clinicians choose to administer anticoagulant therapy and diagnostic testing will be completed within 12 h, we suggest using a 12-h over a 24-h dose of LMWH. VKA therapy usually should not be started before VTE has been confirmed.

Recommendations

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

2.3 Whether and How to Prescribe Anticoagulants to Patients With Isolated Distal DVT

Whether to Look for Isolated Distal DVT and When to Prescribe Anticoagulants if Distal DVT Is Found:

Whether patients with isolated distal DVT (DVT of the calf [peroneal, posterior tibial, anterior tibial veins] without involvement of the popliteal or more proximal veins) are identified depends on how suspected DVT is investigated.[57] If all patients with suspected DVT have ultrasound examination of the calf veins (whole-leg ultrasound), isolated distal DVT accounts for about one-half of all DVT diagnosed.[58] If a diagnostic approach is used that does not include ultrasound examination of the calf veins or that only performs ultrasound examination of the calf veins in selected patients, isolated distal DVT is rarely diagnosed.[59]

The primary goal of diagnostic testing for DVT is to identify patients who will benefit from anticoagulant therapy. This does not mean that all symptomatic DVT need to be identified. Isolated distal DVT do not need to be sought and treated provided that (1) there is strong evidence that the patient does not have a distal DVT that will extend into the proximal veins (ie, the patient is unlikely to have a distal DVT, and if a distal DVT is present, it is unlikely to extend); (2) if this criterion is not satisfied, a follow-up proximal ultrasound is done after 1 week to detect distal DVT that has extended into the proximal veins, in which case anticoagulant therapy is started; and (3) the patient does not have severe symptoms that would require anticoagulant therapy if the symptoms were due to a distal DVT.

Diagnostic approaches to suspected DVT that do not examine the calf veins (eg, use of a combination of clinical assessment, D-dimer testing, single and serial proximal vein ultrasound examination to manage patients) or only examine the calf veins in selected patients (eg, those who cannot have DVT excluded using the previously noted tests) have been proven safe and are presented in Bates et al[57] in these guidelines. If the calf veins are imaged (usually with ultrasound) and isolated distal DVT is diagnosed, there are two management options: (1) treat patients with anticoagulant therapy or (2) do not treat patients with anticoagulant therapy unless extension of the DVT is detected on a follow-up ultrasound examination (eg, after 1 and 2 weeks or sooner if there is concern [there is no widely accepted protocol for surveillance ultrasound testing]).[60] Natural history studies suggest that when left untreated, ~15% of symptomatic distal DVT will extend into the proximal veins and that if extension does not occur within 2 weeks, it is unlikely to occur subsequently.[7,60-62] The risk of extension of isolated distal DVT will vary among patients (see later discussion).

As noted in Bates et al,[57] these guidelines favor diagnostic approaches to suspected DVT other than routine whole-leg ultrasound. If isolated distal DVT is diagnosed, depending on the severity of patient symptoms (the more severe the symptoms, the stronger the indication for anticoagulation) and the risk for thrombus extension (the greater the risk, the stronger the indication for anticoagulation), we suggest either (1) anticoagulation or (2) withholding of anticoagulation while performing surveillance ultrasound examinations to detect thrombus extension. We consider the following to be risk factors for extension: positive D-dimer, thrombosis that is extensive or close to the proximal veins (eg, >5 cm in length, involves multiple veins, >7 mm in maximum diameter), no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status.[7,60,63,64] Thrombosis that is confined to the muscular veins has a lower risk of extension than true isolated distal DVT.[63,65] We anticipate that isolated distal DVT detected using a selective approach to whole-leg ultrasound often will satisfy criteria for initial anticoagulation, whereas distal DVT detected by routine whole-leg ultrasound often will not. A high risk for bleeding (Table 2) favors ultrasound surveillance over initial anticoagulation, and the decision to use surveillance or initial anticoagulation is expected to be sensitive to patient preferences. The evidence supporting recommendations to prescribe anticoagulants for isolated calf DVT is low quality because it is not based on direct comparisons of the two management strategies, and the ability to predict extension of distal DVT is limited.

How to Treat With Anticoagulants: A single controlled trial of 51 patients with symptomatic isolated distal DVT, all of whom were initially treated with heparin, found that 3 months of VKA therapy prevented DVT extension and recurrent VTE (29% vs 0%, $P < .01$).[66] The evidence in support of parenteral anticoagulation and VKA therapy for isolated distal DVT, which includes indirect evidence from patients with acute proximal DVT and PE that is presented elsewhere in this article, is of moderate quality (there is high-quality evidence that anticoagulation is effective, but uncertainty that benefits outweigh risks). There have not been evaluations of alternatives to full-dose anticoagulation of symptomatic isolated distal DVT, and it is possible that less-aggressive anticoagulant strategies may be adequate. Duration of anticoagulation for isolated distal DVT is discussed in section 3.1.

Recommendations

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C)**.**

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors

for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C)**.**

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

Recommendations

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)**.**

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B)**; we suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C)**; we recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B)**.**

2.4 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

Until ~20 years ago, initiation of VKA therapy was delayed until patients had received about 5 days of heparin therapy, which resulted in patients remaining in the hospital until they had received ~10 days of heparin. Three randomized trials[41,67,68] provided moderate-quality evidence that early initiation of VKA, with shortening of heparin therapy to ~5 days, is as effective as delayed initiation of VKA with about a 10-day course of heparin (Table 4, Table S2). Shortening the duration of initial heparin therapy from about 10 to 5 days is expected to have the added advantage of reducing the risk of heparin-induced thrombocytopenia.[69] If the international normalized ratio (INR) exceeds the therapeutic range (ie, INR > 3.0) prematurely, it is acceptable to stop parenteral therapy before the patient has received 5 days of treatment.

Recommendation

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B)**.**

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

Initial anticoagulant regimens vary according to the drug, the route of administration, and whether dose is adjusted in response to laboratory tests of coagulation. Six options are available for the initial treatment of DVT: (1) SC LMWH without monitoring, (2) IV UFH with monitoring, (3) SC UFH given based on weight initially, with monitoring, (4) SC UFH given based on weight initially, without monitoring, (5) SC fondaparinux given without monitoring, and (6) rivaroxaban given orally. We considered the SC UFH options as a single category because results were similar in studies that used SC UFH with and without laboratory monitoring (Table 5, Tables S3-S5). Rivaroxaban is used in the acute treatment of VTE without initial parenteral therapy; studies of its use for the acute treatment of VTE are reviewed under long-term treatment of DVT (section 3.1) and PE (section 6) of this article. Recommendations for dosing and monitoring of IV UFH, SC UFH, and SC LMWH are addressed in Garcia et al[1] and Holbrook et al[3] in these guidelines. Because LMWH, fondaparinux, and rivaroxaban have substantial renal excretion, these agents should be avoided (eg, use UFH instead) or should be used with coagulation monitoring (test selection is specific to each agent and requires expert interpretation) in patients with marked renal impairment (eg, estimated creatinine clearance < 30 mL/min [in a 70-year-old weighing 70 kg, a creatinine clearance of 30 mL/min corresponds to a serum creatinine of about 200 μmol/L (2.3 mg/dL) in a man and 175 μmol/L (2.0 mg/dL) in a woman] http://www.nephron.com/cgi-bin/CGSIdefault.cgi).

LMWH Compared With IV UFH for the Initial Treatment of DVT: A number of meta-analyses[72-75] have summarized the trials addressing this question. The evidence suggests that LMWH is associated with decreased mortality, lower recurrence of VTE, and decreased incidence of major bleeding compared with IV UFH (Table 6, Table S6). However, the quality of supporting evidence is low due to a high risk of bias in the primary studies, and evidence of publication bias in favor of LMWH. LMWH has the advantage over IV UFH that it is much easier to administer (which makes outpatient treatment feasible) and that it has a lower potential for heparin-induced thrombocytopenia,[69] but the disadvantage is that it accumulates in patients with renal failure.

SC UFH Compared With LMWH for the Initial Treatment of DVT: Four randomized trials have compared SC UFH with SC LMWH (Table 6, Tables S3-S5).[70,71,76,77] This evidence suggests that SC UFH is associated with a similar frequency of

Table 4—*[Recommendation 2.4] Summary of Findings: Early Warfarin (and Shorter Duration Heparin) vs Delayed Warfarin (and Longer Duration Heparin) for Acute VTE*[a-d,41,67,68]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Delayed Warfarin Initiation (and Longer Duration Heparin)	Anticipated Absolute Effects: Risk Difference With Early Warfarin Initiation (and Shorter Duration Heparin) (95% CI)
Mortality	688 (3 studies), 3 mo[e]	Moderate[f,g] due to imprecision	RR 0.9 (0.41-1.95)	24 per 1,000[h]	2 fewer per 1,000 (from 14 fewer to 23 more)
Recurrent VTE	688 (3 studies), 3 mo[e]	Moderate[f,g] due to imprecision	RR 0.83 (0.4-1.74)	47 per 1,000[h]	8 fewer per 1,000 (from 28 fewer to 35 more)
Major bleeding	688 (3 studies), 3 mo[i]	High[f,j,k]	RR 1.48 (0.68-3.23)	16 per 1,000[h]	14 more per 1,000 (from 9 fewer to 66 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Most patients had proximal DVT, some had isolated distal DVT, most DVT were symptomatic (asymptomatic DVT included in Hull et al[41]), and few had PE (only included in Gallus et al[67]).

[b]The early initiation of VKA was associated with a fewer number of days of heparin therapy (4.1 vs 9.5 in Gallus et al[67]; 5 vs 10 in Hull et al[41]) and a fewer number of days of hospital stay (9.1 vs 13.0 in Gallus et al; 11.7 vs 14.7 in Hull et al; 11.9 vs 16.0 in Leroyer et al[68]).

[c]VKA therapy started within 1 day of starting heparin therapy (UFH in two studies and LMWH in one study).

[d]VKA therapy delayed for 4 to 10 d.

[e]Outcome assessment was at hospital discharge in the study by Gallus et al[67] (although there was also extended follow-up) and 3 mo in the studies by Hull et al[41] and Leroyer et al.[68]

[f]Patients and investigators were not blinded in two studies (Gallus et al[67] and Leroyer et al[68]) and were blinded in one study (Hull et al[41]). Concealment was not clearly described but was probable in the three studies. Primary outcome appears to have been assessed after a shorter duration of follow-up in the shorter treatment arm of one study because of earlier discharge from hospital, and 20% of subjects in this study were excluded from the final analysis postrandomization (Gallus et al).

[g]The 95% CI on relative effect includes both clinically important benefit and clinically important harm.

[h]Event rate corresponds to the median event rate in the included studies.

[i]Bleeding was assessed early (in hospital or in the first 10 d) in two studies (Gallus et al[67] and Hull et al[41]) and at 3 mo in one study (Leroyer et al[68]).

[j]It is unclear whether bleeding was assessed at 10 d in all subjects or just while heparin was being administered, which could yield a biased estimate in favor of short-duration therapy in one study (Hull et al[41]).

[k]Because the shorter duration of heparin therapy is very unlikely to increase bleeding, the wide 95% CIs around the relative effect of shorter therapy on risk of bleeding is not a major concern.

mortality, recurrent VTE, and major bleeding as LMWH. However, the quality of the evidence is moderate because of imprecision. LMWH has the disadvantage of a higher cost but is more convenient to use (LMWH can be administered once daily [see later discussion]), is more widely available for use in outpatients, has a lower potential for heparin-induced thrombocytopenia,[69] and there is much more experience with its use than with SC UFH.

Fondaparinux Compared With LMWH for the Initial Treatment of DVT: The Matisse-DVT trial[78] compared fondaparinux with LMWH for short-term treatment of DVT (Table 7, Table S7). This study suggests that fondaparinux is associated with a similar frequency of mortality, recurrent VTE, and major bleeding as LMWH. However, the quality of the evidence from this study was moderate because of imprecision. Evidence that fondaparinux is effective for the treatment of PE[79] (section 5.4) supports the equivalence of fondaparinux to LMWH for the treatment of acute VTE.

Fondaparinux Compared With IV UFH for the Initial Treatment of DVT: In the absence of direct evidence in patients with DVT, indirect evidence in patients with acute PE (section 5.4) suggests that fondaparinux is equivalent to IV UFH.[79] As noted previously, we judge that fondaparinux and LMWH are equivalent; fondaparinux also shares the advantages that LMWH has over IV UFH and the disadvantage that it is renally excreted (section 2.5). The quality of the evidence regarding the comparison of fondaparinux and UFH is moderate as, although there is some indirectness, it is minor.

Fondaparinux Compared With SC UFH for the Initial Treatment of DVT: There is no direct evidence for this comparison in any patient population. Our recommendation is based on our assessment that

Table 5—*[Section 2.5.1] Summary of Findings: LMWH vs SC UFH for Initial Anticoagulation of Acute VTE*[70,71,76,77]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With SC UFH	Risk Difference With LMWH (95% CI)
All-cause mortality	1,566 (3 studies), 3 mo	Moderate[a,b] due to imprecision	RR 1.1 (0.68-1.76)	33 per 1,000[c]	3 more per 1,000 (from 11 fewer to 25 more)
Recurrent VTE	1,563 (3 studies), 3 mo	Moderate[a,b] due to imprecision	RR 0.87 (0.52-1.45)	42 per 1,000[c]	5 fewer per 1,000 (from 20 fewer to 19 more)
Major bleeding	1,634 (4 studies), 3 mo	Moderate[a,b] due to imprecision	RR 1.27 (0.56-2.9)	16 per 1,000[c]	4 more per 1,000 (from 7 fewer to 30 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. SC = subcutaneous. See Table 1 and 3 legends for expansion of abbreviations.

[a]In the two largest trials (Prandoni et al,[70] Kearon et al;[71] 87% of patients), allocation was concealed, outcome adjudicators and data analysts were concealed, analysis was intention to treat, and there were no losses to follow-up.

[b]Precision judged from the perspective of whether SC heparin is noninferior to LMWH. The total number of events and the total number of participants were relatively low.

[c]Event rate corresponds to the median event rate in the included studies.

fondaparinux and LMWH are equivalent and that fondaparinux shares the advantages that LMWH has over SC UFH (section 2.5). This recommendation does not take into account difference in purchase cost between SC UFH and fondaparinux and is based on low-quality evidence.

Once- vs Twice-Daily Administration of LMWH for Initial Treatment of DVT: Two meta-analyses[80,81] summarized six studies comparing once-daily and twice-daily administrations of the same LMWH.[82-87] Table 8 and Table S8 summarize the findings of five of these studies[83-87] that had unconfounded comparisons. This evidence suggests that LMWH once daily and twice daily are associated with similar mortality, recurrent VTE, and major bleeding. However, the quality of the evidence is low because of imprecision and inconsistency. The sixth study that used a lower total daily dose of LMWH with once-daily compared with twice-daily administration (enoxaparin 1.5 mg/kg once daily vs 1.0 mg/kg bid; enoxaparin 2 mg/kg once daily is not used) suggested that outcomes might be inferior with this once-daily regimen.[85]

Table 6—*[Section 2.5.1] Summary of Findings: LMWH vs IV UFH for Initial Anticoagulation of Acute VTE*[74]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With IV UFH	Risk Difference With LMWH (95% CI)
All-cause mortality	7,908 (17 studies), 3 mo	Low[a,b] due to risk of bias, publication bias	RR 0.79 (0.66-0.95)	46 per 1,000[c]	10 fewer per 1,000 (from 2 fewer to 16 fewer)
Recurrent VTE	7,976 (17 studies), 3 mo	Low[a,b] due to risk of bias, publication bias	RR 0.72 (0.58-0.89)	55 per 1,000[c]	15 fewer per ,1000 (from 6 fewer to 23 fewer)
Major bleeding	6,910 (20 studies), 3 mo	Low[a,b,d] due to risk of bias, publication bias	RR 0.67 (0.45-1)	15 per 1,000[c]	5 fewer per 1,000 (from 8 fewer to 0 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Of the 20 trials, allocation was concealed in nine and was unclear whether concealed in the remaining 11. In 18 trials, outcome assessors were blinded. Seven trials did not have any postrandomization exclusions or losses to follow-up. Ten trials reported the number of participants lost to follow-up, which ranged from 1.0% to 12.7%. One trial did not report the drop-outs.

[b]Inverted funnel plot very suggestive of publication bias. Many of the included studies are of small size, and all were funded by industry.

[c]Event rate corresponds to the median event rate in the included studies.

[d]CI includes values suggesting significant benefit and no effect.

Table 7—*[Section 2.5.1] Summary of Findings: Fondaparinux vs LMWH for Initial Anticoagulation of Acute DVT*[a-c,78]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With LMWH	Risk Difference With Fondaparinux (95% CI)
Mortality	2,205 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 1.25 (0.8-1.97)	30 per 1,000	7 more per 1,000 (from 6 fewer to 29 more)
Recurrent VTE	2,205 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 0.96 (0.64-1.45)	41 per 1,000[f]	2 fewer per 1,000 (from 15 fewer to 18 more)
Major bleeding	2,205 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 0.93 (0.43-2.03)	12 per 1,000[g]	1 fewer per 1,000 (from 7 fewer to 12 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]All patients had acute symptomatic DVT.

[b]Fondaparinux 7.5 mg (5.0 mg in patients weighing < 50 kg and 10.0 mg in patients weighing > 100 kg) SC once daily for at least 5 d and until VKAs induced an INR > 2.0.

[c]Enoxaparin 1 mg/kg of body weight SC bid for at least 5 d and until VKAs induced an INR > 2.0.

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Analysis excluded 0.6% of randomized patients. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]Five fatal VTE in fondaparinux group and five fatal VTE in LMWH group.

[g] Twelve patients in the fondaparinux group and 13 in the LMWH group had a major bleeding event during the initial period (7 d). Of these, two in the fondaparinux group and none in the LMWH group were fatal.

Recommendations

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.

Table 8—*[Section 2.5.2] Summary of Findings: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE*[a,b,81]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Twice Daily	Risk Difference With LMWH Once Daily (95% CI)
Mortality	1,261 (3 studies), 3 mo	Low[c-e] due to inconsistency and imprecision	RR 1.05 (0.57-1.94)	31 per 1,000	2 more per 1,000 (from 13 fewer to 29 more)
VTE recurrence	1,261 (3 studies), 3 mo	Low[c,e,f] due to inconsistency and imprecision	RR 0.86 (0.52-1.42)	49 per 1,000	7 fewer per 1,000 (from 24 fewer to 21 more)
Major bleeding	1,522 (5 studies), 10 d	Moderate[c,e] due to imprecision	RR 1.13 (0.48-2.66)	12 per 1,000	2 more per 1,000 (from 6 fewer to 20 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Of the five included studies, one included patients with PE and DVT and four included only patients with DVT. All studies addressed the initial management of VTE.

[b]The five included studies used four brands of LMWH (enoxaparin, tinzaparin, dalteparin, and nadroparin). In Merli et al,[85] enoxaparin 1 mg/kg bid was compared with 1.5 mg/kg once daily. Holmström et al[84] adjusted the dose to anti-Xa levels, which resulted in different daily doses after a number of days. In the remaining studies, the dose of the once-daily administration was double the dose of the twice-daily administration (equal total daily dose).

[c]All included studies concealed allocation. Two studies had a double-blind design, and two others were single blind. One study did not mention blinding. Intention to treat likely used in all studies. Participants were lost to follow-up in only two studies (0.3% and 2.2%).

[d]$I^2 = 37\%$; point effect estimate in favor of twice-daily dose in Merli et al[85] and in favor of once-daily dose in Charbonnier et al.[83]

[e]Imprecision judged relative to no difference.

[f]$I^2 = 65\%$; point effect estimate in favor of twice-daily dose in Merli et al[85] and in favor of once-daily dose in Charbonnier.[83]

2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

2.6 Initial Treatment With Rivaroxaban vs Parenteral Therapy

One trial directly compared short- and long-term rivaroxaban (without initial parenteral anticoagulation) with parenteral anticoagulation (LMWH) and VKA in patients with acute DVT.[88] The findings of this study and associated recommendations are presented in section 3.3.

2.7 At-Home vs In-Hospital Initial Treatment of DVT

One trial of 201 patients directly compared outpatient and inpatient administration of the same initial anticoagulant regimen (three LMWH preparations were used); there were few recurrent VTE and major bleeds in each group.[89] A number of trials[90-94] have compared LMWH administered at home (without hospital admission or after early discharge) in a substantial proportion of patients, with IV UFH administered in the hospital (Table 9, Table S9). This evidence suggests that home treatment is not associated with an increase in mortality, recurrent VTE, or major bleeding and may be associated with improved outcomes. However, the quality of the evidence is moderate because of indirectness (patients were not explicitly randomized to home therapy in most studies) and imprecision.

Health economic evaluations that have assessed initial treatment of DVT at home, although they have weaknesses (eg, industry funded, not derived from trials in which LMWH was used both in the hospital and at home, short time horizon (ie, $\leq$3 months), and limited use of sensitivity analyses), all conclude that home treatment is cost-saving (about US $500-$2,500 per patient).[95-101]

Recommendation

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B)**.**

Remarks: The recommendation is conditional on the adequacy of the following home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

2.8 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 of developing PTS. Patients with DVT that involves the iliac and common femoral veins are at highest risk for PTS and, therefore, are the subset with the greatest potential to benefit from thrombus removal strategies.[102] Thrombus removal strategies are indicated in patients with the very rare complication of impending venous gangrene despite optimal anticoagulant therapy; such patients are not the focus of the following sections. A recent trial that randomized 183 patients with proximal DVT to percutaneous endovascular intervention or to anticoagulant therapy alone reported reduced acute symptoms, hospital stay, recurrent VTE, and PTS at 6 months in the thrombus removal group.[103] This trial, which had a high potential for bias (randomization not described, no blinding), is not considered further because it was not possible to determine outcomes in patients treated with mechanical thrombectomy alone and in those treated with thrombolytic therapy.

2.9 Catheter-Directed Thrombolysis for Acute DVT

The rationale for catheter-directed thrombolysis (CDT) is that compared with systemic thrombolysis, it will achieve lysis of thrombus more rapidly and with lower doses of thrombolytic therapy, thereby reducing serious bleeding. The addition of mechanical thrombus fragmentation (collectively referred to as pharmacomechanical thrombolysis) with or without aspiration can further reduce the dose of thrombolytic therapy and shorten the procedure.[104]

One randomized trial of CDT has been completed,[105] and a second has reported short-term outcomes (but not the development of PTS).[106,107] Table 10 and Table S10 present the combined findings from these studies (see also Tables S11 and S12). This evidence suggests that CDT may reduce PTS and improve quality of life without being associated with an unacceptable increase in bleeding. However, the quality of evidence is low for mortality, recurrent VTE, and major bleeding because of very serious imprecision, and is low for PTS because of indirectness (ie, use of surrogate outcome [PTS has yet to be measured directly during follow-up]).

In addition to the two randomized trials,[105,106] findings of observational studies suggest that CDT improves venous patency and preserves venous valve function (Tables S11 and S12). Use of CDT, however, requires

Table 9—*[Section 2.7] Summary of Findings: Home Treatment vs Hospital Treatment of Acute DVT*[a-d,442]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence(GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Hospital Treatment	Risk Difference With Home Treatment (95% CI)
Mortality	1,708 (6 studies), 3 mo	Low[c-f] due to indirectness and imprecision	RR 0.72 (0.45-1.15)	46 per 1,000	13 fewer per 1,000 (from 25 fewer to 7 more)
Recurrent VTE	1,708 (6 studies), 3 mo	Moderate[c-e] due to indirectness	RR 0.61 (0.42-0.9)	74 per 1,000	29 fewer per 1,000 (from 7 fewer to 43 fewer)
Major bleeding	1,708 (6 studies), 3 mo	Moderate[c-e,g] due to indirectness	RR 0.67 (0.33-1.36)	21 per 1,000	7 fewer per 1,000 (from 14 fewer to 8 more)
QOL	0 (3 studies[h]), 3 mo	Low[i-k] due to indirectness and imprecision	Not estimable	…	[h]

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Studies included in the systematic review should have recruited patients whose home circumstances were adequate.

[b]All studies included patients with lower-extremity DVT and excluded patients with suspected or confirmed PE. Studies also excluded patients who were pregnant.

[c]Four studies had partial hospital treatment of many in the home arm: Koopman et al[92] (mean hospital stay, 2.7 in home arm vs 8.1 d in hospital arm), Levine et al[93] (2.1 vs 6.5 d), Boccalon et al[89] (1 vs 9.6 d), and Ramacciotti et al[94] (3 vs 7 d). In Daskalopoulos et al,[91] there was no hospital stay at all in the home group. Chong et al[90] did not report duration of hospital stay.

[d]Only one study (Boccalon et al[89]) used LMWH in both treatment arms. Remaining studies used UFH in the inpatient arm and LMWH in the outpatient arm.

[e]Out of six studies, allocation was clearly concealed in three (unclear in remaining three), outcome adjudicators were blinded in the two largest studies (unclear in remaining four), loss to follow-up was significant in only one small study, intention-to-treat analysis was conducted in four (unclear in remaining two), and no study was stopped early for benefit. Overall, the judgment was that these limitations would not warrant downgrading of quality; it has already been downgraded by at least one level based on other factors.

[f]The CI includes values suggesting benefit and harm.

[g]Judged as precise based on the narrow CI around absolute effect.

[h]Bäckman et al[95] reported evaluation of health-related QOL using the EQ-5D. They found no differences in mean QOL scores or in the proportion of patients showing improvement in self-rated health state. Koopman et al[92] evaluated health-related QOL using the Medical Outcome Study Short Form-20 and an adapted version of the Rotterdam Symptom Checklist. The changes over time were similar in both groups, except that the patients receiving LMWH had better scores for physical activity ($P = .002$) and social functioning ($P = .001$) at the end of the initial treatment. The authors did not report enough data to assess precision and clinical significance of results. O'Brien et al[96] assessed changes in QOL using the Medical Outcome Study Short Form-36 in 300 patients participating in Levine et al.[93] They found that the change in scores from baseline to day 7 was not significantly different between the treatment groups for seven of the eight domains. The one exception was the domain of social functioning, where a greater improvement was observed for the outpatient group.

[i]Potential inconsistency as Bäckman et al[95] showed no effect, whereas Koopman et al[92] and O'Brien et al[96] showed potential benefit.

[j]Two of the three studies had partial hospital treatment of many in the home arm: Koopman et al[92] (mean hospital stay, 2.7 in home arm vs 8.1 d in hospital arm) and Levine et al[93] (2.1 vs 6.5 d).

[k]Not able to evaluate, but imprecision is possible. Taken together with the potential inconsistency, we downgraded the quality of evidence by one level.

substantial resources and expertise. Patients who are most likely to benefit from CDT have iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and a low risk of bleeding (Table 11). Because the balance of risks and benefits with CDT is uncertain, anticoagulant therapy alone is an acceptable alternative to CDT in all patients with acute DVT who do not have impending venous gangrene.

There is no single standardized approach to performing CDT or pharmacomechanical thrombolysis. If these interventions are performed, the technique used will vary with local resources and expertise. If CDT has been successful but there are residual lesions in the common femoral or more proximal veins, balloon angioplasty and stenting often are used to relieve obstruction. There are inadequate data to assess the benefit or risk of inserting an IVC filter in patients who have CDT performed (recommended by manufacturer with some endovascular devices and techniques, whereas not with others). Percutaneous mechanical venous thrombectomy without concomitant thrombolysis has not been evaluated in randomized trials, and its use is discouraged because small retrospective studies suggest that it often fails to remove much of the thrombus[115,116] and is associated with a high risk of PE.[117,118]

Recommendation

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C)**.**

Table 10—*[Section 2.9] Summary of Findings: CDT vs No CDT for Extensive Acute DVT of the Leg*[a,b,105,106]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No CDT	Anticipated Absolute Effects: Risk Difference With CDT (95% CI)
Mortality	153 (2 studies), 3 mo	Low[c,d] due to imprecision	RR 0.14 (0.01-2.71)	39 per 1,000[e]	34 fewer per 1,000 (from 39 fewer to 67 more)
Nonfatal recurrent VTE	153 (1 study), 3 mo	Low[c,d] due to imprecision	RR 0.35 (0-8.09)	48 per 1,000[f]	31 fewer per 1,000 (from 48 fewer to 340 more)
Nonfatal major bleeding	153 (2 studies), 7 d	Low[c,d] due to imprecision	RR 2.00 (0.19-19.46)	29 per 1,000[6,7]	29 more per 1,000 (from 23 fewer to 535 more)
PTS (complete lysis on venography [Elsharawy et al[73]]; patency on ultrasound and air plethysmography [Enden et al[74]])	138 (2 studies), 2 y	Moderate[c,g] due to indirectness	RR 0.46 (0-0.79)	588 per 1,000[h]	318 fewer per 1,000 (from 123 fewer to 588 fewer)[i]
QOL (SF-12, HUI Mark version 2/3 questionnaires)	98 (1 study[j]), 16 mo	Low[k,l]			See footnote[m]

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. HUI = Health Utilities Index; SF-12 = Medical Outcomes Survey Short Form-12; VETO = Venous Thrombosis Outcomes. See Table 1 and 3 legends for expansion of other abbreviations.

[a]In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for < 14 d, good functional status, life expectancy ≥ 1 y) who have a low risk of bleeding.

[b]All patients prescribed anticoagulants per protocol, but the intervention group receives CDT in addition to anticoagulation.

[c]Allocation was concealed in Enden et al[106] but unclear in Elsharawy et al.[105] Outcome assessor blinded in both studies. Follow-up rates were 87% in Enden et al and 100% in Elsharawy et al. Neither of the studies was stopped early for benefit.

[d]CI includes values suggesting both benefit and harm.

[e]Three control patients died of cancer.

[f]Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[108]

[g]Surrogate outcome: absence of patency at 6 mo in Enden et al[106] study; absence of complete lysis at 6 mo in Elsharawy et al[105] study.

[h]This estimate is based on the findings of the VETO study.[102] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[i]Severe PTS: assuming the same RR of 0.46 and a baseline risk of 13.8%,[102] the absolute reduction is 75 fewer severe PTS per 1,000 (from 29 fewer to 138 fewer) over 2 y.

[j]Camerota et al.[109]

[k]Participation rate was 65%.

[l]Recall was used to measure QOL prior to the thrombotic event; we did not consider these measurements.

[m]At the initial follow-up (mean, 16 mo), patients treated with CDT reported a trend toward a higher mental summary scale ($P = .087$) and improved HUI ($P = .078$). They reported better overall role physical functioning ($P = .046$), less stigma ($P = .033$), less health distress ($P = .022$), and fewer overall symptoms ($P = .006$) compared with patients who were treated with anticoagulation alone.

Remarks: Patients who are most likely to benefit from CDT (see text) and attach a high value to prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding with CDT are likely to choose CDT over anticoagulation alone.

2.10 Systemic Thrombolytic Therapy for Acute DVT

Many trials of systemic thrombolysis for the treatment of DVT assessed early lysis, often reported bleeding, but rarely reported recurrent VTE or development of PTS (Table S13 and S14).[119-137] A meta-analysis[138] summarized the findings of trials that assessed mortality, recurrent VTE, major bleeding, and PTS (Table 12, Table S15). This evidence suggests that systemic thrombolysis has the potential to reduce PTS at the expense of an increase in major bleeding. However, the overall quality of this evidence is low because of imprecision and risk of bias.

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. No randomized trial has compared systemic thrombolysis with CDT, but a single-center, retrospective study[127] suggested that systemic thrombolysis achieves less

Table 11—*[Section 2.9, 2.10, 5.6, 9.2] Risk Factors for Bleeding With and Contraindications to Use of Thrombolytic Therapy (Both Systemic and Locally Administered)*

Major contraindications[a]
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 mo
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications[b]
Systolic BP > 180 mm Hg
Diastolic BP > 110 mm Hg
Recent bleeding (nonintracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke more that 3 mo previously
Anticoagulation (eg, VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age > 75 y
Low body weight (eg, < 60 kg)
Female sex
Black race

Among 32,000 Medicare patients (≥ 65 y) with myocardial infarction who were treated with thrombolytic therapy, the following factors were independently associated with intracranial hemorrhage: age ≥ 75 y (OR, 1.6), black race (OR, 1.6), female sex (OR, 1.4), previous stroke (OR, 1.5), systolic BP ≥ 160 mm Hg (OR, 1.8), women weighing ≤ 65 kg or men weighing ≤ 80 kg (OR, 1.5), and INR > 4 (OR, 2.2).[110] The rate of intracranial hemorrhage increased from 0.7% with none or one of these risk factors to 4.1% with five or more of these risk factors. Among 32,000 patients with myocardial infarction who were treated with thrombolytic therapy in five clinical trials, the following factors were independently associated with moderate or severe bleeding: older age (OR, 1.04 per year), black race (OR, 1.4), female sex (OR, 1.5), hypertension (OR, 1.2), and lower weight (OR, 0.99/kg).[111] We estimated that systemic thrombolytic therapy is associated with a relative risk of major bleeding of 3.5 within 35 d (RR, ~7 for intracranial bleeding); about three-fourths of the excess of major bleeds with thrombolytic therapy occur in the first 24 h.[112] See Table 1 legend for expansion of abbreviations.

[a]The presence of major contraindications usually precludes use of thrombolytic therapy and, consequently, these factors have not been well studied as risk factors for bleeding associated with thrombolytic therapy. The factors listed in this table are consistent with other recommendations for the use of thrombolytic therapy in patients with PE.[72,259,260,454 104,111,113,114]

[b]Risk factors for bleeding during anticoagulant therapy noted in Table 10 that are not included in this table are also likely to be relative contraindications to thrombolytic therapy. The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor (eg, extent of trauma or recent surgery) and (2) temporal relationships (eg, interval from surgery or a previous bleeding episode believed to decrease markedly after ~2 wk). Risk factors for bleeding at critical sites (eg, intracranial, intraocular) or noncompressible sites are stronger contraindications for thrombolytic therapy.

lysis (31% vs 50%) and less preservation of valve function (13% vs 44%) (Tables S13 and S14), and the higher doses of thrombolytic agent used with systemic thrombolysis are expected to be associated with a higher risk of nonprocedure-related bleeding.

We believe that systemic thrombolysis should be considered only in patients who meet all of the following criteria: iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and low risk of bleeding (Table 11). Based on low-quality evidence of greater effectiveness and less bleeding, if resources and expertise are available to perform CDT, we consider it the preferable approach. Because the balance of risks and benefits with systemic thrombolysis is uncertain, and particularly because of concerns about major bleeding, anticoagulant therapy alone is an acceptable alternative to systemic thrombolysis in all patients with acute DVT who do not have impending venous gangrene.

Recommendation

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C)**.**

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11 Operative Venous Thrombectomy for Acute DVT

Operative venous thrombectomy, with contemporary operative techniques[140] and more effective anticoagulant regimens, appears to achieve improved outcomes compared with earlier reports.[141,142] A single small randomized trial with extended follow-up compared iliofemoral venous thrombectomy with a temporary arteriovenous fistula plus anticoagulation with anticoagulation alone.[143-145] Results at 6 months, 5 years, and 10 years suggested improved iliac vein patency, less leg swelling, and fewer leg ulcers with thrombectomy (Table 13, Tables S16-S18).[143-145] Evidence from this trial is of low quality because of imprecision and risk of bias.

We believe that operative venous thrombectomy should be considered only if all of the following criteria are met: iliofemoral DVT, symptoms for < 7 days (criterion used in the single randomized trial), good functional status, life expectancy of ≥ 1 year, and both resources and expertise are available. Based on low-quality evidence of greater effectiveness and less bleeding, we consider

Table 12—*[Section 2.10] Summary of Findings: Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg*[138]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Systemic Lysis	Anticipated Absolute Effects: Risk Difference With Systemic Lysis (95% CI)
Mortality	688 (5 studies), 3 mo[a]	Low[b-e] due to imprecision	RR 0.86 (0.27-2.68)	21 per 1,000	3 fewer per 1,000 (from 16 fewer to 36 more)
Nonfatal recurrent VTE	687 (3 studies), 3 mo[f]	Low[d,e,g] due to imprecision	RR 1.28 (0.25-6.68)	48 per 1,000[h]	13 more per 1,000 (from 36 fewer to 273 more)
Nonfatal major bleeding	688 (10 studies), 3 mo[f]	Moderate[c,d,i] due to imprecision	RR 1.84 (0.94-3.59)	29 per 1,000[h,j]	24 more per 1,000 (from 2 fewer to 75 more)
PTS	678 (2 studies), 2 y[k]	Low[d,e,l,m] due to risk of bias and imprecision	RR 0.71 (0.49-1.04)	588 per 1,000[n]	171 fewer per 1,000 (from 300 fewer to 24 more)[o]
QOL not measured	…	…	…	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 10 legends for expansion of abbreviations.

[a]Range of follow-up in included studies, 1 to 72 mo.

[b]Allocation was concealed in three of five studies. Follow-up inadequate in one of five studies (Common et al[139]). Excluding this study from the analysis does not change the effect estimate. All studies had blinded outcome assessors. None of the studies used a placebo control.

[c]The population of one study (Schulman et al[131]) comprised patients with calf vein thrombosis.

[d]Interventions varied across studies with regard to agent (eg, tissue plasminogen activator, streptokinase, urokinase), dose, use of the pedal vein administration, duration of treatment, and concomitant drugs (eg, steroids). However, we did not downgrade for indirectness given that there was no standard regimen and all analyses showed no heterogeneity in results.

[e]CI included both no effect and a potentially significant effect.

[f]Range of follow-up in included studies, 1 to 30 d.

[g]Allocation was concealed in two of three studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used a placebo control.

[h]Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[108]

[i]Allocation was concealed in seven of 10 studies. Follow-up inadequate in one of 10 studies (Common et al[139]). Excluding this study from the analysis does not affect the effect estimate. All studies had blinded outcome assessors. Two studies used placebo (Turpie et al[135] and Verhaeghe et al[136]).

[j]Only 4% of all major bleeding events were intracranial bleeds.

[k]Range of follow-up in included studies, 1 to 6 y.

[l]Allocation was concealed in two of two studies. Follow-up adequate in both studies. Both studies had blinded outcome assessors. Neither study used placebo control.

[m]No use of a standardized validated tool reported.

[n]This estimate is based on the findings of the VETO study.[102] This probably underestimates PTS baseline risk, given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[o]Severe PTS: Assuming the same RR of 0.71 and a baseline risk of 13.8%,[102] the absolute reduction is 40 fewer severe PTS per 1,000 (from 70 fewer to 6 more) over 2 y.

CDT preferable to the operative venous thrombectomy approach.

Recommendation

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C)**.**

2.12 Anticoagulation in Patients Who Have Had Any Method of Thrombus Removal Performed

There are no randomized trials or observational studies that have compared different anticoagulant regimens or durations of therapy in patients with acute proximal DVT of the leg who have had any method of thrombus removal (including systemic thrombolysis). Mechanical components of these procedures are associated with a high early risk of early recurrent thrombosis, and thrombus removal is not known to alter the long-term risk of recurrent VTE. We used evidence from patients with DVT who did not have thrombus removal to guide anticoagulant decisions in those who had thrombus removal. This evidence is rated down to moderate quality because of its indirectness in this patient population.

Recommendation

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend

Table 13—*[Section 2.11] Summary of Findings: Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg*[a,144]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Surgical Thrombectomy	Risk Difference With Surgical Thrombectomy (95% CI)
Mortality not reported	…	…	…	…	…
Nonfatal recurrent VTE	51 (1 study), 3 mo	Low[b,c] due to risk of bias and imprecision	RR 0.37 (0.02-8.75)	48 per 1,000[d,e]	30 fewer per 1,000 (from 47 fewer to 372 more)
Nonfatal major bleeding	51 (1 study), 3 mo	Low[b,c] due to risk of bias and imprecision	Not estimable (no events)	…	-
PTS	51 (1 study), 2 y	Low[f,g] due to risk of bias and imprecision	RR 0.63 (0.44-0.9)[h]	588 per 1,000[i]	218 fewer per 1,000 (from 59 fewer to 329 fewer)[j]
QOL not measured	…	…	…	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3 and 10 legends for expansion of abbreviations.

[a]The study included patients with DVT with symptoms of leg swelling not exceeding 7 d and a proximal extension of the thrombus above the inguinal ligament but not into the vena cava.

[b]Not clear whether allocation was concealed. No blinding reported. Not clear whether analysis was intention to treat. Follow-up rate was 88% at 6 mo. Study not stopped early for benefit.

[c]CI includes values suggesting either harm or benefit.

[d]Baseline risks for nonfatal recurrent VTE derived from Douketis et al.[108]

[e]One event was a symptomatic PE.

[f]In addition to other study limitations, this outcome was assessed by those who did the surgery and anticoagulation. No standardized tool was used. One surgical patient had an amputation secondary to venous gangrene and was not counted in the PTS assessment.

[g]Few number of events. This warrants rating down the quality of evidence by a second level when considered along with study limitations.

[h]The RR is based on the 6-mo data.

[i]This estimate is based on the findings of the VETO study.[102] This probably underestimates PTS baseline risk, given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[j]Severe PTS: assuming the same RR of 0.63 and a baseline risk of 13.8% over 2 y,[102] the absolute reduction is 51 fewer severe PTS per 1,000 (from 14 fewer to 77 fewer) over 2 y.

the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombosis removal (Grade 1B)**.**

2.13 Vena Caval Filters for the Initial Treatment of DVT

No randomized trial or prospective observational study has evaluated IVC filters as sole therapy (ie, without concurrent anticoagulation) in patients with DVT. A single, large, randomized controlled trial evaluated permanent IVC filter insertion as an adjunct to anticoagulant therapy in patients with acute DVT who were considered to be at high risk for PE (Table 14, Table S19). The findings at 2 years[146] and 8 years[149] of follow-up, suggest that IVC filters increase the risk of recurrent DVT, reduce the risk of PE, do not alter the combined frequency of DVT and PE (ie, recurrent VTE), do not increase the risk of PTS, and do not alter mortality.

In assessing the role of an IVC filter in patients who cannot receive anticoagulant therapy (eg, actively bleeding), we assume that the relative risk of outcomes will be the same as in patients who received anticoagulant therapy in the Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) study. However, their absolute rate of symptomatic PE and recurrent DVT will be higher compared with the PREPIC participants who were prescribed anticoagulants. A comprehensive review of mostly retrospective case series of IVC filter insertions (6,500 patients in 89 reports) suggested that venous thrombosis at the site of filter insertion occurs in ~10% of patients and that filters can be placed above the renal veins and in the superior vena cava if necessary.[150] A prospective observational study also suggested that symptomatic VTE and asymptomatic filter thrombosis are common,[151] and a systematic review suggested that the prevalence of PTS may be increased[152] in patients with permanent IVC filters. A small single-center randomized trial suggested a higher complication rate with the Trapease compared with the Greenfield permanent filter.[153]

Table 14—*[Section 2.13] Summary of Findings: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation*[a,b,146,443]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No vena cava Filters	Anticipated Absolute Effects: Risk Difference With Vena cava Filters (95% CI)
Mortality	400 (1 study), 8 y	Moderate[c,d] due to imprecision	RR 0.95 (0.78-1.16)[e]	515 per 1,000	26 fewer per 1,000 (from 113 fewer to 82 more)
Symptomatic PE	304 (1 study), 8 y	Moderate[c,f] due to imprecision	RR 0.41 (0.2-0.86)[g]	151 per 1,000	89 fewer per 1,000 (from 21 fewer to 121 fewer)
Recurrent DVT	310 (1 study), 8 y	Moderate[c,f] due to imprecision	RR 1.3 (0.93-1.82)[h]	273 per 1,000	82 more per 1,000 (from 19 fewer to 224 more)
Major bleeding	337 (1 study), 8 y	Moderate[c,d] due to imprecision	RR 0.83 (0.52-1.34)[i]	185 per 1,000	31 fewer per 1,000 (from 89 fewer to 63 more)
PTS	308 (1 study), 8 y	Low[d,j] due to risk of bias and imprecision	RR 0.87 (0.66-1.13)	699 per 1,000	91 fewer per 1,000 (from 238 fewer to 91 more)
Complications	379 (1 study), 2 y	Moderate[f] due to imprecision	…	…	[k]
QOL not reported	…	…	…	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. PREPIC = Prevention du Risque d'Embolie Pulmonaire par Interruption Cave. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Anticoagulation consisted of LMWH or UFH initially (according to a 2 × 2 factorial design) followed by oral anticoagulation for at least 3 mo.

[b]Four types of permanent vena cava filters were used: Vena Tech LGM (B. Braun Melsugen AG), titanium Greenfield (Boston Scientific Corporation), Cardial (C.R. Bard, Inc), and Bird's Nest (Cook Group Incorporated).

[c]Allocation was concealed. Data collectors and outcome adjudicators were blinded. Intention-to-treat analysis. Data missing for 4% at 2 y and 1% at 8 y. Enrollment was stopped at 400 instead of targeted 800 because of slow recruitment.

[d]CI includes both negligible effect and appreciable benefit or appreciable harm.

[e]RR, 1.0 (95% CI, 0.29-3.4) at 12 d; RR, 1.08 (95% CI, 0.73-1.58) at 2 y.

[f]Small number of events.

[g]RR. 0.23 (95% CI, 0.05-1.05) at 12 d (both symptomatic and asymptomatic PE). RR, 0.54 (0.21-1.41) at 2 y (symptomatic PE).

[h]RR, 1.78 (95% CI, 1.09-2.94) at 2 y.

[i]RR, 1.5 (95% CI, 0.54-4.14) at 12 d. RR, 0.74 (95% CI, 0.41-1.36) at 2 y.

[j]No standardized validated tool used to measure PTS.

[k]No complications directly related to the filter or its insertion reported in the PREPIC trial.[146] Mismetti et al[147] (prospective study) reported an incidence of 3.2% (excluding filter tilting and puncture site hematoma) among 220 patients receiving a retrievable vena cava filter for secondary prevention of VTE, whereas Athanasoulis et al[148] (retrospective study) reported an incidence of 0.3% for major complications among 1,731 patients receiving vena cava filters predominantly for secondary prevention of VTE.

If an IVC filter is indicated 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 it when it is safe to start anticoagulant therapy. However, most retrievable filters are not removed; retrievable filters that are not removed may have a higher long-term complication rate than permanent filters, and there currently is no good evidence that retrievable IVC filters improve patient outcomes.[104,147,154,155]

Insertion of an IVC filter does not eliminate the risk of PE and increases the risk of DVT (Table 14, Table S19). Consequently, we suggest that patients who have an IVC filter inserted should receive a conventional course of anticoagulation (eg, parenteral and long-term anticoagulation) if the contraindication to anticoagulation resolves. Such patients should be treated for the same length of time as if the same patient had not had an IVC filter inserted (see section 3.1). The duration of anticoagulation, therefore, will vary according to whether the DVT was provoked by a temporary risk factor, was unprovoked, or was associated with cancer, and may be influenced by the patient's ongoing risk of bleeding and preferences.

Our recommendation to treat patients with an IVC filter with anticoagulants when contraindications to anticoagulation resolve is weaker than for anticoagulation of most patients with VTE because the risks of bleeding may remain elevated, and the patient's risk of recurrence is expected to be lower if the acute episode of thrombosis occurred remotely. The evidence for IVC filter use in patients with acute proximal DVT who cannot be treated with anticoagulation is moderate because of serious imprecision and indirectness (ie, extrapolated from the PREPIC study in which

patients were routinely treated with anticoagulants; this indirectness, however, is minor).

Recommendations

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B)**.**

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B)**.**

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B)**.**

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14 Early Ambulation of Patients With Acute DVT

Treatment of acute DVT with bed rest and anticoagulation (originally IV UFH) has given way to early mobilization with anticoagulation (often administered SC). Two meta-analyses[156,157] summarized evidence from four relevant trials (Table 15, Tables S20-S22). This evidence is of low quality because of risk of bias and imprecision. We suggest early ambulation (eg, without a period of bed rest) when feasible because of its potential to decrease PTS and improve quality of life.

Recommendation

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C)**.**

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we recommend the use of compression therapy in these patients.

Table 15—*[Section 2.14] Summary of Findings: Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg*[a,b,273,309,310,314,315]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Delayed Ambulation	Anticipated Absolute Effects: Risk Difference With Early Ambulation (95% CI)
Mortality	385 (4 studies), 3 mo[c]	Low[d,e] due to risk of bias, imprecision	RR 1.3 (0.23-7.55)	11 per 1,000	3 more per 1,000 (from 8 fewer to 70 more)
PE (symptomatic or asymptomatic)	385 (4 studies), 4-12 d	Low[d-g] due to risk of bias, imprecision	RR 1.16 (0.66-2.05)	118 per 1,000	19 more per 1,000 (from 40 fewer to 124 more)
QOL questionnaire in chronic limb venous insufficiency (CIVIQ)	53 (1 study), 2 y	Low[h,i] due to risk of bias, indirectness			See footnote[j]
PTS Villata-Prandoni scores (value, >5)	37 (1 study), 2 y	Low[e,h] due to risk of bias, imprecision	RR 0.66 (0.42-1.03)	400 per 1,000	136 fewer per 1,000 (from 232 fewer to 12 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. CIVIQ = ChronIc Venous Insufficiency Questionnaire. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Two of four eligible studies excluded patients with symptomatic PE; in the third study, 24% of participants had symptomatic PE at baseline. It was not clear whether the fourth study excluded patients with symptomatic PE.

[b]In two of four eligible trials, all patients received early compression therapy (bandages or stockings). In the two other trials, only patients randomized to early ambulation received early compression therapy.

[c]Three studies reporting acute-phase mortality reported no deaths.

[d]Concealment of allocation was reported in one of four studies; blinding of outcome assessors was reported in two of four studies; intention-to-treat analysis reported in two of four studies. Follow-up was 97% to 100%. In two of four trials, only patients randomized to early ambulation received early compression therapy (bandages or stockings). In the other two trials, all patients received early compression therapy.

[e]CI includes both values of clinically significant benefit and values of clinically significant harms.

[f]PE assessed as both symptomatic and asymptomatic PE.

[g]Funnel plot reported as not asymmetrical by Aissaoui et al.[156]

[h]Concealment of allocation was not reported; outcome assessors were not blinded for this outcome. Seventy percent follow-up rate; compression stockings used on patients with early mobilization but not in patients with delayed mobilization.

[i]No explanation was provided.

[j]Psychologic and overall somatic QOL did not differ significantly between the treatment groups, whereas DVT-related items, especially those reflecting the ease of locomotion, showed significantly greater improvement with compression than with bed rest ($P < .001$ for bandages, $P < .05$ for stockings).

3.0 Long-term Anticoagulation of Acute DVT of the Leg

In this review, the term *long-term treatment* refers to treatments (eg, VKA therapy, LMWH, dabigatran) that are continued after initial therapy (eg, parenteral anticoagulation, thrombolytic therapy) (Fig 1). In addition, we consider treatment with rivaroxaban, which is used without initial parenteral therapy. 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 use the term *extended anticoagulation* to refer to anticoagulation that is continued beyond 3 months without a scheduled stop date. However, regular (eg, yearly) reassessments are needed to assess whether a patient's risk of bleeding increased or the patient's preferences changed.

Three lines of evidence from randomized trials support the need for long-term anticoagulant treatment of DVT (ie, after 5-10 days of initial heparin therapy): (1) a randomized controlled trial of long-term anticoagulant therapy in 51 patients with symptomatic calf-vein thrombosis that documented a 25% rate of symptomatic extension of thrombosis within 3 months in the control group,[66] (2) a randomized trial comparing long-term SC low-dose UFH (5,000 units bid) with VKA therapy in patients with proximal DVT that found that low-dose UFH was ineffective and resulted in a high rate of recurrent VTE (47% within 3 months),[158] and (3) randomized trials in which reduced durations of treatment of 4 or 6 weeks resulted in important increases in recurrent VTE compared with conventional durations of treatment of 3 or 6 months (section 3.1).[159-161] This evidence is of moderate quality because of imprecision and indirectness.

Recommendation

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after 1 week of initial therapy (Grade 1B)**.**

3.1 Duration of Long-term Anticoagulant Therapy

Weighing the Benefits and Risks of Different Durations of Anticoagulant Therapy: General Considerations: Anticoagulant therapy for VTE should be continued until (1) the reduction of recurrent VTE no longer clearly outweighs the increase in bleeding or (2) it is patient preference (which may be influenced by financial burden) to stop treatment, even if the reduction in VTE would outweigh the increase in bleeding.

Increase in Risk of Recurrent VTE After Stopping Therapy—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 (duration of therapy) and (2) the patient's intrinsic risk of having a new episode of VTE (individual risk of recurrence).

Duration of therapy: The primary goal of trials that compare different time-limited durations of anticoagulation is to identify the shortest duration of therapy that results in a posttreatment risk of recurrence that is as low as can be achieved. The findings of these trials generally are not sensitive to differences in individual patient risk of bleeding.

Individual risk of recurrence: Primary factors for estimating risk of recurrence: Presence of a reversible provoking risk factor,[47,159,160,162-168,169,170] unprovoked VTE, [47,159,160,162-168,169,170] and presence of active cancer[9,47,165,166] are the most important factors that influence risk of recurrent VTE after stopping VKA. Among patients with VTE provoked by a reversible factor, the risk of recurrence is much lower if the provoking factor was recent surgery compared with a nonsurgical trigger (eg, estrogen therapy, pregnancy, leg injury, flight of >8 h).[162,171] In patients with proximal DVT and PE, the estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy of each of these categories is as follows: VTE provoked by surgery, 1% after 1 year and 3% after 5 years; VTE provoked by a nonsurgical reversible risk factor, 5% after 1 year and 15% after 5 years; and unprovoked VTE, 10% recurrence after 1 year and 30% after 5 years.

There are sparse data addressing the risk of recurrent VTE after stopping therapy in patients with cancer because treatment is rarely stopped in these patients because of a high risk for recurrence.[38,47,165,166,172] A reasonable estimate for this risk, expressed as an annualized rate, may be 15%. However, the risk of recurrence is expected to vary according to whether the cancer is metastatic, being treated with chemotherapy, or rapidly progressing.[38,165] The high mortality in patients with VTE and cancer (40% at 6 months in one large study[173]) precludes estimating the cumulative risk of recurrence after long-term follow-up. We categorize patients with VTE according to these primary individual risk factors for recurrence when we make recommendations for duration of anticoagulant therapy.

Secondary factors for estimating risk of recurrence: Additional factors that influence the risk of recurrence

strongly enough to modify some recommendations about duration of therapy include (1) whether DVT was confined to the distal veins (isolated distal [or calf] DVT), which is estimated to be associated with about one-half of the risk of recurrence of proximal DVT and PE,[10,164,167,169,170] and (2) whether the VTE was a second or subsequent episode of VTE, which is estimated to be associated with about a 50% higher risk of recurrence compared with a first VTE.[9,173,175]

Additional factors for estimating risk of recurrence: Other factors predict risk of recurrence, but not strongly or consistently enough to influence recommendations on duration of therapy once the primary and secondary factors noted previously have been considered. These factors, which have mostly been evaluated in patients with unprovoked VTE, include negative D-dimer testing 1 month after withdrawal of VKA (risk ratio [RR], ~0.4),[48,176-181] antiphospholipid antibody (RR, ~2),[182-185] hereditary thrombophilia (RR, ~1.5),[162,163,174,177,180-182,185-190] male vs female sex (RR, ~1.6),[191,192] Asian ethnicity (RR, ~0.8),[193] and residual thrombosis in the proximal veins (RR, ~1.5).[149,182,185,194-198] Combinations of factors have the potential to be more important predictions of recurrence risk than single factors (eg, low risk of recurrence in women with unprovoked proximal DVT or PE who have a negative D-dimer test before[185] or 1 month after[180,199] stopping anticoagulant therapy). PTS may be a risk factor for recurrent VTE,[183,185,200] and recurrent ipsilateral DVT is a risk factor for development of PTS.[201,202] Both associations may contribute to a decision to use extended therapy in a patient with established PTS.

Increase in Risk of Bleeding While Remaining on Anticoagulant Therapy—Although the decision to treat patients with different time-limited durations of anticoagulant therapy generally are insensitive to an individual's risk of bleeding, the decision to use extended anticoagulation, particularly in patients with an unprovoked proximal DVT or PE, is sensitive to risk of bleeding. There is no validated prediction tool to stratify the risk of major bleeding during extended anticoagulant therapy specifically in patients with VTE, but this risk appears to increase with the prevalence of the factors noted in Table 2. This table also provides our estimate of the absolute risk of bleeding without anticoagulation (baseline risk), the increase with anticoagulation, and the sum of these two risks (ie, risk of bleeding on therapy).

Comparisons of Time-Limited Durations of Therapy: Randomized trials have compared either a short (eg, 4 or 6 weeks) with an intermediate (eg, 3 or 6 months) duration of therapy, or two intermediate durations of therapy, (eg, 3 months vs 6 or 12 months). VKA therapy targeted to an INR of 2.5 was the anticoagulant regimen in all comparisons.

Short vs Intermediate Durations of Therapy—Five trials 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 16, Tables S23-S25).[159,160,167,169] This evidence, which is high quality, indicates that with the shorter duration of therapy, the absolute decrease in bleeding was small compared with the absolute increase in recurrent VTE. Patients with isolated distal DVT provoked by a major transient risk factor have a very low risk of recurrence after anticoagulant therapy is stopped (~1% per year[170]). It is uncertain whether this risk is lowered by treating for 3 months compared with 4 or 6 weeks (hazard ratio [HR] for 4 or 6 weeks vs ≥ 3 months at 2 years after stopping therapy, 0.36; 95% CI, 0.09-1.54[170]). For this reason, we make a weaker recommendation for 3 months compared with a shorter duration of therapy in patients with isolated distal DVT that was provoked by a reversible risk factor. The evidence supporting this weaker recommendation is rated down to low quality because of serious imprecision and because it is a post hoc observation.

Different Intermediate Durations of Therapy (6 or 12 months vs 3 months)—We considered trials that randomized patients with VTE to 3 months vs to 6 or 12 months of treatment to determine, when using a time-limited duration of therapy, whether there was any benefit to treating for > 3 months. Five reports, which included six randomized comparisons, contributed to this analysis (Table 17, Tables S24-S26).[167,194,203-205] These studies found that 6 or 12 months of therapy did not convincingly lower risk of recurrence but increased major bleeding about 2.5-fold. In a meta-analysis of individual patient data from randomized trials, during the 2 years after stopping anticoagulant therapy, treatment of 3 months compared with ≥ 6 months was associated with an HR of 1.19 (95% CI, 0.86-1.65) in all patients and an HR of 1.39 (95% CI, 0.96-2.01) in patients with unprovoked DVT or PE.[170] Therefore, although anticoagulants are very effective at preventing recurrence while patients are receiving therapy, when anticoagulants are stopped, there is a similar risk of recurrence whether patients have been treated for 3 months or longer.[170] This evidence is of moderate quality because of serious imprecision.

As an alternative to comparing two time-limited durations of anticoagulant therapy, the AESOPUS (Ultrasound Findings to Adjust the Duration of Anticoagulation) trial compared a predefined duration of therapy with a flexible duration of therapy that depended on whether there was residual thrombosis during follow-up in patients with a first proximal

Table 16—*[Section 3.1.1-3.1.4] Summary of Findings: Four or Six Weeks vs Three or Six Months as Minimum Duration of Anticoagulation for VTE*[a,b,16,159,167,169,195]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Control	Risk Difference With 4 or 6 wk vs 3 or 6 mo Months of Anticoagulation (95% CI)
Recurrent VTE	2,185 (5 studies[c]), 1-2 y[d]	High[e-g]	RR 1.83 (1.39-2.42)	64 per 1,000	53 more per 1,000 (from 25 more to 91 more)
Major bleeding	2,185 (5 studies), 1-2 y	High[f]	RR 0.54 (0.22-1.32)	12 per 1,000	5 fewer per 1,000 (from 9 fewer to 4 more)
Mortality	2,098 (5 studies), 1-2 y	High[e,f,h]	RR 0.97 (0.68-1.38)	55 per 1,000	2 fewer per 1,000 (from 18 fewer to 21 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Populations varied among studies: first provoked isolated distal DVT, proximal DVT, or PE provoked in Kearon et al[195]; first isolated distal DVT in Pinede et al[167]; first isolated distal DVT, proximal DVT, or PE in Schulman et al[169]; proximal DVT (21% had cancer) in Levine et al[159]; DVT or PE (29% not objectively confirmed) in British Thoracic Society.[160]

[b]Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al[169], 6 wk vs 3 mo for Pinede et al,[167] and 4 wk vs 3 mo for the other three studies.

[c]Timing of randomization relative to the start of treatment varied across studies: Pinede et al,[167] Schulman et al,[169] and British Thoracic Society[160] randomized at diagnosis, and Kearon et al[195] and Levine et al[159] randomized to stop or to continue treatment for 2 mo more after the initial 4 wk of treatment.

[d]Follow-up was for ~1 y in all studied except for Schulman et al[169] in which it was 2 y.

[e]Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al,[195] Pinede et al[167]). In one study (British Thoracic Society[160]), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al[159]). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appear to have used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

[f]No heterogeneity with $I^2 = 0\%$.

[g]No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.

[h]Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

DVT[206] (Tables S24 and S25). Its findings suggest that the latter approach may be helpful for tailoring the duration of therapy.

Extended vs Time-Limited Anticoagulant Therapy: Five trials compared extended anticoagulation with VKA therapy (target INR 2.0-2.85,[161] 2.0-3.0,[48,182,207] and 1.5-2.0[174]) with stopping VKA therapy at 3 or 6 months in patients who were judged to have a high risk of recurrence (Table 18, Table S24, S25, and S27). The results indicate that randomization to indefinite treatment with conventional-intensity VKA (target INR 2.5) reduces recurrent VTE by about 90% (RR for the four studies, 0.12; 95% CI, 0.05-0.25[48,161,182,207]), and randomization to low-intensity therapy (target INR 1.75) reduces VTE by 64% (95% CI for HR, 23%-81%),[174] with about one-half of recurrent VTE in the active treatment groups in these studies occurring in patients who had prematurely stopped VKA therapy. Extended anticoagulant therapy was associated with about a 2.6-fold increase in major bleeding. The quality of evidence for the reduction in recurrent VTE with extended therapy is high but is rated down to moderate for bleeding and mortality because of imprecision.

Weighing the Benefits and Risks of Extended VKA Therapy—The decision to extend anticoagulation therapy beyond 3 months is sensitive to both baseline risks of recurrent VTE and major bleeding. We did not identify a validated prediction tool for either outcome that takes into account all relevant risk factors. As an alternative, for patients without cancer, we chose to stratify our recommendations according to four primary risk groups for recurrent VTE (section 3.1) and three risk groups for major bleeding (section 3.1) (Table 2). This approach resulted in a total of 12 combinations of risk profiles. Table 19 shows the estimated total (and fatal) number of recurrent episodes of VTE prevented and the number of major bleeds caused by 5 years of extended therapy for each of the 12 combinations. In the absence of robust trial data for mortality for recurrent VTE and

Table 17—*[Section 3.1.1-3.1.4] Summary of Findings: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE*[a,b,167,203,204]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With 3 mo	Risk Difference With 6 or 12 mo (95% CI)
Recurrent VTE	2,061 (6 studies), 1-3 y	Moderate[c-e] due to imprecision	RR 0.89 (0.69-1.14)	115 per 1,000	13 fewer per 1,000 (from 36 fewer to 16 more)
Major bleeding	2,061 (6 studies), 1-3 y	High[f]	RR 2.49 (1.2-5.16)	9 per 1,000	13 more per 1,000 (from 2 more to 37 more)
Mortality[g]	1,331 (5 studies), 1-3 y	Moderate[d] due to imprecision	RR 1.3 (0.81-2.08)	44 per 1,000	13 more per 1,000 (from 8 fewer to 47 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Study populations varied across studies: Pinede et al[167] enrolled provoked and unprovoked proximal DVT and PE; Campbell et al[203] enrolled provoked and unprovoked isolated distal DVT, proximal DVT, and PE; Agnelli et al[194] had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); and Agnelli et al[204] enrolled unprovoked proximal DVT.

[b]Timing of randomization relative to the start of treatment and length of treatment in the non-3 mo group varied across studies: Pinede et al[167] and Campbell et al[203] randomized at diagnosis; and Agnelli et al[194,204] randomized after the initial 3 mo of treatment to stop or continued treatment. The longer duration of treatment was 6 mo in Agnelli et al[194] (provoked PE) and 12 mo in Agnelli et al[204] and Agnelli et al[194] (unprovoked PE).

[c]Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Campbell et al,[203] Pinede et al[167]) and one because of lack of benefit (Agnelli et al[204]). In one study (Campbell et al), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were not blinded in any study. Adjudicators of outcomes were blinded in all but one study (Campbell et al). All studies used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

[d]CIs include both values suggesting no effect and values suggesting either benefit or harm.

[e]Low number of events and a total number of participants $< 2{,}000$.

[f]One study may have confined the assessment of bleeding to when subjects were receiving anticoagulant therapy, which could have inflated the increase in bleeding associated with the longer duration of therapy (Campbell et al[203]).

[g]Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

bleeding, we assumed that 3.6% of recurrent VTE and 11.3% of major bleeds will be fatal.[12]

We make (1) a strong recommendation for extended therapy when it is associated with a reduction in VTE that is substantially more frequent than the increase in major bleeding and with a mortality advantage, (2) a weak recommendation for extended therapy when it is associated with a reduction in VTE that is more frequent than the increase in major bleeding but the magnitude of this difference and the suggested mortality advantage are more modest, (3) a weak recommendation against extended therapy when extended therapy is associated with a reduction in VTE that is less frequent than the increase in major bleeding and no mortality advantage exists, and (4) a strong recommendation against extended therapy when extended therapy is associated with a reduction in VTE that is less frequent than the increase in major bleeding and a mortality disadvantage may exist. We assume that on average, extended anticoagulation with VKA therapy is a modest burden to patients.[15] However, this differs markedly among patients; some do not find anticoagulant therapy a burden and have an enhanced feeling of well-being because they feel protected from recurrence, whereas others find it a major burden that greatly erodes their sense of well-being.[210]

The presence of additional risk factors for VTE recurrence (section 3.1), the patient's relative value for the different outcome of interest (recurrence of VTE, major bleeding, PTS), and the patient's perceived burden of anticoagulant therapy may influence decisions about the use of extended anticoagulant therapy in patient groups for which we provide a weak recommendation but are unlikely to influence this decision in patients groups for which we provide a strong recommendation.[16] Similarly, the costs of therapy and how those costs are paid (eg, patient, third party) are more likely to influence treatment decisions when there is a weak recommendation (Grade 2) in favor of extended therapy.

Patients With VTE and Cancer: As previously noted (section 3.1), because they have a high risk of recurrence, patients with active cancer (eg, treated within the past 6 months, persistent or progressive) should benefit from extended anticoagulant therapy unless they have a very high risk of bleeding. The quality of the evidence supporting this recommendation is moderate because of indirectness (the relative effects of anticoagulation are based, in part, on evidence

Table 18—*[Section 3.1.1-3.1.4] Summary of Findings: Extended Anticoagulation vs No Extended Anticoagulation for Different Groups of Patients with VTE and Without Cancer*[a,b,48,161,182,207]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Extended Duration Oral Anticoagulation	Risk Difference With Extended Duration Oral Anticoagulation (95% CI)
Mortality	1,184 (4 studies), 10-36 mo	Moderate[c-e] due to imprecision	RR 0.57 (0.31-1.03)	63 per 1,000	27 fewer per 1,000 (from 44 fewer to 2 more)
Recurrent VTE at 1 y	1,184 (4 studies), 10-36 mo	High	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
				10 per 1,000	10 fewer per 1,000 (from 6 fewer to 9 fewer)
				First proximal DVT or PE provoked nonsurgical/ first unprovoked distal DVT[f-j]	
				50 per 1,000	44 fewer per 1,000 (from 31 fewer to 45 fewer)
				First unprovoked VTE[f-j]	
				100 per 1,000	88 fewer per 1,000 (from 62 fewer to 91 fewer)
				Second unprovoked VTE[f-j]	
				150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
Major bleeding at 1 y	1,184 (4 studies), 10-36 mo	Moderate due to imprecision	RR 2.63 (1.02-6.76)	Low[k,l] (see Table 2)	
				3 per 1,000	5 more per 1,000 (from 0 more to 15 more)
				Moderate[k,l] (see Table 2)	
				6 per 1,000	10 more per 1,000 (from 1 more to 29 more)
				High[k,l] (see Table 2)	
				25 per 1,000	40 more per 1,000 (from 3 more to 122 more)
Recurrent VTE at 5 y	1,184 (4 studies), 10-36 mo	High	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
				30 per 1,000	26 fewer per 1,000 (from 19 fewer to 27 fewer)
				First proximal DVT or PE provoked nonsurgical/ first unprovoked distal DVT[f-j]	
				150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
				First unprovoked VTE[f-j]	
				300 per 1,000	264 fewer per 1,000 (from 186 fewer to 273 fewer)
				Second unprovoked VTE[f-j]	
				450 per 1,000	396 fewer per 1,000 (from 279 fewer to 409 fewer)
Major bleeding at 5 y	1,184 (4 studies), 10-36 mo	Moderate due to imprecision	RR 2.63 (1.02-6.76)	Low[k,l] (see Table 2)	
				15 per 1,000	24 more per 1,000 (from 2 more to 73 more)
				Moderate[k,l] (see Table 2)	
				30 per 1,000	48 more per 1,000 (from 4 more to 146 more)
				High[k,l] (see Table 2)	
				125 per 1,000	199 more per 1,000 (from 17 more to 609 more)

(Continued)

Table 18—*Continued*

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Extended Duration Oral Anticoagulation	Anticipated Absolute Effects: Risk Difference With Extended Duration Oral Anticoagulation (95% CI)
Burden of anticoagulation not reported	…	…	…	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits[m]	…
PTS not reported	…	…	…	[n]	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. PREVENT = Prevention of Recurrent Venous Thromboembolism. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Studies vary in follow-up duration (10 mo to 3 y) and in duration of time-limited VKA (3-6 mo).

[b]We excluded PREVENT trial because target INR was 1.75 (low intensity), which has been shown in an RCT[44] to be less effective than a target of 2.5.

[c]$I^2 = 0\%$.

[d]CI includes both values suggesting no effect and values suggesting either appreciable harms or appreciable benefit.

[e]Small number of events. Decision to rate down also takes into account that two studies were stopped early for benefit.

[f]Annual risk of VTE recurrence after discontinuing oral anticoagulation therapy in patients with first VTE provoked by surgery: 1% (Iorio et al[171]); we assumed a 0.5% yearly risk thereafter (3% over 5 y).

[g]Annual risk in patients with first VTE provoked by nonsurgical factor: ~5% the first year (Iorio et al[171]); we assumed a 2.5% yearly thereafter (15% over 5 y).

[h]Annual risk in patients with first episode of unprovoked VTE: 9.3% over 1 y in Rodger et al[185]; 11.0% over 1 y, 19.6% over 3 y, and 29.1% over 5 y in Prandoni et al.[208] We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).

[i]Annual risk in patients with second episode of unprovoked VTE: we assumed an RR of 1.5 compared with a first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).

[j]Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier et al[12]).

[k]Annual risk of major bleeding is based on three risk levels: low, intermediate, and high. The corresponding 0.3%, 0.6%, and 1.2% risks are estimates based on control arms of included studies (see Table 2).

[l]Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al[12]) (no data available for after discontinuing oral anticoagulation therapy).

[m]Burden of anticoagulation: endured by all patients who continue extended-duration anticoagulation (100%) and applies to patients who stop anticoagulation (no extended duration anticoagulation) who subsequently experienced a recurrent VTE (5%/10%/15% at 1 y; 15%/30%/45% at 5 y).

[n]PTS: baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (Kahn et al[102]). There was a threefold (Prandoni et al[202]) to 10-fold (van Dongen et al[209]) increase in PTS with recurrent VTE in the ipsilateral leg.

from patients without cancer). Presence of factors associated with a lower risk of recurrence that may support stopping anticoagulant therapy, particularly if the risk of bleeding was high, include the following: (1) VTE was associated with a superimposed reversible risk factor (eg, recent surgery, chemotherapy), (2) the cancer has responded to treatment, (3) the cancer has not metastasized, and (4) the VTE was an isolated distal DVT.

Follow-up of Patients on Extended Therapy: Patients who are treated with extended anticoagulant therapy should be reviewed regularly (eg, annually) to ensure that (1) they have not developed contraindications to extended therapy, (2) their preferences have not changed (eg, anticoagulation has become an excessive burden), (3) they can benefit from improved ways of selecting a patient for extended therapy if these have become available, and (4) they are being treated with the anticoagulant regimen that best suits them.

LMWH for Extended Therapy: We identified no direct evidence for LMWH compared with (1) VKA, (2) other anticoagulant strategies, or (3) control for the extended phase of anticoagulation in patients who were treated with a standardized initial long-term anticoagulant regimen. Based on indirect evidence from comparisons of LMWH with VKA therapy during the initial 3 or 6 months of long-term therapy, we judged LMWH to be at least as effective in terms of recurrent VTE and as safe in terms of major bleeding (Table 20, Table S28). The potential for drug-induced osteoporosis, however, may be greater with extended therapy LMWH than with VKA therapy.[1]

Table 19—*[Section 3.1.1-3.1.4] Estimated Absolute Difference in Recurrent VTE and Major Bleeding Events (Including Fatal Events) With 5 Years of vs No Extended Anticoagulation*

	Outcomes After 5 y of Treatment	Risk of Bleeding		
		Low	Intermediate	High[a]
First VTE provoked by surgery	Recurrent VTE reduction per 1,000	↓26 (19-27) (1 fatal)[b]	↓26 (19-27) (1 fatal)[b]	↓26 (19-27) (1 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[b]	↑49 (1-173) (5 fatal)[b]	↑98 (1-346) (11 fatal)[b]
First VTE provoked by a nonsurgical factor/first unprovoked distal DVT	Recurrent VTE reduction per 1,000	↓132 (93-137) (5 fatal)[c]	↓132 (93-137) (5 fatal)[c]	↓132 (93-137) (5 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[c]	↑49 (1-173) (5 fatal)[c]	↑98 (1-346) (11 fatal)[b]
First unprovoked proximal DVT or PE	Recurrent VTE reduction per 1,000	↓264 (186-273) (10 fatal)[d]	↓264 (186-273) (10 fatal)[d]	↓264(186-273) (10 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[d]	↑49 (1-173) (5 fatal)[d]	↑98 (1-346) (11 fatal)[b]
second unprovoked VTE	Recurrent VTE reduction per 1,000	↓396 (279-409) (14 fatal)[e]	↓396 (279-409) (14 fatal)[d]	↓396 (279-409) (14 fatal)[c]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[e]	↑49 (1-173) (5 fatal)[d]	↑98 (1-346) (11 fatal)[c]

Recommendations:

Risk of dying in patients with a recurrent VTE or a major bleed:

- Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier et al[12]).
- Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al[12]) (no data available for after discontinuing oral anticoagulation therapy).

Annual risks of recurrent VTE after discontinuation of anticoagulation:

- First VTE provoked by surgery: 1% (Iorio et al[171]); we assumed a 0.5% yearly risk thereafter (3% over 5 y).
- First episode of VTE provoked by nonsurgical factor: ~5% the first year (Iorio et al[171]); we assumed a 2.5% yearly thereafter (15% over 5 y)
- First episode of unprovoked VTE: 9.3% over 1 y (Rodger et al[185]); 11.0% over 1 y, 19.6% over 3 y, 29.1% over 5 y (Prandoni et al[208]). We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).
- Second episode of unprovoked VTE: we assumed that this inflicts 1.5 the risk of recurrent VTE relative to first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).

Relative risk reduction with extended anticoagulant therapy:

- 82% based on Table 18

Annual risks of major bleeding in patients not on anticoagulant therapy:

- Low risk, 0.3%/y; intermediate risk 0.6%/y; high risk, 2.4%/y (Table 2).

Relative risk of major bleeding with extended anticoagulant therapy:

- 2.6 based on Table 18.

Criteria used to decide on direction and strengths of recommendations:

- Criterion for a strong recommendation against whenever the estimated number of fatal bleeding events exceeded the estimated number of fatal recurrent VTE prevented.
- Criterion to go from a strong recommendation against to weak recommendation against: difference between the lower boundary of increased major bleeding and upper boundary of reduction in recurrent VTE $<2\%$ (risk over 5 y averaged per year).
- Criterion to go from a weak recommendation against to a weak recommendation in favor of: difference between point estimate of reduction of recurrent VTE and point estimate for increase in major bleeding is $>2\%$ (risk over 5 y averaged per year) (2% to account for the burden and cost of VKA).
- Criterion to go from a weak recommendation for to strong recommendation for: difference between the lower boundary of reduction in VTE and upper boundary of increased major bleeding $>4\%$ (risk over 5 y averaged per year).

Another way of interpreting the direction and strength of recommendation based on the number of deaths (related to either bleeding or recurrent VTE) is as follows:

- A strong recommendation against: extended anticoagulation is estimated to be associated with an increase in deaths.
- A weak recommendation against: extended anticoagulation is estimated to be associated with from no effect on deaths to only a very small reduction in deaths (0-4/1,000 prevented over 5 y or $<0.5\%$/patient-y).
- A weak recommendation for: extended anticoagulation is estimated to be associated with a small reduction in deaths (5 to 9/1,000 prevented over 5 y or 0.5%-0.9%/patient-y).
- A strong recommendation for: extended anticoagulation is estimated to be associated with a large reduction in deaths ($>$ 10/1,000 prevented over 5 y or $>1\%$/patient-y).

[a]With an eightfold risk of bleeding in the high-risk group compared with the low-risk group, a strong recommendation against extended anticoagulation for a second unprovoked VTE is justified. The high-risk group, however, includes patients who have a risk of bleeding that is less than this estimate (eg, patients aged >75 y without additional risk factors for bleeding [Table 2]) and, therefore, may benefit from extended anticoagulant therapy. For this reason, we provide a weak rather than a strong recommendation against extended anticoagulation for patients with a second unprovoked VTE in the high-bleeding-risk group.

[b]Strong against

[c]Weak against

[d]Weak in favor

[e]Strong in favor

Rivaroxaban for Extended Therapy: Use of rivaroxaban compared with initial parenteral therapy followed by VKA therapy for the short- and long-term treatment of DVT is reviewed in section 3.3 (Table 21, Table S29). In the current section, we consider rivaroxaban compared with no anticoagulation in patients with proximal DVT or PE who have completed 6 or 12 months of anticoagulant therapy, which has been evaluated in a single study (Table 22, Table S30).[127] This study found that rivaroxaban markedly reduced recurrent VTE at the expense of a modest absolute increase in major bleeding. The evidence from this one study is of moderate quality because of serious imprecision.

Dabigatran for Extended Therapy: There are no completed studies that have compared dabigatran with no anticoagulation for extended treatment of VTE.

Choice of Anticoagulant Regimen for Extended Therapy: This question is addressed in section 3.3.

Recommendations

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over: (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, or (iii) extended therapy** (Grade 1B regardless of risk of bleeding)**.**

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, and (iii) extended therapy if there is a high bleeding risk (Table 2)** (Grade 1B)**. We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Table 2)** (Grade 2B)**.**

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) **and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B) **or extended therapy** (Grade 1B regardless of bleeding risk)**.**

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). **After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.**

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk (Table 2), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)**.**

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk (Table 2), we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)**.**

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low bleeding risk (Table 2) (Grade 2B)**, and recommend 3 months of anticoagulant treatment in those with a moderate or high bleeding risk (Table 2)** (Grade 1B)**.**

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Table 2) (Grade 1B)**, and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Table 2)** (Grade 2B)**.**

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk (Table 2), we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B)**.**

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high (Table 2), we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk (Table 2), we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are given a diagnosis of isolated distal DVT will be prescribed anticoagulants (see section 2.3). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

Table 20—*[Section 3.3] Summary of Findings: LMWH vs VKA for Long-term Treatment of VTE*[a-c,173,211,213,223,224,226-228]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With VKA	Risk Difference With LMWH (95% CI)
Death	2,496 (7 studies), 6 mo	Moderate[d,e] due to imprecision	RR 0.96 (0.81-1.13)	164 per 1,000	7 fewer per 1,000 (from 31 fewer to 21 more)
Recurrent VTE	2,727 (8 studies), 6 mo	Moderate[f] due to risk of bias	RR 0.62 (0.46-0.84)	No cancer[g]	
				30 per 1,000	11 fewer per 1,000 (from 5 fewer to 16 fewer)
				Nonmetastatic cancer[g]	
				80 per 1,000	30 fewer per 1,000 (from 13 fewer to 43 fewer)
				Metastatic cancer[g]	
				200 per 1,000	76 fewer per 1,000 (from 32 fewer to 108 fewer)
Major bleeding	2,737 (8 studies), 6 mo	Moderate[h,i] due to imprecision	RR 0.81 (0.55-1.2)	No cancer or nonmetastatic cancer[j]	
				20 per 1,000	4 fewer per 1,000 (from 9 fewer to 4 more)
				Metastatic cancer[j]	
				80 per 1,000	15 fewer per 1,000 (from 36 fewer to 16 more)
Burden of anticoagulation	…	High[k]	…	Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits	LMWH: daily injection, no dietary restrictions, no frequent blood testing/monitoring
PTS (self-reported leg symptoms and signs)	100 (1 study), 2 y	Low[l,m] due to risk of bias, indirectness	RR 0.85 (0.77-0.94)	200 per 1,000[n]	30 fewer per 1,000 (from 12 fewer to 46 fewer)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Two of these studies enrolled only patients without cancer, three enrolled only patients with cancer, and three enrolled both patients with and without cancer (separate data provided for patients with cancer and without cancer in one study).

[b]Limited to LMWH regimens that used ≥ 50% of the acute treatment dose during the extended phase of treatment.

[c]The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al[211]) in which patients randomized to LMWH initially received the same LWMH, whereas patients randomized to VKA received initially UFH.

[d]One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

[e]CI includes both no effect and harm with LMWH.

[f]None of the studies were blinded, whereas the diagnosis of recurrent VTE has a subjective component and there could be a lower threshold for diagnosis of recurrent VTE in VKA-treated patients because switching the treatment of such patients to LMWH is widely practiced. At the same time, there is reluctance to diagnose recurrent VTE in patients who are already taking LMWH because there is no attractive alternative treatment option.

[g]Risk of recurrent VTE: low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate corresponds to patients with local or recently resected cancer (based on average rate across the six studies in this analysis and appears to be consistent with Prandoni et al[38] [particularly if low risk is increased to 4%]), and high corresponds to patients with locally advanced or distant metastatic cancer (Prandoni et al).

[h]No study was blinded; diagnosis of major bleeding has a subjective component.

[i]The 95% CIs for the RR for major bleeding includes a potentially clinically important increase or decrease with LMWH and may vary with the dose of LMWH used during the extended phase of therapy.

[j]Risk of bleeding: low corresponds to patients without risk factor for bleeding (ie, age > 75 y, cancer, metastatic disease; chronic renal or hepatic failure; platelet count < 80,0000; requirement for antiplatelet therapy; history of bleeding without a reversible cause) (Table 2). Based on Prandoni et al[38] and Beyth et al[212] and adjusted to a 6-mo time frame.

[k]Hull et al[213] reported no significant difference in QOL but suggested greater satisfaction with LMWH over VKA (questionnaire did not directly assess the burden of injections).

[l]Patients and investigators not blinded. Self-reported leg symptoms and signs after 3 mo of treatment.

[m]The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

[n]Baseline risk assumes that patients all wear pressure stockings. Control event rate comes from observational studies in a review by Kahn et al,[214] adjusted to a 2-y time frame.

Table 21—*[Section 3.3] Summary of Findings: Rivaroxaban vs LMWH and VKA Therapy for Acute and Long-term Treatment of VTE*[a-c,88]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With LMWH and VKA Therapy	Risk Difference With Rivaroxaban (95% CI)
Mortality	3,449 (1 study), 6-12 mo[d]	Moderate[e,f] due to imprecision	HR 0.67 (0.44-1.02)	29 per 1,000	9 fewer per 1,000 (from 16 fewer to 1 more)
Recurrent VTE	3,449 (1 study), 6-12 mo[d]	Moderate[e,g] due to imprecision	HR 0.68 (0.44-1.04)	30 per 1,000[h]	9 fewer per 1,000 (from 17 fewer to 1 more)
Major bleeding	3,429 (1 study), 6-12 mo[d]	Moderate[e,g] due to imprecision	HR 0.68 (0.34-1.38)[i]	11 per 1,000[j]	4 fewer per 1,000 (from 7 fewer to 4 more)
Burden of anticoagulation not reported	…	…	…	Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits	Rivaroxaban: daily medication, no dietary restrictions, no frequent blood testing/monitoring

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. HR = hazard ratio. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs (unprovoked, 62%; cancer, 6%; previous, VTE 19%).

[b]Rivaroxaban 15 mg bid for 3 wk and then 20 mg/d for a total of 3 (12%), 6 (63%), or 12 (25%) mo.

[c]Enoxaparin 1 mg/kg bid for ~8 d and then VKA therapy targeted to an INR of 2.5 for 3, 6, or 12 mo.

[d]Follow-up was prespecified to be 3 (12%), 6 (63%), or 12 (25%) mo.

[e]Allocation was concealed. Patients, providers, and data collectors were not blinded, but outcome adjudicators were blinded. Intention-to-treat analysis; 1.0% were loss to follow-up. Not stopped early for benefit.

[f]CI includes values suggesting benefit or no effect; relatively low number of events.

[g]CI includes values suggesting benefit and harm.

[h]One definite or possible fatal VTE in the rivaroxaban group and one in the LMWH/VKA group.

[i]Calculated from reported data.

[j]Bleeds contributing to death: one in the rivaroxaban group and five in the warfarin group.

3.2 Intensity of Anticoagulant Effect

Ageno et al[2] and Holbrook et al[3] in these guidelines present evidence for the optimal intensity of VKA therapy (ie, target INR) during the long-term (eg, first 3 months of treatment) and extended phases of treatment of VTE.

Recommendation

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

3.3 Choice of Anticoagulant Regimen for Long-term Therapy

VKA therapy has been the standard method of anticoagulant therapy for VTE. Adjusted-dose SC UFH is an effective alternative to VKA therapy, but it has never been popular because it requires initial laboratory monitoring and twice-daily injection and is associated with osteoporosis.[215,216] SC LMWH has advantages over SC UFH in that it does not require laboratory monitoring, is less likely to cause osteoporosis,[216] and can be given once a day. For these reasons, LMWH has been used for the long-term treatment of VTE. The synthetic pentasaccharide, fondaparinux, has not been evaluated or widely used for long-term treatment of VTE. Idraparinux, a long-acting pentasaccharide, is effective for the long-term treatment of VTE,[217] but it is not being marketed because of concerns about bleeding given its prolonged duration of action (once weekly injection) and lack of reversibility. The direct antithrombin dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban have been evaluated for treatment of VTE and are now available in many countries. In this section, we compare VKA therapy (target INR 2.5), LMWH, dabigatran, and rivaroxaban for the long-term treatment of VTE (ie, first 3 months and extended therapy).

Table 22—*[Section 3.3] Summary of Findings: Rivaroxaban vs Placebo for Extended Anticoagulation of VTE*[a,b,88]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Placebo	Anticipated Absolute Effects: Risk Difference With Rivaroxaban (95% CI)
Mortality	1,196 (1 study), 6 or 12 mo[c]	Moderate[d,e] due to imprecision	RR 0.49 (0.04-5.4)[f]	3 per 1,000	2 fewer per 1,000 (from 3 fewer to 15 more)
Recurrent VTE	1,196 (1 study), 6 or 12 mo[c]	High[d]	HR 0.18 (0.09-0.39)	71 per 1,000[g]	58 fewer per 1,000 (from 43 fewer to 64 fewer)
Major bleeding	1,188 (1 study), 6 or 12 mo	Moderate[d,h] due to imprecision	RR 4.9 (0.58-42)[f]	[i]	7 more per 1,000 (from 3 more to 16 more)
Burden of anticoagulation not reported	…				Rivaroxaban: daily medication
PTS not reported	…	…	…	…	[j]

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 21 legends for expansion of abbreviations.

[a]Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs or PE (unprovoked, 73%; cancer, 5%; previous VTE, 19%).

[b]Rivaroxaban 20 mg/d for 6 or 12 mo after initial long-term therapy.

[c]Follow-up was prespecified to be 6 (60%) or 12 (40%) mo.

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Intention-to-treat analysis; 0.2% were loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting benefit or no effect; relatively low number of events.

[f]Calculated from reported data with addition of one event to each event rate because event rate was 0 in the control group.

[g]One definite or possible fatal VTE in the rivaroxaban group and one in the LMWH/VKA group.

[h]CI includes values suggesting benefit and harm.

[i]Bleeds contributing to death: none in the rivaroxaban group and none in the warfarin group.

[j]PTS: baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (Kahn et al[102]). There is threefold (Prandoni et al[202]) to 10-fold (van Dongen et al[209]) increase in PTS with recurrent VTE in the ipsilateral leg.

LMWH vs VKA Therapy for the Long-term Treatment of DVT: Two meta-analyses compared LMWH in widely differing doses with VKAs.[218,219] In an analysis by Iorio and colleagues,[218] which included seven studies[168,221-225] and a total of 1,379 patients, among study differences of mean daily dose of LMWH, little effect on the efficacy of LMWH compared with VKA therapy was found, but the dose of LMWH appeared to influence the risk of major bleeding (OR, ~0.2 with ~4,000 International Units/d to ~0.7 with 12,000 International Units/d, relative to the VKA groups; $P = .03$ for dose-dependent interaction). Because prophylactic doses of LMWH are rarely used as an alternative to VKA therapy in patients with VTE, we restricted our analysis to eight studies that used ≥ 50% of the full therapeutic dose of LMWH for long-term treatment of VTE (Table 20, Table S28).[173,211,213,223,224,226-228] This evidence suggests that compared with VKA therapy, LMWH is associated with a reduction of recurrent VTE and a similar frequency of major bleeding and mortality. The quality of this evidence is moderate because of potential for bias in the assessment of recurrent VTE (nonblinded outcome assessment) and serious imprecision for major bleeding and mortality.

Cancer vs No Cancer—There are differences between patients with and without cancer with VTE that may influence response to anticoagulant therapies. These include about a 10-fold higher risk of dying and a threefold higher risk of recurrent VTE and major bleeding during the first 3 or 6 months of treatment[38]; different mechanisms of thrombosis that may be associated with a poor response to VKA therapy[229]; use of cancer chemotherapy that is associated with thrombocytopenia, vomiting, and anorexia and may have other interactions with VKA therapy; and the need for invasive therapeutic interventions (eg, drainage procedures) that require reversal of anticoagulation. Many of these factors make LMWH more attractive and VKA therapy less attractive in patients with VTE and cancer and suggest that cancer may alter the response of VTE to LMWH vs VKA therapy (ie, presence of an interaction).

Among the eight studies included in Table 20 and Table S28, separate data are provided for 1,114 patients with cancer and 660 patients without cancer. Subgroup analyses suggest the possibility that the response to LMWH vs VKA therapy may differ between patients with cancer and without cancer (recurrent VTE: RR, 0.52 with cancer

[95% CI, 0.36-0.76] vs 0.99 without cancer [95% CI, 0.46-2.13]); major bleeding: RR, 0.92 with cancer [95% CI, 0.59-1.44] vs 0.43 without cancer [95% CI, 0.16-1.17]); mortality: RR, 0.93 with cancer [95% CI, 0.79-1.09] vs 1.85 without cancer [95% CI, 0.59-5.77]). However, none of these differences is statistically significant, making it less likely that there is a true difference in response to LMWH vs VKA in the two patient populations. For this reason, we have applied the same relative effects for LMWH vs VKA in patients with and without cancer. The baseline risks of events, however, are clearly different in the two populations.

Patient Preferences—As discussed in the Methods section, the ultimate judgment of the entire Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) panel is that most patients prefer VKA therapy over LMWH therapy. The higher purchase cost of LMWH compared with VKA therapy is an additional barrier to the long-term use of LMWH.

Quality of Evidence and Strength of Recommendations—Evidence for the comparison of long-term LMWH vs VKA therapy in patients without cancer is of low quality. The subgroup effect discussed previously was not sufficiently convincing to allow us to generate an effect estimate specifically for patients without cancer, but still reduced our confidence that the overall effect estimate applies to the noncancer subgroup that contributed a minority of data. Considerations favoring use of VKA over LMWH in patients without cancer include (1) the evidence of benefit with LMWH is of low quality, (2) the estimated absolute reductions in recurrent VTE events with LMWH compared with VKA therapy is small, (3) the high cost of LMWH, and (4) our assessment that LMWH is a greater burden to patients than VKA therapy. Considerations favoring use of LMWH over warfarin in patients with cancer include (1) a large absolute reduction in recurrent VTE with LMWH over VKA therapy and (2) that LMWH is better suited to the care of patients with cancer than is VKA therapy. Among patients with VTE and cancer, the advantages of LMWH over VKA therapy are expected to be greatest in patients (1) with metastatic disease, (2) being treated with aggressive chemotherapy, (3) presenting with extensive VTE, (4) with liver dysfunction, (5) with poor or unstable nutritional status, and (6) who wish to avoid laboratory monitoring of coagulation.

Dabigatran vs VKA Therapy for the Long-term Treatment of DVT: One completed study has directly compared dabigatran and VKA for the first 6 months of treatment of VTE (Table 23, Table S31).[343] Like patients treated with VKA therapy, patients treated with dabigatran initially received parenteral therapy (usually IV UFH or LMWH). This study suggests that treatment with dabigatran or VKA therapy is associated with a similar frequency of recurrent VTE, major bleeding, and death. This evidence is of moderate quality because of serious imprecision for each outcome and lack of long-term safety data for dabigatran in this patient population. Because the study included few patients with cancer, we were unable to assess whether its findings apply equally to patients with and without cancer. In the absence of evidence of such an interaction, however, we have not further rated down the quality of evidence for patients with VTE and cancer.

Rivaroxaban vs VKA Therapy for the Long-term Treatment of DVT: A single study has directly compared rivaroxaban (without initial parenteral anticoagulation) with parenteral anticoagulation and VKA in patients with acute DVT (Table 21, Table S29).[88] Results suggested that treatment with rivaroxaban and VKA therapy are associated with a similar frequency of recurrent VTE, major bleeding, and death. This evidence is of moderate quality because of serious imprecision for each outcome. Because the study included few patients with cancer, we were unable to assess whether its findings apply equally to patients with and without cancer. In the absence of evidence of such an interaction, however, we have not further rated down the quality of evidence for patients with VTE and cancer.

Comparisons Among LMWH, Dabigatran, and Rivaroxaban for the Long-term Treatment of DVT: There are no direct comparisons of these three agents for the long-term treatment of VTE. Recommendations about the use of one of these agents over the other are based on indirect comparisons, and the evidence is low quality.

Recommendations

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2B)**.**

Table 23—*[Section 3.3] Summary of Findings: Dabigatran vs VKA Therapy for Long-term Treatment of VTE*[a-c,343]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Warfarin	Anticipated Absolute Effects: Risk Difference With Dabigatran (95% CI)
Mortality	2,539 (1 study), 6 mo	Moderate[d,e] due to imprecision	HR 0.98 (0.53-1.79)	17 per 1,000	0 fewer per 1,000 (from 8 fewer to 13 more)
Recurrent VTE	2,539 (1 study), 6 mo	Moderate[d,e] due to imprecision	HR 1.01 (0.65-1.84)	19 per 1,000[f]	0 more per 1,000 (from 7 fewer to 16 more)
Major bleeding	2,539 (1 study), 6 mo	Moderate[d,e] due to imprecision	HR 0.82 (0.45-1.48)	19 per 1,000[g]	3 fewer per 1,000 (from 10 fewer to 9 more)
Burden of anticoagulation not reported	…	…	…	Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits	Dabigatran: daily medication, no dietary restrictions, no frequent blood testing/monitoring

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 21 legends for expansion of abbreviations.

[a]Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs or PE.

[b]Dabigatran 150 mg bid taken orally for 6 mo after an initial treatment with LMWH or IV UFH.

[c]Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 mo after an initial treatment with LMWH or IV UFH.

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Modified intention-to-treat analysis; 1.1% loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]One fatal VTE in dabigatran group and three fatal VTE in warfarin group.

[g]One fatal major bleeding in dabigatran group and one fatal major bleeding in warfarin group.

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4 Choice of Anticoagulant Regimen for Extended Therapy

Other than a comparison of low-intensity (target INR 1.75) with conventional-intensity VKA therapy[44] (Table S24 and S25), there are no completed studies that have compared different anticoagulant agents or regimens for extended therapy after a standardized initial period (eg, ≥ 3 months) of anticoagulation in either patients without or with cancer. Because a decision about using extended therapy occurs after an initial period of anticoagulation (eg, 3 months) and because the relative efficacy and safety of anticoagulant regimens are expected to be similar during the early and extended phases of therapy, we anticipate that most patients will continue to use their initial anticoagulant regimen for extended therapy. Possible reasons for switching from LMWH to VKA therapy include the following: cancer becomes less active, chemotherapy is completed, patient tires of SC injections, development of renal impairment causes concern about accumulation of LMWH (also applies to rivaroxaban and dabigatran), and LMWH costs become prohibitive. Reasons for switching from VKA therapy to LMWH could include difficulty with INR control and need for repeated invasive procedures. New anticoagulant therapies may expand indications for extended anticoagulant therapy because they are less burdensome than VKA or LMWH therapy and because they may be associated with improved clinical outcomes (ie, more effective or safer).

Recommendation

3.4. In patients with DVT of the leg who choose extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C)**.**

3.5 Treatment of Asymptomatic DVT of the Leg

Rather than screen postoperative patients for the presence of asymptomatic DVT, clinicians should prescribe primary prophylaxis for VTE to surgical patients.[230,231] If imaging studies performed for other reasons (eg, CT scanning for staging of cancer) incidentally detect asymptomatic proximal DVT, the high frequency of false-positive results in patients without a prior suspicion of DVT dictates caution in assuming that a DVT is truly present. Reasons for a high rate of false-positive results include (1) the imaging technique may not have been optimal for the diagnosis of DVT, (2) incidentally diagnosed DVT often is seen in the pelvis where DVT is harder to image (eg, unable to be assessed with compression ultrasound), and (3) the prevalence of DVT in asymptomatic patients is much lower than in symptomatic patients. Consequently, when there is evidence of incidental DVT, additional diagnostic testing (eg, ultrasound) to confirm the presence of DVT may be necessary. Because many cases of asymptomatic VTE are detected as PE, see also section 6.9 of this article for recommendations on the management of this condition.

No randomized trials have evaluated anticoagulant therapy in patients with incidental VTE; therefore, evidence is of moderate quality because of indirectness. Moreover, benefits of anticoagulant therapy may be less than in symptomatic patients because asymptomatic DVT may be chronic or less extensive and because the prevalence of false-positive results will be higher than in patients who were suspected of having DVT.

Factors that justify a more-aggressive approach to anticoagulation in patients with incidentally diagnosed DVT include certainty of diagnosis, extensive thrombosis that appears to be acute (eg, not present on a previous imaging study), progression of thrombosis on a follow-up imaging study, ongoing risk factors for VTE (eg, cancer), and a low risk of bleeding. A less-aggressive approach to anticoagulation could include (1) withholding of anticoagulation with surveillance to detect DVT extension or (2) limiting anticoagulant therapy to 3 months in patients with continuing risk factors for VTE (eg, cancer). Many patients have left the hospital by the time incidental DVT is reported. If it would be difficult for patients to return the same day, it is often reasonable to defer further assessment and anticoagulant therapy until the next day.

Recommendation

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B)**.**

4.0 PTS of the Leg

PTS is a cluster of leg symptoms and signs attributable to previous DVT. PTS occurs in about one-third of patients after acute DVT and up to two-thirds who have had an iliofemoral DVT.[102,232] The initial treatment of acute DVT, particularly with the use of thrombus removal strategies, may influence the risk of developing PTS (section 2.8). The most prominent symptoms are chronic dependent swelling and pain, discomfort on walking, and skin discoloration. The severity of symptoms may vary over time, and the most severe manifestation is a venous ulcer of the lower leg. In this section, we address prevention of PTS first and then its treatment. Unlike the last edition of these guidelines,[6] we do not address treatment of leg ulcers associated with venous insufficiency.

4.1 Compression Stockings and Bandages to Prevent PTS

Five randomized trials evaluated compression stockings used at various times after diagnosis of acute DVT for the prevention of PTS (Tables S32 and S33).[201,202,233-235] Two of these trials[163,164] randomized patients soon after diagnosis of a first episode of symptomatic proximal DVT to prolonged use of stockings (30-40 mm Hg pressure at the ankles) or no stockings and otherwise treated patients the same way (Table 24, Table S34). These trials suggest that compression stockings started within 2 weeks of DVT and continued for 2 years reduce PTS by about 50% and do not alter the frequency of recurrent VTE. Patients with proximal DVT and a previous DVT in the same leg and who have marked symptoms are expected to gain the most benefit from compression stockings.[102,201,202] The evidence is of moderate quality because the assessment of PTS, which includes a large subjective component, was not blinded, and the estimate for recurrent VTE was imprecise.

Compression stockings applying an ankle pressure of 30 to 40 mm Hg and a lower pressure higher up the leg (ie, graduated pressure) should be started as soon as feasible after starting anticoagulant therapy. Bandages may be used to provide initial compressive therapy because it may not be possible to fit compression stockings immediately and if stockings can be worn, a rapid decrease in leg swelling will require them to be refitted. The findings from a randomized trial of 69 patients suggest that immediate compression bandaging improves acute symptoms but does not reduce PTS at 1 year (RR, 0.9; 95% CI, 0.4-1.8).[236] Patients or their caregivers need to be able to apply and remove stockings for their use to be feasible. Alternative approaches to the use of stockings, such as routinely wearing stockings after acute DVT but stopping them if there are no symptoms of PTS after 6 months[235,237] or

only wearing stockings if there is persistent leg swelling, have not been adequately evaluated.

Recommendation

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2 Physical Treatment of PTS

Treatment of PTS with compression stockings has only been evaluated in two small trials[233,238] (Table 25, Tables S35 and S37) (all patients received rutosides in one study[238]). These studies did not find compression stockings to be of benefit. However, the quality of the evidence is low because of imprecision and risk of bias. There is anecdotal evidence that compression therapy is of benefit in many patients with PTS, and the potential benefit of a trial of compression stockings in individual patients is likely to outweigh its harm and cost. We suggest below-knee stockings in most patients, but thigh-length stockings may be preferable in those with marked thigh swelling.

Two small crossover randomized trials have evaluated the treatment of severe PTS with intermittent compression devices[239,240] (Table 26, Table S36). Both studies suggested benefit from intermittent compression therapy. The quality of the evidence, however, is moderate because of imprecision. The goal of intermittent compression therapy is to reduce PTS symptoms rather than to alter the natural history of its development. These devices can be used with or without compression stockings, depending on patient preference. Leg swelling and associated symptoms (eg, heaviness, tightness) are more likely to respond to compression stockings or intermittent compression devices than are other symptoms.

Table 24—*[Section 4.1] Summary of Findings: Elastic Compression Stockings vs No Elastic Compression Stockings to Prevent PTS of the Leg*[a,b,451]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Elastic Compression Stockings	Anticipated Absolute Effects: Risk Difference With Elastic Compression Stockings (95% CI)
PTS	421 (2 studies), 2 y	Moderate[c] due to risk of bias	RR 0.46 (0.34-0.63)[d]	479 per 1,000[e,f]	259 fewer per 1,000 (from 177 fewer to 316 fewer)[g]
Recurrent VTE	374 (2 studies), 5 y	Moderate[h,i] due to imprecision	RR 1.01 (0.61-1.67)[d]	210 per 1,000[j]	2 more per 1,000 (from 82 fewer to 141 more)
QOL not reported		…	…	[k]	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3 and 10 legends for expansion of abbreviations.

[a]Prandoni et al[202] excluded patients with recurrent ipsilateral DVT, preexisting leg ulcers, or signs of chronic venous insufficiency, bilateral thrombosis, a short life expectancy or a contraindication for use of stockings (eg, advanced-stage peripheral arterial insufficiency). Brandjes et al[201] excluded patients with short life expectancy, paralysis of the leg, bilateral thrombosis, leg ulcers, or extensive varicosis.

[b]Brandjes[201] used graded elastic compression stockings (40 mm Hg of pressure at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf); stockings were applied 2 to 3 wk after the first episode of proximal DVT. Prandoni et al[202] used flat-knitted stockings (30 to 40 mm Hg of pressure at the ankle); stockings were started at hospital discharge, an average of 1 wk after admission. In both studies, stockings were used for 2 y.

[c]Patients were not blinded to the treatment assignment, and outcomes were partly based on subjective report of symptoms.

[d]The effect estimate shown here results from a meta-analysis (Mantel-Haenszel fixed-effects model) of the two relevant trials. A fixed-effects model was chosen because of the small number of studies available.

[e]This estimate is based on the findings of the VETO study.[70] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[f]In Prandoni et al,[202] most events occurred during the first 6 mo. The cumulative incidence of the PTS in the control group was 40% after 6 mo, 47% after 1 y, and 49% after 2 y.

[g]Severe PTS: assuming the same RR of 0.46 and a baseline risk of 8.1% over 2 y, the absolute reduction is 44 fewer severe PTS per 1,000 (from 30 fewer to 53 fewer) over 2 y.

[h]We did not rate down the quality of evidence for recurrent VTE for the lack of blinding because this a more objective outcome than PTS.

[i]CI includes both negligible effect and appreciable benefit or appreciable harm.

[j]This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE (Heit et al[165]) and 29.1% confirmed VTE (Prandoni et al[208]).

[k]This is an important outcome that should be considered in future studies.

Recommendations

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C)**.**

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B)**.**

4.3 Pharmacologic Treatment of PTS

Hydroxyrutosides, a class of flavonoid drug produced from plant glycosides, may reduce capillary permeability, reduce inflammation, improve lymphatic function, and promote ulcer healing in patients with chronic venous insufficiency.[6,241,242] Two studies compared treatment of PTS (without ulceration) with rutosides vs control[238,243] (all patients wore compression stockings in one study[238]), and one study compared rutosides with hidrosmina[244](Table S37). The two controlled studies suggest that rutosides do not reduce most symptoms of PTS, although they may reduce ankle swelling (Table 27). This evidence is of low quality because of inconsistency and imprecision. Furthermore, rutosides may be associated with important side effects.

Recommendation

4.3. In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C)**.**

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial

5.0 Initial Treatment of Acute PE

As we noted in Methods (section 1.1), recommendations for management of patients with PE, particularly those addressing anticoagulant therapy and IVC filter insertion, are based on studies that enrolled patients with only DVT , patients with both DVT and PE, and patients with only symptoms of PE. The following sections emphasize studies that enrolled only patients with symptoms of PE (who could also have symptoms of DVT), emphasize differences in

Table 25—*[Section 4.2.1] Summary of Findings: Compression Stockings vs No Compression Stockings for Patients With PTS*[a-c,233,238]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Compression Stockings	Anticipated Absolute Effects: Risk Difference With Compression Stockings (95% CI)
Symptomatic relief treatment success[g]	115 (2 studies), 12 to 26 mo	Low[d-f] due to risk of bias and imprecision	RR 0.96 (0.70-1.31)	579 per 1,000	23 fewer per 1,000 (from 174 fewer to 179 more)
QOL not reported	…		Not estimable		
Recurrent VTE not reported	…		Not estimable		
Ulceration[h] not reported	…		Not estimable[h]		

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. CLOTS1 = Clots in Legs or Stocking After Stroke. See Table 1 and 3 legends for expansion of other abbreviations.

[a]Ginsberg et al[233] included patients with PTS 1 y after chronic, typical proximal DVT. Frulla et al[238] included patients with clinical symptoms and signs suggestive of PTS.

[b]Ginsberg et al[233]: Graduated compression stockings (30-40 mm Hg, calf or thigh length, depending on symptoms). Patients were encouraged to wear stockings as much as possible during waking hours. Frulla et al[238]: below-knee graded elastic compression stockings (ECS) (30-40 mm Hg at the ankle). Patients in both study arms received hydroxyethylrutosides (HR) (we considered the ECS + HR vs HR comparison).

[c]Ginsberg et al[233]: placebo stockings (calf or thigh length, depending on symptoms).

[d]Ginsberg et al[233]: Adequacy of sequence generation and allocation concealment were unclear; patients and outcome assessors were adequately blinded; unclear whether analysis followed the intention-to-treat principle; unclear whether follow-up was complete. Frulla et al[238]: outcome assessors were blinded; follow-up was complete; intention-to-treat principle was adhered to, but sequence generation and allocation concealment were unclear, and patients were not blinded.

[e]Very small number of patients

[f]Publication bias was not detected but not ruled out given that we identified only one small study partially supported by industry (provision of graduated compression stockings).

[g]Ginsberg et al[233] reported treatment failure (defined a priori based on any of five clinical criteria, including symptoms and ulcer development). Treatment success refers to the absence of treatment failure. Frulla et al[238] used the Villalta scale.

[h]Indirect evidence from the CLOTS1 trial suggests that compression stockings is associated with an RR of 4 for skin complications.

Table 26—*[Section 4.2.2] Summary of Findings: Intermittent Compression Device vs No Intermittent Compression Device for Patients With Severe PTS*[a-c,233,240]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Intermittent Compression Device	Anticipated Absolute Effects: Risk Difference With Intermittent Compression Device (95% CI)
Symptomatic relief: symptom score includes scoring of pain, swelling, and limitation of activity on a scale of 10-70	82 (2 studies[d]), 8 wk	Moderate[e-i] due to imprecision		The mean symptomatic relief in the control groups was 0	The mean symptomatic relief in the intervention groups was 0.41 SDs higher (0.02 lower to 0.85 higher)
QOL: VEINES-QOL scale of 0-100.	0 (1 study[d,j]), 8 wk	Moderate[g-i,k,l] due to imprecision		The mean QOL in the control groups was 50.2	The mean QOL in the intervention groups was 2.3 higher (1.04 lower to 5.64 higher)
Recurrent VTE[m] not reported	…		Not estimable[m]		
Ulceration[n] not reported	…		Not estimable[n]		

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. VEINES = Venous Insufficiency Epidemiological and Economic Study. See Table 1, 3, and 25 legends for expansion of other abbreviations.

[a]Patients with previous DVT with symptoms of severe PTS.

[b]Intervention group: Ginsberg et al[239]: Extremity pump used bid for 20 min each session; 50 mm Hg (therapeutic pressure) for 1 mo. O'Donnell et al[240]: Venowave lower-limb venous return assist device to wear for most of the day for 8 wk.

[c]Control group: Ginsberg et al[239]: Extremity pump used bid for 20 min each session; 15 mm Hg (placebo pressure) for 1 mo. O'Donnell et al[240]: Venowave lower-limb venous return assist device with no connection between motor and planar sheet for 8 wk.

[d]Crossover RCTs.

[e]In both studies, sequence generation was adequate; patients were blinded, analysis adhered to intention-to-treat principle, and there were no missing outcome data. In Ginsberg et al[239] (but not O'Donnell et al[240]), outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[f]$I^2 = 0\%$.

[g]Some concerns with indirectness, given relatively short follow-up (8 wk).

[h]Very small number of patients. CI includes both values suggesting no effect and values suggesting a beneficial effect.

[i]Publication bias not detected but not ruled out given that we identified only two small studies, with one (Ginsberg et al[239]) partially supported by industry (provision of devices).

[j]O'Donnell et al et al.[240]

[k]Sequence generation was adequate; patients were blinded, analysis adhered to intention-to-treat principle, and there were no missing outcome data. However, outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[l]Publication bias was not detected but not ruled out given that we identified only a small study.

[m]O'Donnell et al[240] indicated no cases of recurrent VTE by the end of this study but judged the follow-up period to be short.

[n]O'Donnell et al[240] indicated that one patient in the control group developed a venous ulceration. Three other participants developed nonserious skin-related side effects. Indirect evidence from the CLOTS1 suggests that compression stockings are associated with an RR of 4 for skin complications. Common side effects attributed to Venowave were heat sensation, skin irritation, and increased sweating.

the management of patients who present with PE compared with DVT, and make recommendations for the management of patients with PE. We do not repeat evidence that was presented in the corresponding section that addresses treatment of DVT; instead, the reader is directed to those sections of the article and to the related tables. We do not comment in the text on the quality of the evidence that underlies treatment recommendations for PE unless the quality of this evidence differs from that for patients who present with DVT.

5.1 Initial Anticoagulation for Acute PE

See section 2.1, Table 3, and Table S1.

Recommendation

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

5.2 Whether to Treat With Parenteral Anticoagulation While Awaiting the Results of Diagnostic Work-up for PE

See section 2.2. For the purpose of implementing this recommendation, validated prediction rules help with estimation of clinical probability of having PE.[55,56]

Table 27—*[Section 4.3] Summary of Findings: Venoactive Medication vs No Venoactive Medication for Patients With PTS*[a,b,202,238]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Venoactive Medication	Risk Difference With Venoactive Medication (95% CI)
Symptomatic relief: PTS score (Villalta scale) <5 or decreased by 30% at 12 mo compared with baseline in Frulla et al[238]; improved tiredness of the leg at 8 wk in de Jongste et al[243,c]	163 (2 studies)	Low[d-g] due to inconsistency, imprecision	RR 1.14 (0.85-1.52)	476 per 1,000	67 more per 1,000 (from 71 fewer to 247 more)
QOL not reported	…		Not estimable		
Recurrent VTE not reported	…		Not estimable		
Ulceration not reported	…		Not estimable		
Side effects	203 (2 studies)	Moderate[d,f,h] due to imprecision	RR 2.04 (0.76-5.51)	61 per 1,000	63 more per 1,000 (from 15 fewer to 275 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Patients with PTS and history of DVT in PTS leg.

[b]Included studies that assessed rutosides.

[c]Investigators assessed other symptoms (pain, heaviness, swelling feeling, restless legs, and cramps) but did not report a composite score. The symptom we chose to report showed the most benefit; the effect estimates for the other symptoms ranged from 0.8 to 1.4, and none were statistically significant.

[d]In both studies, sequence generation and allocation concealment were unclear. Both studies blinded outcome assessors and had complete follow-up. Although de Jongste et al[243] blinded patients, the authors did not adhere to the intention-to-treat principle and did not use a validated scale to measure symptomatic relief. Although Frulla et al[238] adhered to the intention-to-treat principle, the author did not blind patients.

[e]$I^2 = 77\%$.

[f]Small number of patients. CI included both values suggesting harms and values suggesting benefits.

[g]Publication bias was not detected but not ruled out given that we identified only two small studies, and it unclear whether they were funded by industry.

[h]$I^2 = 7\%$.

Recommendations

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests provided that test results are expected within 24 h (Grade 2C)**.**

5.3 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

See section 2.4, Table 4, and Table S2.

Recommendation

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B)**.**

5.4 Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

See section 2.5.

LMWH Compared With IV UFH for the Initial Treatment of PE: See section 2.5 and Table 6. Consistent with findings in patients with DVT, LMWH has been found to be as effective and safe as IV UFH in studies that included both patients with PE and DVT or only in patients with PE (Table 6). A meta-analysis of 12 studies[85,146,245-254] that included a total of 1,951 patients with either submassive symptomatic PE or asymptomatic PE in conjunction with symptomatic DVT failed to demonstrate or

exclude a beneficial or detrimental effect of LMWH on recurrent VTE (OR, 0.63; 95% CI, 0.33-1.18), major bleeding (OR, 0.67; 95% CI, 0.36-1.27), and all-cause mortality (OR, 1.20; 95% CI, 0.59-2.45).[255]

SC UFH Compared With SC LMWH for the Initial Treatment of PE: See section 2.5, Table 5, and Tables S3 through S5.

Fondaparinux Compared With IV UFH for the Initial Treatment of PE: The Matisse-PE trial compared fondaparinux with IV UFH for acute treatment of PE[79] (Table 28, Table S38). This study suggested that fondaparinux is associated with a similar frequency of mortality, recurrent VTE, and major bleeding as LMWH. The quality of this evidence is moderate because of imprecision. In making recommendations, we also considered evidence that fondaparinux is equivalent to LMWH for the treatment of DVT (see section 2.5, Table 7, and Table S38) and that fondaparinux shares the advantages that LMWH has over IV UFH.

Fondaparinux Compared With LMWH for the Initial Treatment of PE: In the absence of direct evidence in patients with PE, indirect evidence in patients with acute DVT (see section 2.5, Table 7, and Table S7) suggests that fondaparinux is equivalent to LMWH.

Fondaparinux Compared With SC UFH for the Initial Treatment of PE: There is no direct evidence for this comparison. In making recommendations, we considered that fondaparinux and LMWH are equivalent and that fondaparinux shares the advantages that LMWH has over IV UFH. We did not take into account the lower purchase cost of SC UFH compared with fondaparinux.

Once- vs Twice-Daily Administration of LMWH for Initial Treatment of PE: See section 2.5, Table 8, and Table S8. Patients who presented with PE were included in only one of the five studies with an unconfounded comparison of once- and twice-daily LMWH[85] and in one additional large study that compared once-daily LMWH therapy with IV UFH in patients who presented with PE.[252]

Recommendations

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux)**, and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom

Table 28—*[Section 5.4] Summary of Findings: Fondaparinux vs IV UFH for Initial Anticoagulation of Acute PE*[a-c,79]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With UFH	Risk Difference With Fondaparinux (95% CI)
Mortality	2,213 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 1.20 (0.82-1.74)	43 per 1,000	9 more per 1,000 (from 8 fewer to 32 more)
Recurrent VTE	2,213 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 0.75 (0.51-1.12)	50 per 1,000[f]	13 fewer per 1,000 (from 25 fewer to 6 more)
Major bleeding	2,213 (1 study), 3 mo	Moderate[d,e] due to imprecision	RR 0.85 (0.49-1.49)	23 per 1,000[g]	4 fewer per 1,000 (from 12 fewer to 11 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]All patients had acute, symptomatic, hemodynamically stable PE.

[b]Fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing <50, 50 to 100, or >100 kg, respectively) SC once daily given for at least 5 days and until the use of VKAs resulted in an INR >2.0.

[c]UFH continuous IV infusion (ratio of the activated partial thromboplastin time to a control value of 1.5-2.5) given for at least 5 days and until the use of VKAs resulted in an INR >2.0.

[d]Allocation was concealed. Patients, providers, and data collectors were not blinded. Outcome adjudicators were blinded; 0.6% of randomized patients were lost to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]Sixteen fatal VTE in fondaparinux group and 15 fatal VTE in UFH group.

[g]Fourteen patients in the fondaparinux group and 12 patients in the LMWH group had a major bleeding event during the initial period (6-7 d). Of these, one in the fondaparinux group and one in the UFH group were fatal.

thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5 Early vs Standard Discharge of Patients With Acute PE

Consistent with our discussion of outpatient treatment of acute DVT (section 2.7), LMWH has made it feasible to treat acute PE at home either without admission to the hospital (ie, discharge from the emergency department) or with admission and early discharge. However, because acute PE is associated with much higher short-term mortality than acute DVT, the safety of treating PE at home is uncertain. Consequently, PE is treated at home much less often than DVT, and the proportion of outpatients with PE that clinical centers treat at home varies from almost none to about 50%.

Two studies randomized patients with acute PE and a low risk of complications to receive LMWH either (1) in the hospital for only 3 days vs entirely in the hospital[256] or (2) entirely out of the hospital (discharged within 24 h) vs at least partly in hospital[257] (Table 29, Table S39). This evidence suggests that treating appropriately selected patients with acute PE at home does not increase recurrent VTE, bleeding, or mortality.

There are a number of prediction rules for identifying patients with acute PE who have a low risk of serious complications and may be suitable for treatment at home.[258-263] Of these, the PE Severity Index (PESI) is best validated[261,262,264-266] and was used to select patients for home treatment in the larger of the previously noted clinical trials (Table 29, Table S39). Patients with acute PE who meet the following criteria appear to be suitable for treatment out of the hospital: (1) Clinically stable with good cardiopulmonary reserve (eg, PESI score of <85[257] or simplified PESI score of 0,[262] including none of hypoxia, systolic BP <100, recent bleeding, severe chest pain, platelet count $<70{,}000/mm^3$, PE while on anticoagulant therapy, and severe liver or renal disease)[257], (2) good social support with ready access to medical care, and (3) expected to be compliant with follow-up. Patients also need to feel well enough to be treated at home (eg, absence of severe symptoms or comorbidity).

Consistent with the findings of these two trials, a systematic review of 11 observational studies (seven prospective, four retrospective; 928 patients)[267] and four more recent observational studies (two retrospective with 584 patients[268,269]; two prospective with 449 patients[270,271]) reported a very low frequency of complications in low-risk patients with acute PE who were initially treated partially or entirely at home. About one-third to one-half of outpatients with acute PE appear to be in this low-risk group.[272] The evidence from the randomized trials is of moderate quality (rated down for serious imprecision), with additional supportive findings from the observational studies.

Recommendation

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2 B)**.**

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6 Systemic Thrombolytic Therapy for PE

5.6.1 Systemic Thrombolytic Therapy vs Anticoagulation Alone for PE: Randomized trials have established that, at 24 h, thrombolytic therapy improves (1) pulmonary artery hemodynamic measurements (eg, mean pulmonary artery pressure improvement, 4.4 mm Hg; 95% CI, −4.6-4.2 mm Hg), (2) arteriovenous oxygen (difference of −0.3 [−0.4 to −0.2]), (3) pulmonary perfusion (50% early improvement in perfusion scan, OR, 3.8; 95% CI, 0.9-15.7), and (4) echocardiographic assessment (OR for improved right ventricular wall movement, 3.1; 95% CI, 1.5-6.3).[273] Thrombolytic therapy, however, does not appear to reduce the extent of residual thrombosis. It is uncertain whether the benefits of more-rapid resolution of PE outweigh the risk of increased bleeding associated with thrombolytic therapy. In patients with PE, severity of presentation is expected to depend on the extent of embolism (ie, degree of pulmonary artery obstruction) and the presence and severity of chronic cardiopulmonary impairment.[104,274,275] Patients with the most severe presentations who have the highest risk of dying from an acute PE have the most to gain from thrombolysis.

Prognosis in Patients With Acute PE—Of patients who are diagnosed with PE and start treatment, ~5% die of the initial PE or another PE within the next 7 days.[9,104,276-279] However, although the risk of dying of PE differs markedly among patients, no validated

Table 29—*[Section 5.5] Summary of Findings: Early Discharge vs Standard Discharge in the Treatment of Acute PE*[a,b,256,257]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Standard Discharge	Anticipated Absolute Effects: Risk Difference With Early Discharge (95% CI)
Mortality	471 (2 studies), 3 mo	Moderate[c,d] due to imprecision	RR 0.58 (0.17-1.97)	26 per 1,000	11 fewer per 1,000 (from 22 fewer to 26 more)
Nonfatal recurrent PE	471 (2 studies), 3 mo	Moderate[c,d] due to imprecision	RR 1.23 (0.25-6.03)	9 per 1,000	2 more per 1,000 (from 7 fewer to 44 more)
Major bleeding	471 (2 studies), 3 mo	Moderate[c,d] due to imprecision	RR 2.74 (0.45-16.71)	4 per 1,000	8 more per 1,000 (from 2 fewer to 69 more)
QOL not reported	…	…	…	…	…
PTS not reported	…	…	…	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]The two RCTs included only patients with low risk: risk classes I or II on the Pulmonary Embolism Severity Index in Aujesky et al[216]; low risk on clinical prediction rule by Uresandi et al.[258]

[b]Mean length of hospital stay: 3.4 (SD 1.1) vs 9.3 (SD 5.7) d in Otero et al[256] and 0.5 (SD 1.0) vs 3.9 (SD 3.1) d in Aujesky et al[257]; low risk on clinical prediction rule by Uresandi et al[258] in Otero et al.

[c]Otero et al[256]: allocation concealed; no patients lost to follow-up; intention-to-treat analysis; no blinding of outcome assessors reported; study stopped early because the rate of short-term mortality was unexpectedly high in the early discharge group (2 [2.8%] vs 0 [0%]). Aujesky et al[257]: unclear whether allocation was concealed; three (1%) patients had missing outcome data; intention-to-treat analysis; blinding of outcome adjudicators; no early stoppage.

[d]CI includes both values suggesting no effect and values suggesting appreciable harm or appreciable benefit.

risk prediction tool is available. Risk of dying of PE is estimated to be ~70% if cardiopulmonary arrest occurs (~1% of patients at presentation), 30% if there is shock requiring inotropic support (~5% of patients), and ~2% in patients who are not hypotensive.[104,276-278,280,281] In the presence of normal systemic arterial pressure, prognosis can also differ, depending on (1) clinical evaluation,[276] (2) cardiac biomarkers such as troponin or brain natriuretic peptide,[279,282-291] and (3) assessment of right ventricular size and function.[279,280,283,285,290-295]

Clinical evaluation involves assessment of general appearance, BP, heart rate, respiratory rate, temperature, pulse oximetry, and signs of right ventricular dysfunction (eg, distended jugular veins, tricuspid regurgitation, accentuated P_2).[104] Clues on the ECG include right bundle branch block, $S_1Q_3T_3$, and T-wave inversion in leads V_1 through V_4.[296] Elevation of cardiac troponins indicates right ventricular microinfarction, and echocardiography may show right ventricular hypokinesis; both are risk factors for early mortality and are associated with a worse outcome when they occur together.[238,241-245,250] Right ventricular enlargement on the CT pulmonary angiogram, defined as a right ventricular diameter ≥ 90% than the left ventricular diameter may also be an independent risk factor for death and nonfatal complications.[279,291,293,295,297]

Risk of Bleeding With Thrombolytic Therapy—We have not identified any validated risk prediction tool for bleeding with thrombolytic therapy in patients with PE. However, we assume that the assessment of bleeding risk with thrombolytic therapy is similar in patients with PE and with acute ST-segment elevation myocardial infarction.[104,110-113,298,299] Table 11 lists risk factors for bleeding with thrombolytic therapy, categorized as major and relative contraindications.

Trials Evaluating Thrombolytic Therapy in Patients With Acute PE—The findings of 13 randomized trials that compared thrombolytic therapy to anticoagulant therapy alone in patients with acute PE are summarized in Table 30 and Tables S40 through S42.[300-313] A number of meta-analyses of these studies have been performed.[104,273,315,315] This evidence suggests that thrombolysis may be associated with a reduction in mortality and recurrent PE and is associated with an increase in major bleeding, as has been established in patients with myocardial infarction.[112] The quality of evidence regarding mortality and recurrent PE is low because of risk of bias, serious imprecision, and suspected publication bias. A previous meta-analysis that categorized studies as either including, or not including, patients with cardiopulmonary compromise, suggested that thrombolytic therapy reduced the composite outcome of death and recurrent PE in studies that included the sickest patients.[315] However, we found that the data available from these studies are not sufficiently detailed to enable a subgroup

analysis evaluating outcomes in patients with hemodynamic compromise or other markers of heightened risk of death (eg, right ventricular dysfunction).

Balancing Benefits and Harms of Thrombolytic Therapy—In patients who present with PE and hypotension (eg, systolic pressure BP < 90 mm Hg or a documented drop in systolic BP > 40 mm Hg with evidence of poor perfusion), especially if they have a low risk of bleeding, even modest efficacy of thrombolytic therapy is likely to reduce deaths from PE more than it would increase fatal bleeds and nonfatal intracranial bleeds (Table 30, Tables S40-S42). The ultimate judgment of the entire AT9 panel was to issue a weak recommendation for patients with PE and hypotension given the uncertainty of the benefit. In most patients with PE, given the certain risks of bleeding and less-certain benefits, thrombolysis is likely to be harmful. Selected patients without hypotension may benefit from thrombolysis because their initial clinical presentation or clinical course after starting anticoagulant therapy suggest that they are at high risk of dying.

There is no explicit clinical prediction rule that identifies this subgroup of patients. We suggest that such patients are identified predominantly by clinical evidence of instability (eg, a decrease in systolic BP that still remains > 90 mm Hg, tachycardia, elevated jugular venous pressure, clinical evidence of poor tissue perfusion, hypoxemia) and failure to improve on anticoagulant therapy. As noted previously, laboratory (eg, troponin, brain natriuretic peptide), ECG, echocardiography, and CT evidence of right ventricular dysfunction or enlargement, can supplement the clinical evaluation of instability; however, they are not sufficiently predictive to serve as indications for thrombolytic therapy on their own,[289] and we do not recommend that they are routinely measured.

Recommendations

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high risk of bleeding, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C)**.**

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C)**.**

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulant therapy suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C)**.**

5.6.2 Systemic Thrombolytic Therapy Regimen for PE: Twelve randomized trials (total of 938 patients) have compared the rate of thrombus resolution achieved with various IV thrombolytic regimens.[316-327] These regimens included urokinase given over 2 h[319,326] or 12 h[316,321,326]; streptokinase given over 2 h, 12 h,[320] or 24 h[316]; and recombinant tPA (rt-PA) given over 15 min[317,322,325] or 2 h,[317-325,327] reteplase in two boluses 30 min apart,[325] and desmoteplase in three different doses as a bolus[323].

An additional study compared IV with pulmonary artery catheter administration of rt-PA (50 mg over 2 h).[328] The results of studies that compared different approaches to thrombolysis in patients with PE (noted previously) suggest that (1) prolonged infusions of thrombolytic agents (eg, ≥ 12 h) are associated with higher rates of bleeding[316,318]; (2) 2-h infusions achieve more rapid clot lysis than 12- or 24-h infusions[318,320,321]; (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[327]; (4) bolus rt-PA regimens (eg, ~50 mg in ≤ 15 min) appears to be as effective and safe as a 2-h infusion of 100 mg of rt-PA[313,317,322,325]; 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).[328] When a lytic agent is appropriate for PE, current evidence supports that thrombolytic therapy should be infused into a peripheral vein over ≤ 2 h. At a dose of 100 mg over 2 h, rt-PA is currently the most widely used and evaluated regimen. In patients with imminent or actual cardiac arrest, bolus infusion of thrombolytic therapy is indicated.

The quality of evidence for comparisons of systemic thrombolytic agents and regimens (eg, different doses or durations of infusion) is low based on very serious imprecision and risk of bias. In addition, there is substantial potential for publication bias. Based on this evidence, we provide only weak recommendations for all comparisons of thrombolytic agents and regimens in the short-term treatment of PE.

Recommendations

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C)**.**

Table 30—*[Section 5.6.1] Summary of Findings: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE*[a-d,273,309,310,314,315]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Systemically Administered Thrombolytic Therapy	Anticipated Absolute Effects: Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)
Mortality	847 (12 studies), 30 d	Low[e-h] due to risk of bias and imprecision	RR 0.7 (0.37-1.31)		Low[i,j]
				11 per 1,000	3 fewer per 1,000 (from 7 fewer to 3 more)
					High[i,j]
				89 per 1,000	27 fewer per 1,000 (from 56 fewer to 28 more)
Recurrent PE	801 (9 studies), 30 d	Low[e-h] due to risk of bias and imprecision	RR 0.7 (0.4-1.21)	57 per 1,000	17 fewer per 1,000 (from 34 fewer to 12 more)
Major bleeding	847 (12 studies), 10 d	Moderate[e,f,h,k] due to risk of bias and imprecision	RR 1.63 (1-2.68)[l]		Low[m]
				1 per 1,000	1 more per 1000 (from 0 more to 2 more)
					High[m]
				62 per 1,000	39 more per 1,000 (from 0 more to 104 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]One study included exclusively patients with hemodynamic compromise (shock), six excluded them, whereas the rest either included a number of such patients or did not specify related eligibility criteria. Of studies not restricted to patients with hemodynamic compromise (n = 11), only three were clearly restricted to patients with right ventricular dysfunction; the rest either did not specify related eligibility criteria or included both patients with and without right ventricular dysfunction. As a result, it was not possible to perform reliable categorization of studies to conduct subgroup analyses based on the presence or absence of right ventricular dysfunction or hemodynamic compromise.

[b]Studies included patients at low risk for bleeding.

[c]Included studies that used different thrombolytic agents with varying doses and durations of administration; no statistical heterogeneity was noted.

[d]Thrombolysis was in addition to anticoagulation (most of the studies used heparin followed by warfarin; three studies used warfarin only).

[e]Report of methodologic quality was poor in most studies. Of the 12 eligible studies, allocation was concealed in five, three were single blind (outcome assessor), six were double blind, and three were not blinded. Most studies did not report on missing outcome data. None of the studies were stopped early for benefit. For the increase in bleeding with thrombolytic therapy, quality of evidence is increased from low to moderate because there is high quality evidence of this association in patients with myocardial infarction and the indirectness of this evidence to patients with PE is minor.

[f]$I^2 = 0\%$.

[g]CI includes values suggesting both benefit and no effect or harm; small number of events.

[h]Inverted funnel plots suggestive of possible publication bias in favor of thrombolytics.

[i]Recurrent PE stratification based on the simplified Pulmonary Embolism Severity Index validated in the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) cohort.[262]

[j]Some studies suggested that the baseline risk of mortality in patients with hemodynamic instability is as high as 30%.[274] In that case, the absolute number of deaths associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).

[k]CI includes values suggesting both harm and no effect; small number of events.

[l]Major bleeding risk stratification derived from the RIETE cohort.[30] The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of major bleeding events with thrombolysis would be 20 more per 1,000 (from 0 more to 52 more).

[m]Indirect evidence from studies of thrombolysis for myocardial infarction and acute stroke provide more precise estimates of increase major bleeding with thrombolytics use.

5.6.2.2. In patients with acute PE, when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C)**.**

5.6.3 Initial Anticoagulant Therapy in Patients Treated With Thrombolytic Therapy: Trials that evaluated thrombolysis for PE used IV UFH in conjunction with thrombolytic therapy (Table 30, Tables S40-S42), and no randomized trials have compared different regimens of IV UFH in this setting. IV UFH should be given in full therapeutic doses[1,3] before thrombolytic therapy is administered, and it is acceptable to either continue or suspend the UFH infusion during administration of thrombolytic therapy (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. US authorities recommend checking the activated partial thromboplastin time immediately after completion of the tPA infusion and, provided that the activated antithrombin time is not > 80 s, restarting IV UFH without a bolus at the same infusion rate as before tPA was started.

5.7 Catheter-Based Thrombus Removal 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.[329-336] Pharmacologic thrombolysis and mechanical interventions are usually combined unless bleeding risk is high. Catheter embolectomy does not result in extraction of intact pulmonary arterial thrombus; instead, clot fragments are suctioned through the catheter or displaced distally with modest angiographic improvement.

No randomized trials have evaluated interventional catheterization techniques for PE. Most observation studies are retrospective series of < 30 patients.[334] Consequently, evidence for the use of interventional catheter techniques in patients with acute PE is of low quality, and our recommendations are weak. Catheter selection, catheter deployment, and adjunctive thrombolytic regimen should be based on local expertise and resources.

Recommendation

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C)**.**

5.8 Surgical Embolectomy for the Initial Treatment of PE

Emergency surgical embolectomy with cardiopulmonary bypass is another management strategy for acute PE associated with hypotension.[337-340] This operation is also suited for patients with acute PE who require surgical excision of a right atrial thrombus, paradoxical arterial embolism, or closure of a patent foramen ovale. Surgical embolectomy also can be performed to rescue patients in whom thrombolysis has been unsuccessful. The procedure is best performed on a warm, beating heart, without aortic cross-clamping, cardioplegia, or fibrillatory arrest.

No randomized trials or prospective observational studies have evaluated surgical embolectomy in patients with acute PE. Consequently, evidence related to surgical embolectomy in patients with acute PE is of low quality, and our recommendations are weak.

Recommendation

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C)**.**

5.9. Vena Caval Filters for the Initial Treatment of PE

As previously noted in section 2.13, IVC filters can be used instead of initial anticoagulant therapy in patients with acute PE if there is an unacceptable risk of bleeding or as an adjunct to anticoagulation. As in 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 2.13, the PREPIC study, 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 PE combined) or mortality[146,149] (Table 14; Table S19).

The PREPIC study included 145 (36%) patients with symptomatic PE and 52 (13%) patients with asymptomatic PE at enrollment. If a patient has an acute PE and a short-term contraindication to anticoagulation, provided there is no proximal DVT on ultrasound, it is reasonable not to insert an IVC filter immediately; serial ultrasound examinations can be performed to ensure that the patient remains free of proximal DVT while anticoagulation is withheld.

There is uncertainty about the risk and benefits of inserting IVC filters as an adjunct to anticoagulant and thrombolytic therapy in patients with PE and hypotension. 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] Consequently, our recommendation

against insertion of an IVC filter in patients with acute PE who are treated with anticoagulants may not apply to this select subgroup of patients.

Recommendations

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B)**.**

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B)**.**

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B)**.**

Remarks: We do not consider that a permanent IVC filter of itself is an indication for extended anticoagulation.

6.0 Long-term Treatment of PE

In the following sections, we emphasize studies that were performed exclusively in patients with PE and patients with PE who were enrolled in other studies. For the reasons noted in section 1.1, we make the same recommendations for long-term treatment of PE as for DVT and rate the quality of the underlying evidence as the same (see corresponding sections for treatment of DVT).

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 [Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism]) (Table S24 and S25).[194] 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.

LMWH for the Long-term Treatment of PE: Two small studies from the same investigator group have compared long-term LMWH (enoxaparin 1 mg/kg SC bid for ~14 days followed by 1.5 mg/kg SC daily) with long-term VKA exclusively in patients who presented with PE.[341,342] The two studies combined found 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.[341] Of the 12 other studies that compared LMWH with VKA therapy for long-term treatment of VTE (see section 3.3), only two[173,227] included patients with PE. In these two studies, all patients had cancer, and 295 had PE (36% of all enrolled patients; some PE may have been asymptomatic in one study[227]); subgroup analyses were not reported for the patients with PE.

Dabigatran for the Long-term Treatment of PE: In the one completed study that compared dabigatran with VKA therapy after initial parenteral therapy (Table 23, Table S31), 786 (31%) patients had symptomatic PE at enrollment.[343] Subgroup analysis did not suggest that patients with symptomatic PE have a different response to dabigatran vs VKA therapy in terms of either recurrent VTE or bleeding.

Rivaroxaban for the Long-term Treatment of PE: In the Einstein Extension study that compared rivaroxaban with placebo after an initial period of long-term anticoagulation (Table 22, Table S30), 454 (38%) patients had symptomatic PE at enrollment.[88] Subgroup analysis did not suggest that patients with symptomatic PE had a different response to rivaroxaban vs VKA therapy in terms of either recurrent VTE or bleeding.

Recommendations

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, or (iii) extended therapy** (Grade 1B regardless of bleeding risk)**.**

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, and (iii) extended therapy if there is a high bleeding risk (Table 2)** (Grade 1B)**. We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Table 2)** (Grade 2B)**.**

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter

duration (Grade 1B). **After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.**

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk (Table 2), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Table 2) (Grade 1B), **and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Table 2)** (Grade 2B).

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk (Table 2), we suggest 3 months of therapy over extended therapy (Grade 2B).

6.4. In patients with PE and active cancer, if the risk of bleeding is not high (Table 2), we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), **and if there is a high bleeding risk (Table 2), we suggest extended anticoagulant therapy** (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). **For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C).

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B). **In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2C).

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to individual patient tolerance for daily injections, need for laboratory monitoring, and treatment costs. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes that VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).

6.9 Treatment of Asymptomatic PE

Diagnosis of asymptomatic PE occurs in ~1% of outpatients and ~4% of inpatients who have contrast-enhanced CT scans, with a majority being in patients with known malignancy.[40,344-355] When PE is diagnosed unexpectedly in patients with cancer, in retrospect, the clinical history may reveal symptoms that were aggravated by the PE (eg, an increase in fatigue).[345] About one-half of such incidental PE involve the lobar or more central pulmonary arteries, whereas the other one-half are more distal.[40,353]

When there is evidence of an asymptomatic PE, the first priority is to review the CT scans to determine whether 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 vein, IVC, iliac vein). If there is any uncertainty about the presence of an acute PE, additional diagnostic testing is required (eg, ultrasonography of the deep veins, dedicated CT pulmonary angiography, D-dimer).

Consistent with recommendations for the treatment of asymptomatic DVT (section 3.5) in patients in whom clinicians are convinced that an asymptomatic PE has occurred, based on moderate-quality evidence, we suggest the same initial and long-term anticoagulation as for similar patients with symptomatic PE. The indication for anticoagulation is most compelling when the presence of PE is unequivocal, PE involves the lobar and more central

pulmonary arteries, PE is a new finding on CT, ultrasound reveals proximal DVT, there are ongoing risk factors for VTE such as active cancer, and the patient is not at high risk for bleeding (Table 2). Many patients have left the hospital by the time an incidental PE is reported. If PE is less extensive and it would be difficult for patients to return the same day, it often is reasonable to defer further assessment and anticoagulant therapy until the next day.

Recommendation

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for similar patients with symptomatic PE (Grade 2B)**.**

7.0 Chronic Thromboembolic Pulmonary Hypertension

Prospective studies suggest that CTPH occurs in ~3% of patients who are treated for PE.[104,354-358] About one-third of patients have a history of VTE, whereas two-thirds have had single or recurrent episodes of PE that were not diagnosed and may have been asymptomatic.[359] Patients with CTPH are likely to have a high risk of recurrent VTE because they have had previous VTE and have cardiopulmonary impairment. Recurrent VTE may be fatal more often in patients with severe cardiopulmonary impairment than in those without such impairment. After PE initiates CTPH, pulmonary vascular remodeling may cause severe pulmonary hypertension out of proportion with pulmonary vascular thrombosis.[104,359,360]

7.1 Pulmonary Thromboendarterectomy, Anticoagulant Therapy, and Vena Caval Filter for the Treatment of CTPH

Primary therapy for CTPH is pulmonary thromboendarterectomy, which, if successful, can reduce or cure pulmonary hypertension and associated symptoms.[104,359-367] The operation is lengthy and complex, requiring a median sternotomy, cardiopulmonary bypass, deep hypothermia with periods of circulatory arrest, and exploration of both pulmonary arteries. At the most experienced centers, mortality is ~5%.[104,360,363,365-367] Management often includes insertion of a permanent IVC filter before or during pulmonary endarterectomy and indefinite anticoagulant therapy.[359,361,363,365] Patients with CTPH who are not candidates for pulmonary endarterectomy because of comorbid disease or surgically inaccessible lesions may be candidates for vasodilator therapy, balloon pulmonary angioplasty, or lung transplantation and may benefit from referral to a center with expertise in pulmonary hypertension.[359,363-365,368-370]

There are no randomized trials of CTPH therapy and, overall, evidence is low quality. There is, however, high-quality indirect evidence that anticoagulant therapy is very effective at preventing recurrent VTE in other patient populations (see section 3.1; Table 18; and Tables S24, S25, and S27). Consequently, the evidence supporting long-term anticoagulation in patients with CTPH is of moderate quality (rated down for indirectness). Features that are expected to be associated with greater benefit with pulmonary thromboendarterectomy include younger age, central disease, progressive clinical deterioration, and access to an expert multidisciplinary thromboendarterectomy team.

Recommendations

7.1.1. In patients with CTPH, we recommend extended anticoagulation over stopping therapy (Grade 1B)**.**

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C)**.**

8.0 Superficial Vein Thrombosis

SVT has been less well studied than DVT but is estimated to occur more often.[371,372] It usually affects the lower limbs; often involves a varicose vein; is associated with chronic venous insufficiency, malignancy, thrombophilia, pregnancy or estrogen therapy, obesity, sclerotherapy, long-distance travel, and a history of VTE; or may be unprovoked.[371-373] The long saphenous vein is involved in about two-thirds of lower-limb SVT.[374]

Although traditionally considered a benign disease, a number of studies indicate that the consequences of SVT may be more serious.[371,372] A prospective study of 844 patients with acute SVT of ≥5 cm found that at initial presentation, ~4% of patients had symptomatic PE, and routine ultrasound detected proximal DVT in 10% and distal DVT in an additional 13% of patients.[374] In patients without VTE at presentation, despite 90% being treated with anticoagulant therapy (therapeutic doses in two-thirds, prophylactic doses in one-third, median duration of 11 days), 3.1% developed symptomatic VTE (0.5% PE, 1.2% proximal DVT, 1.4% distal DVT), 1.9% had recurrent SVT (different location), and 3.3% had an extension of SVT (same location) at 3 months. Male sex, history of VTE, cancer, and absence of varicose veins each was associated with about a doubling of the risk of VTE during follow-up.

Given the high prevalence of concomitant proximal DVT in patients with SVT and the need to treat such patients with higher doses of anticoagulant therapy (ie, therapeutic doses), patients with SVT above the knee should have ultrasonography to exclude proximal DVT. Ultrasound can also help with the diagnosis of SVT if the clinical presentation is uncertain. With greater appreciation of the seriousness of SVT, investigators have evaluated anticoagulant therapy, often in prophylactic or intermediate doses, as a way to reduce acute symptoms, extension, recurrence, and progression to VTE (Table 31, Tables S43-S45).[375]

8.1 Treatment of SVT

Most studies that have evaluated anticoagulant therapy for SVT have been small (eg, ≤ 100 patients per treatment group), with additional methodologic weaknesses[376-381] (Tables S44, S45). Although these studies suggest that prophylactic-dose LMWH, intermediate-dose UFH or LMWH, warfarin therapy, and oral nonsteroidal antiinflammatory agents are beneficial in patients with SVT, the supporting evidence is of low quality. The recently published Comparison of ARIXTRA™ in lower LImb Superficial Thrombophlebitis with placebo (CALISTO) study, which compared fondaparinux (2.5 mg/d for 45 days) with placebo in 3,000 patients with SVT (≥ 5 cm in length), has helped to clarify the role of anticoagulants for the treatment of SVT (Table 31, Table S43), and the natural history of this condition.[382]

CALISTO found that fondaparinux is very effective at reducing VTE, recurrent SVT, extension of SVT, and the need for venous surgery, and is associated with little bleeding. In the placebo group, thrombotic complications occurred more often if SVT involved the greater saphenous vein (92% of patients in the control group), extended to within 10 cm from the saphenofemoral junction (9% of patients), and involved veins above the knee (46% of patients) and if VTE (7% of patients) or SVT (12% of patients) had occurred previously.[382] Age, sex, and presence of varicose veins were not convincingly associated with the frequency of thrombotic complications, and there were too few patients with cancer in CALISTO to assess that association.

The evidence is moderate quality. We have interpreted the findings of the CALISTO study as evidence for anticoagulation in general and assume that prophylactic doses of LMWH and fondaparinux have similar antithrombotic efficacy and safety. Because it is direct and more extensive, the evidence in support of fondaparinux is higher quality than the evidence in support of LMWH. Quality of the evidence for comparison of fondaparinux with LMWH is low because there is no direct comparison in patients with SVT. Factors that favor the use of anticoagulant therapy in patients with SVT (see Recommendation 8.1.1) include: extensive SVT; involvement above the knee, particularly if close to the saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; and recent surgery. An economic evaluation found that treatment of SVT with fondaparinux was not cost-effective; it cost $500,000 per quality-adjusted life year gained compared with no treatment.[383]

Graduated compression stockings often are used in patients with SVT (eg, 83% of patients in the CALISTO study). Oral nonsteroidal antiinflammatory agents may be used to alleviate symptoms if patients are not treated with anticoagulants. Topical nonsteroidal antiinflammatory agents may reduce symptoms and can be used with anticoagulant therapy. Surgical therapy, with ligation of the saphenofemoral junction or stripping of thrombosed superficial veins appears to be associated with higher rates of VTE than treatment with anticoagulants.[380,384,385] Anticoagulant therapy generally is not used to treat SVT that occurs in association with an IV infusion (ie, infusion thrombophlebitis).

Recommendations

8.1.1. In patients with SVT of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B)**.**

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)**.**

9.0 Acute Upper-Extremity DVT

About 5% to 10% of VTE involve the upper extremities.[386-390] UEDVT includes two etiologic groups: primary (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% of cases.[386,388,389,391-394]

UEDVT involves the subclavian, axillary, or brachial veins and may include extension to the brachiocephalic vein, superior vena cava, or the internal

Table 31—*[Section 8.1] Summary of Findings: Fondaparinux vs Placebo for Acute SVT*[a-c,382]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Fondaparinux	Risk Difference With Fondaparinux (95% CI)
Mortality	3,002 (1 study), 3 mo	Moderate[d-g] due to imprecision	RR 1.99 (0.18-21.87)	4 per 1,000[h]	4 more per 1,000 (from 3 fewer to 83 more)
VTE	3,002 (1 study), 3 mo	High[d]	RR 0.18 (0.06-0.53)	33 per 1,000[h]	27 fewer per 1,000 (from 16 fewer to 31 fewer)
SVT recurrence	3,002 (1 study), 3 mo	High[d]	RR 0.31 (0.14-0.68)	19 per 1,000[h]	13 fewer per 1,000 (from 6 fewer to 16 fewer)
Major bleeding	2,987(1 study), 47 d	Moderate[d,e,i] due to imprecision	RR 0.99 (0.06-15.86)[e]	1 per 1,000	0 fewer per 1,000 (from 1 fewer to 10 more)
QOL not measured	…	…	…	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Patients with infusion-related SVT were excluded from CALISTO (Comparison of ARIXTRA in lower Limb Superficial Thrombophlebitis with Placebo).

[b]Fondaparinux 2.5 mg for 45 d.

[c]Patients in the two treatment groups benefited from close clinical monitoring with adequate diagnostic procedures in the event of new or persistent symptoms.

[d]Allocation concealed. Outcome adjudicators, steering committee, patients, providers, and data collectors blinded. Follow-up rate was 98%. Intention-to-treat analysis for efficacy outcomes. Not stopped early for benefit.

[e]CI includes values suggesting large benefit and values suggesting large harm.

[f]We rated down by only one level because of the low event rate and large sample size.

[g]Small number of events.

[h]Baseline risk derived from a large prospective cohort study.[374]

[i]The upper limit of the CI for absolute effect (10 more bleeds) is not low enough to suggest a clear balance of benefits vs harms.

jugular vein. Clinical manifestations include acute and chronic arm pain, swelling, discoloration, and dilated collateral veins over the arm, neck, or chest. UEDVT may lead to complications, including symptomatic PE (~5% of patients[387-389,393,395]), recurrent UEDVT (~8% at 5 years of follow-up[389,390,395]), and PTS of the arm (~20% of patients).[386,387,395,396] In the absence of a central venous catheter, the dominant arm is more often affected.[387] Complications of UEDVT are expected to occur much more often and to be more severe when UEDVT involves the axillary or more-proximal veins than if thrombosis is confined to the brachial vein. In general, when we refer to UEDVT, we are referring to thrombosis that involves the axillary or more-proximal veins.

The most frequent risk factor for UEDVT is a central venous catheter.[386,388,397,398] If UEDVT occurs in association with a central venous catheter and the catheter is no longer required, it should be removed. There are no data to guide whether catheter removal should be preceded by an initial period of anticoagulation, and we do not have a preference for immediate or deferred removal. If UEDVT occurs in association with a central venous catheter and there is a continuing need for the catheter, the catheter need not be removed. If the catheter is not functioning and cannot be made to function (even after a period of systemic anticoagulation), it should be removed.

As with treatment of leg DVT and PE, treatment of UEDVT may be divided into acute (eg, parenteral anticoagulants, thrombolytic therapy) and long-term phases (eg, anticoagulation, treatment of upper-extremity PTS). Because no randomized trials have evaluated treatment of UEDVT, recommendations are based on indirect evidence from studies performed in patients with leg DVT, observational studies (generally small), and understanding of the natural history of UEDVT. Therefore, quality of evidence is, at best, moderate.

9.1 Acute Anticoagulation for UEDVT

No randomized controlled studies have evaluated acute anticoagulation for initial treatment of UEDVT. Several small prospective cohort studies have reported low rates of recurrent DVT, PE, and major bleeding when UEDVT was treated similarly to leg DVT (Tables S46 and S47).[395,399-401] Anticoagulant therapy is used to treat UEDVT because (1) UEDVT causes acute symptoms, can cause PE (including fatal

episodes), and is associated with PTS; (2) observational studies support its use; and (3) there is strong evidence for benefit in patients with leg DVT.

Uncertainty exists about the need to prescribe anticoagulants to patients with thrombosis confined to the brachial vein. Acceptable alternatives to full-dose anticoagulation in such patients include clinical or ultrasound surveillance to detect extension of UEDVT while withholding anticoagulation, or treatment with prophylactic-dose anticoagulation, or treatment with therapeutic doses of anticoagulation for <3 months. We favor anticoagulation if isolated brachial vein thrombosis is symptomatic, associated with a central venous catheter that will remain in place, or associated with cancer in the absence of a central venous catheter. A high risk of bleeding argues against full-dose anticoagulation.

Recommendations

9.1.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B)**.**

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B)**.**

9.2 Thrombolytic Therapy for the Initial Treatment of UEDVT

No randomized controlled studies have evaluated thrombolytic therapy compared with anticoagulation alone in patients with UEDVT. A number of retrospective and small prospective observational studies have evaluated streptokinase, urokinase, or rt-PA administered with varying doses, methods of administration (IV, catheter directed), and infusion durations.[402-409] Three of these studies included nonrandomized control groups who received anticoagulation alone.[402,407,408] In some studies, a few patients also had venous angioplasty[405] or surgical decompression[402,405,408] (Tables S48 and S49).

These studies suggest that thrombolysis can improve early and late venous patency but is associated with increased bleeding. However, it is not known whether thrombolytic therapy reduces PTS of the arm or recurrent VTE. PTS of the arm appears to be a less common complication of thrombosis than PTS of the leg.[386-388,393,395,410] We believe that thrombolysis should be considered only in patients who meet all of the following criteria: severe symptoms, thrombus involving most of the subclavian vein and the axillary vein, symptoms for <14 days, good functional status, life expectancy of ≥ 1 year, and low risk for bleeding (Table 11). If thrombolysis is used, in order to reduce the dose of thrombolytic therapy and the associated risk of bleeding, we encourage catheter-based therapy over systemic thrombolysis. In addition, because the balance of risks and benefits with all forms of thrombolytic therapy is uncertain, anticoagulant therapy alone is acceptable initial therapy in all patients with UEDVT. There is no evidence to suggest that thrombolysis reduces the risk of recurrent VTE.

Resection of the first rib has been advocated when UEDVT is believed to have been due to entrapment of the subclavian vein as it passes between the clavicle and the first rib.[6,386,411-421] Insertion of a filter in the superior vena cava has also been used in patients with acute UEDVT who cannot be given anticoagulants. Complications, however, may be more than with IVC filters.[389,413,422] The evidence in support of these procedures is of low quality, and because there is the potential to cause harm, their use should be confined to exceptional circumstances in specialized centers.

Recommendations

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C)**.**

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B)**.**

9.3 Long-term Anticoagulation for UEDVT

No randomized studies have evaluated duration or intensity of long-term anticoagulation in patients with UEDVT. In prospective observational studies, patients with UEDVT generally were treated with VKA (target INR 2.5) for periods of 3 to 6 months.[393,399-401,423] Rates of recurrent VTE and PTS varied (Tables S50 and S51), but as previously noted, these rates generally were lower than those observed in patients with leg DVT.

The factors that influence long-term anticoagulation in patients with leg DVT (section 3.1) are relevant to long-term treatment of UEDVT. Some differences between UEDVT and leg DVT are worthy of emphasis, especially that UEDVT often is associated with a central venous catheter that may or may not be removed (section 9.0). The most important continuing risk factors for UEDVT are (1) the presence of a central venous catheter in the same arm and (2) active cancer in patients with UEDVT not associated with a central venous catheter.

Another important distinction between UEDVT and leg DVT relates to long-term anticoagulation in patients with unprovoked thrombosis. Because the risk of recurrent VTE is substantially lower in patients with UEDVT compared with in those with proximal leg DVT,[387,388,393,395] we discourage extended anticoagulant therapy (ie, beyond 3 months) in patients with an unprovoked UEDVT.

No data are available for the long-term use of LMWH monotherapy or newer anticoagulants for the long-term treatment of UEDVT. We make the same recommendations for choice of initial, long-term, and extended anticoagulant regimens for UEDVT as for leg DVT (recommendations 3.1.1, 3.1.2, and 3.1.4) and note that the supporting evidence for these weak recommendations is further weakened in this population because of indirectness.

Recommendations

9.3.1. In most patients with UEDVT that is associated with a 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)**.**

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B)**.**

Remarks: This recommendation also applies if the UEDVT is associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B)**, and we suggest this in patients with cancer** (Grade 2C)**.**

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C)**, and we suggest this in patients with no cancer** (Grade 2C)**.**

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B)**.**

9.4 Prevention of PTS of the Arm

PTS of the arm occurs in ~20% of patients after treatment for UEDVT[38,395,396] and can be a disabling condition that adversely affects quality of life, particularly if the dominant arm is involved.[410,424] No randomized trials have evaluated compression bandages, compression sleeves, or venoactive drugs to prevent PTS after UEDVT. We have not considered indirect evidence from the legs for use of compression therapy to prevent PTS of the arms because (1) the pathophysiology of PTS is believed to be different in the arms than in the legs (less dependent venous hypertension), (2) arm sleeves are more difficult to fit than stockings, and (3) PTS occurs less often after UEDVT than after leg DVT.

Recommendation

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C)**.**

9.5 Treatment of PTS of the Arm

Symptoms of PTS of the arm include swelling, heaviness, and limb fatigue with exertion.[395,410] No randomized trials have evaluated compression bandages, compression sleeves (as are used for lymphedema), or venoactive drugs to treat PTS after UEDVT. We considered anecdotal evidence that compression therapy benefits some patients with PTS of the arm and that the benefits of a trial of compression therapy will outweigh its harms and costs. There is no evidence that venoactive drugs are of benefit in PTS of the arm.

Recommendations

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C)**.**

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C)**.**

10.0 Splanchnic Vein Thrombosis

Thrombosis in the portal venous system, which includes the superior mesenteric, inferior mesenteric, splenic, and portal veins, is collectively termed *splanchnic vein thrombosis*. Depending on the location and extent of thrombosis, how rapidly thrombosis develops, speed and extent of thrombus recannulation, presence of collateral portal venous drainage, and adequacy of arterial inflow, splanchnic vein thrombosis may result in bowel or splenic infarction and chronic portal hypertension.[425-430] Acute and chronic splanchnic vein thrombosis may be symptomatic, but many episodes are detected incidentally in imaging studies performed for other indications, such as assessing response to surgical or medical therapy in patients with cancer.[348,429] Limited understanding of the natural history of both symptomatic and incidentally detected splanchnic vein thrombosis in patients who are not treated with anticoagulants (ie, frequency of bowel infarction, development of portal hypertension, recurrence), a paucity of data from prospective cohort studies,[428,431] and a lack of randomized trials of standardized anticoagulant therapy for splanchnic vein thrombosis result in uncertainty about the role of anticoagulation for this condition. Increased risk of bleeding associated with esophageal varices (secondary to portal hypertension), thrombocytopenia (secondary to hypersplenism), and the presence of cirrhosis and malignancy (which predispose to splanchnic vein thrombosis) add to this uncertainty.

A number of retrospective,[425,429,430] and two prospective,[428,431] studies suggested that bowel ischemia is uncommon in patients with symptomatic splanchnic vein thrombosis who are treated with anticoagulants (~2%[428]), that recurrent venous thrombosis (both involving the splanchnic and nonsplanchnic veins) is common without anticoagulation or after stopping anticoagulation (~5% per year[425,429,430]), and that anticoagulation is effective at preventing progression and recurrent thrombosis,[425,428-431] although it is associated with an increased (particularly GI), but usually acceptable, frequency of bleeding.[428-431] Efficacy of anticoagulant therapy in other forms of symptomatic venous thrombosis also provides indirect evidence for anticoagulation of patients with symptomatic splanchnic vein thrombosis and, supported by the previously noted observational studies, this evidence is of moderate quality. We are not aware of studies of treated or untreated asymptomatic splanchnic vein thrombosis.

Factors that may encourage anticoagulant therapy in patients with incidental splanchnic vein thrombosis include extensive thrombosis that appears to be acute (eg, not present on a previous imaging study, presence of an intraluminal filling defect, lack of cavernous transformation), progression of thrombosis on a follow-up imaging study, and ongoing cancer chemotherapy. Esophageal varices secondary to acute portal vein thrombosis are not necessarily a contraindication to anticoagulant therapy because such treatment may improve the portal hypertension. LMWH may be preferred over VKA if there is active malignancy, liver disease, or thrombocytopenia.[431] The presence of a reversible provoking factor for splanchnic vein thrombosis, such as intraabdominal sepsis or recent surgery, supports stopping anticoagulant therapy after 3 months. Absence of a reversible risk factor (eg, "unprovoked" thrombosis or presence of a persistent risk factor, such as myeloproliferative disease) and a low risk of bleeding support extended anticoagulant therapy.

Recommendations

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B)**.**

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

11.0 Hepatic Vein Thrombosis

Hepatic vein thrombosis, particularly Budd-Chiari syndrome with occlusion of the main hepatic vein, can result in impairment of liver function and an associated coagulopathy.[432,433] Because there is limited understanding of the natural history of this condition and a paucity of prospective studies that have evaluated anticoagulant therapy, the role of anticoagulant therapy is uncertain.[432]

In a prospective registry of 163 patients with Budd-Chiari syndrome of variable extent, of whom 86% were treated with anticoagulation, one-half of patients did not require invasive interventions (ie, transjugular intrahepatic portosystemic shunting in 34% of all patients, surgical portosystemic shunting in 2% of patients, liver transplantation in 12% of patients), and survival was 82% after 2 years.[432] In an earlier retrospective study of 237 patients with Budd-Chiari syndrome performed when use of surgical portosystemic shunting was common (49% of patients), use of anticoagulant therapy (72% of patients) had no apparent effect on survival (RR, 1.05; 95% CI, 0.62-1.76).

Factors that encourage anticoagulant therapy in patients with incidental hepatic vein thrombosis include extensive thrombosis that appears to be acute (eg, not present on a previous imaging study, presence of an intraluminal filling defect), progression

of thrombosis on a follow-up imaging study, and ongoing cancer chemotherapy. Coagulopathy due to liver dysfunction caused by hepatic vein thrombosis is not a contraindication to anticoagulant therapy because anticoagulants may improve hepatic function. LMWH usually will be preferred to VKA therapy when there is hepatic dysfunction and if there is active malignancy. Presence of a reversible provoking factor for hepatic vein thrombosis, such as oral contraceptive therapy, encourages a time-limited course of therapy. Absence of a reversible risk factor encourages the use of extended therapy. Treatment of hepatic vein obstruction is complex and best undertaken by a multidisciplinary team.

Recommendations

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C)**.**

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

12.0 Future Research

Several questions in the treatment of VTE need to be answered. Current evidence relating to these questions is of moderate or low quality. We list the questions roughly as they arise in this article rather than in order of importance. We do not present the rationale for each question because this is addressed in the corresponding sections of the article. We have confined ourselves to the primary question (eg, Should patients with proximal DVT be treated with anticoagulant therapy alone, or should they be treated with pharmacomechanical CDT?); however, once the primary question is answered, we anticipate that secondary questions will need to be addressed (eg, Which patients with proximal DVT should, or should not, be treated with CDT?). We are pleased to note that many of the these questions are being addressed in ongoing trials.

- Should patients with an isolated distal DVT routinely be treated with anticoagulant therapy, or should they have serial testing to determine whether the DVT is extending and only be treated if extension is detected?
- Should patients with proximal DVT be treated with anticoagulant therapy alone, or should they be treated with pharmacomechanical CDT?
- Which patients with unprovoked proximal DVT or PE or cancer-associated VTE should stop anticoagulant therapy at 3 months, and which should remain on extended anticoagulant therapy?
- Which patients with unprovoked VTE or cancer-associated VTE have an unacceptable risk of bleeding if they remain on extended anticoagulant therapy?
- How should risk of recurrent VTE if anticoagulant therapy is stopped be balanced against risk of bleeding is anticoagulant therapy is continued?
- What is the preferred anticoagulant regimen for the short- and long-term treatment of VTE in patients with and without cancer?
- Should patients receiving an incidental diagnosis of asymptomatic VTE routinely be treated with anticoagulant therapy, or should they have serial testing to determine whether they have evolving DVT and only be treated if this is detected?
- Should patients with symptomatic DVT routinely wear graduated compression stockings from the time of diagnosis, or should stockings be used selectively (eg, in selected patients, in patients whose symptoms do not rapidly resolve)?
- Should patients with PE that causes right ventricular dysfunction be treated with anticoagulant therapy alone, or should they be treated with thrombolytic therapy?
- If patients have catheter-associated UEDVT and the catheter is removed, should they be treated with anticoagulant therapy or can they be treated without anticoagulant therapy?
- Can UEDVT be treated with less-intense or a shorter duration of anticoagulant therapy than leg DVT?

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Dr Kearon: served as Deputy Editor.
Dr Akl: served as Topic Editor.
Dr Comerota: served as a panelist.
Dr Prandoni: served as a panelist.
Dr Bounameaux: served as a panelist.
Dr Goldhaber: served as a panelist.
Dr Nelson: served as a frontline clinician.
Dr Wells: served as a panelist.
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Dr Dentali: served as a panelist.
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CHEST Online Data Supplement

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Anthony J. Comerota, MD; Paolo Prandoni, MD; Henri Bounameaux, MD; Samuel Z. Goldhaber, MD, FCCP; Michael Nelson, MD, FCCP; Philip Wells, MD; Michael K. Gould, MD, MS, FCCP; Francesco Dentali, MD; Mark Crowther, MD; and Susan R. Kahn, MD

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Table S1—*[Section 2.1] Evidence Profile: Parenteral Anticoagulation vs No Parenteral Anticoagulation in Acute VTE*[a]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Parenteral Anticoagulation	With Parenteral Anticoagulation	Relative Effect (95% CI)	Risk With No Parenteral Anticoagulation	Risk Difference With Parenteral Anticoagulation (95% CI)
Mortality (important outcome)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Moderate[b,c] due to imprecision	2/60 (3.3)	1/60 (1.7)	RR 0.5 (0.05-5.37)	33 per 1,000	16 fewer per 1,000 (from 31 fewer to 144 more)
Recurrent VTE (critical outcome; assessed with symptomatic extension or recurrence)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[b,d] due to imprecision	12/60 (20)	4/60 (6.7)	RR 0.33 (0.11-0.98)	200 per 1,000	134 fewer per 1,000 (from 4 fewer to 178 fewer)
Major bleeding (critical outcome)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Moderate[b,c] due to imprecision	3/60 (5)	2/60 (3.3)	RR 0.67 (0.12-3.85)	50 per 1,000	16 fewer per 1,000 (from 44 fewer to 142 more)

Bibliography: Brandjes et al.[1] RR = risk ratio.

[a] Both groups treated with acenocoumarol.

[b] Study described as double blinded; outcome adjudicators blinded. None of the study participants were lost to follow-up. Intention-to-treat analysis. Study was stopped early for benefit.

[c] CI includes values suggesting no effect as well as values suggesting either appreciable benefit or appreciable harm.

[d] Low number of events caused by the early stoppage of the trial.

Table S2—*[Section 2.4] Evidence Profile: Early Warfarin (and Shorter Duration Heparin) vs Delayed Warfarin (and Longer Duration Heparin) for Acute VTE*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Delayed Warfarin Initiation (and Longer Duration Heparin)	With Early Warfarin Initiation (and Shorter Duration Heparin)	Relative Effect (95% CI)	Risk With Delayed Warfarin Initiation (and Longer Duration Heparin)	Risk Difference With Early Warfarin Initiation (and Shorter Duration Heparin) (95% CI)
Mortality (important outcome[e])											
688 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[g,h] due to imprecision	13/338 (3.8)	12/350 (3.4)	RR 0.9 (0.41-1.95)	24 per 1,000[i]	2 fewer per 1,000 (from 14 fewer to 23 more)
Recurrent VTE (critical outcome)											
688 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[g,h] due to imprecision	14/338 (4.1)	12/350 (3.4)	RR 0.83 (0.4-1.74)	47 per 1,000[i]	8 fewer per 1,000 (from 28 fewer to 35 more)
Major bleeding (critical outcome)											
688 (3 studies), 3 mo[j]	No serious risk of bias[g,k]	No serious inconsistency	No serious indirectness	No serious imprecision[l]	Undetected	High[g,k,l]	10/338 (3.0)	15/350 (4.3)	RR 1.48 (0.68-3.23)	16 per 1,000[i]	14 more per 1,000 (from 9 fewer to 66 more)

Bibliography: Gallus et al,[2] Hull et al,[3] Leroyer et al.[4] Excluded Mohiuddin et al[5] because 34% of subjects had mural thrombus rather than VTE, in addition to major methodologic limitations).
LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist. See Table S1 legend for expansion of other abbreviation.

[a] VKA therapy started within 1 day of starting heparin therapy (UFH in two studies and LMWH in one study).

[b] VKA therapy delayed for 4 to 10 d.

[c] Most patients had proximal DVT, some had isolated distal DVT; most DVT were symptomatic (asymptomatic DVT included in Hull et al), and few had PE (only included in Gallus et al).

[d] The early initiation of VKA was associated with a lower number of days of heparin therapy (4.1 vs 9.5 in Gallus et al; 5 vs 10 in Hull et al) and a lower number of days of hospital stay (9.1 vs 13.0 in Gallus; 11.7 vs 14.7 in Hull; 11.9 vs 16.0 in Leroyer et al).

[e] Differences in death, independently of differences in recurrent VTE and major bleeding, is unlikely.

[f] Outcome assessment was at hospital discharge in the study by Gallus et al (although there was also extended follow-up) and 3 mo in the studies by Hull et al and Leroyer et al.

[g] Patients and investigators were not blinded in two studies (Gallus et al and Leroyer et al) and were blinded in one study (Hull et al). Concealment was not clearly described but was probable in the three studies. Primary outcome appears to have been assessed after a shorter duration of follow-up in the shorter treatment arm of one study because of earlier discharge from the hospital, and 20% of subjects in this study were excluded from the final analysis postrandomization (Gallus).

[h] The 95% CI on relative effect includes both clinically important benefit and clinically important harm.

[i] Event rate corresponds to the median event rate in the included studies.

[j] Bleeding was assessed early (in hospital or in the first 10 d) in two studies (Gallus et al, Hull et al) and at 3 mo in one study (Leroyer et al).

[k] It is unclear whether bleeding was assessed at 10 d in all subjects or just while heparin was being administered, which could yield a biased estimate in favor of short-duration therapy in one study (Hull et al).

[l] Because the shorter duration of heparin therapy is very unlikely to increase bleeding, the wide 95% CIs around the relative effect of shorter therapy on risk of bleeding is not a major concern.

Table S3—*[Section 2.5.1] Evidence Profile: LMWH vs SC UFH for Initial Anticoagulation of Acute VTE*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With SC UFH	With LMWH	Relative Effect (95% CI)	Risk With SC UFH	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
1,566 (3 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[a,b] due to imprecision	31/780 (4)	34/786 (4.3)	RR 1.1 (0.68-1.76)	33 per 1,000[c]	3 more per 1,000 (from 11 fewer to 25 more)
Recurrent VTE (critical outcome)											
1,563 (3 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[a,b] due to imprecision	31/777 (4)	26/786 (3.3)	RR 0.87 (0.52-1.45)	42 per 1,000[c]	5 fewer per 1,000 (from 20 fewer to 19 more)
Major bleeding (critical outcome)											
1,634 (4 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[b,c] due to imprecision	15/815 (1.8)	19/819 (2.3)	RR 1.27 (0.56-2.9)	16 per 1,000[c]	4 more per 1,000 (from 7 fewer to 30 more)

Bibliography: Lopaciuk et al,[21] Faivre et al,[2] Prandoni et al,[23] Kearon et al.[24] SC = subcutaneous. See Table S1 and S2 legends for expansion of other abbreviations.

[a] In the two largest trials (Prandoni et al and Kearon et al, 87% of patients), allocation was concealed, outcome adjudicators and data analysts were concealed, analysis was intention to treat, and there were no losses to follow-up.

[b] Precision judged from the perspective of whether SC heparin is noninferior to LMWH. The total number of events and the total number of participants are relatively low.

[c] Event rate corresponds to the median event rate in the included studies.

Table S4—*[Section 2.5.1] LMWH vs SC UFH for Initial Anticoagulation of Acute VTE: Clinical Description and Results*

Author/Year (Acronym)	Interventions	Patients Analyzed[a]	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Lopaciuk et al[21]/1992	UFH 5,000 units IV followed by 250 units/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%. Primary outcome was repeat venography.
	Fraxiparine 97 International Units/kg SC bid for 10 d	74/74	0/74 RR 3.1 (0.1-7.5)	0/74RR 3.1 (0.1-7.5)	0/74RR 7.2 (0.4-137)	
Faivreet al[22]/1988	UFH 5,000 units IV followed by 250 units/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). Primary outcome was repeat venography.
	CY222 2,000 International Units IV followed by 150 International Units/kg SC bid for 10 d	30/33	1/33 RR 0.9 (0.1-14.5)	0/33 RR 6.6 (0.3-123)	0/33 RR 2.8 (0.1-67)	
Prandoni et al[23]/2004 (Galilei)	UFH IV (<50 kg: 4,000 units; 50-70 kg: 5,000 units; >70 kg: 6,000 units) followed by SC bid doses (initially <50 kg: 12,500 units; 50-70 kg: 15,000 units; >70 kg: 17,500 units) adjusted to aPTT for ~6.5 d	360/360	15/360 (4.2%)	5/360 (1.4%)	12/360 (3.3%)	Population: Proximal DVT in 65%, distal DVT in 18%, and PE in 17%.
	Nadroparin 85 International Units/kg SC bid for ~6.5 d	360/360	14/360 (3.9%) RR 1.1 (0.5-2.2)	7/360 (1.9%) RR 0.7 (0.2-2.2)	12/360 (3.3%) RR 1.0 (0.5-2.2)	
Kearon et al[24]/2006 (FIDO)	UFH 333 units/kg SC followed by 250 units/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%, and PE in 19%. Seventy percent of patients were treated entirely as an outpatient (76% of DVT and 39% of PE) Postrandomization exclusions in 10 patients receiving UFH and one patient receiving LMWH.
	Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d	352/353	12/352 (3.4%) RR 1.1 (0.5-2.3)	12/352 (3.4%) RR 0.5 (0.2-1.3)	22/352 (6.3%) RR 0.8 (0.4-1.5)	

aPTT = activated prothrombin time; FIDO = Fixed Dose Heparin. See Table S1 and S2 legends for expansion of other abbreviations.

[a]Follow-up was for 3 mo except for the study by Faivre et al[22] in which it was 10 d.

Table S5—*[Section 2.5.1] LMWH vs SC UFH for Initial Anticoagulation of Acute VTE: Methodologic Quality*

Author/Year (Acronym)	Interventions	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Lopaciuk et al[21]/1992	UFH 5,000 units IV followed by 250 units/kg SC bid initially and adjusted to aPTT for 10 d Fraxiparine 97 International units/kg SC bid for 10 d	RCT	PY	Patients: CN Caregivers: CN Adjudicators: CN Data Analysts: PN	Not described	ITT	
Faivre et al[22]/1988	UFH 5,000 units IV followed by 250 units/kg SC bid and adjusted to aPTT for 10 d CY222 2,000 International Units IV followed by 150 International Units/kg SC bid for 10 d	RCT	PN	Patients: PN Caregivers: PN Adjudicators: PN Data Analysts: PN	Three of CY222 group and six of UFH group who did not have repeat venography are assumed to have completed clinical follow-up	ITT	
Prandoni et al[23]/2004 (Galilei)	UFH IV (<50 kg: 4,000 units; 50-70 kg: 5,000 units; >70 kg: 6,000 units) followed by SC bid doses (initially <50 kg: 12,500 units; 50-70 kg: 15,000 units; >70 kg: 17,500 units) adjusted to aPTT for ~6.5 d Nadroparin 85 International Units/kg SC bid for ~6.5 d	RCT	CY	Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY	Nil	ITT	
Kearon et al[24]/2006 (FIDO)	UFH 333 units/kg SC followed by 250 units/kg SC bid (no adjustment) for 6.3 d Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d	RCT	CY	Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY	Nil	ITT	Postrandomization exclusions from the efficacy analysis were 10 (2.8%) for the UFH and one (0.2%) for the LMWH group.

CN = certainly no; CY = certainly yes; ITT = intention to treat; PN = probably no; PY = probably yes; RCT = randomized controlled trial. See Table S1, S2, and S4 legends for expansion of other abbreviations.

Table S6—*[Section 2.5.1] Evidence Profile: LMWH vs IV UFH for Initial Anticoagulation of Acute VTE*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With IV UFH	With LMWH	Relative Effect (95% CI)	Risk With IV UFH	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
7,908 (17 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	Low[a,b] due to risk of bias, publication bias	232/3,789 (6.1)	187/4,119 (4.5)	RR 0.79 (0.66-0.95)	46 per 1,000[c]	10 fewer per 1,000 (from 2 fewer to 16 fewer)
Recurrent VTE (critical outcome)											
7,976 (17 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	Low[a,b] due to risk of bias, publication bias	208/3,869 (5.4)	151/4,107 (3.7)	RR 0.72 (0.58-0.89)	55 per 1,000[c]	15 fewer per 1,000 (from 6 fewer to 23 fewer)
Major bleeding (critical outcome)											
6,910 (20 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[d]	Reporting bias strongly suspected[b]	Low[a,b,d] due to risk of bias, publication bias	69/3,517 (2)	41/3,393 (1.2)	RR 0.67 (0.45-1)	15 per 1,000[c]	5 fewer per 1,000 (from 8 fewer to 0 more)

Bibliography: van Dongen et al.[6] Included studies.[7,20] See Table S1 and S2 legends for expansion of abbreviations.

[a] Of the 20 trials, allocation was concealed in nine and was unclear whether concealed in the remaining 11. Eighteen trials had blinded outcome assessors. Seven trials did not have any postrandomization exclusions or losses to follow-up. Ten trials reported the number of participants lost to follow-up, which ranged from 1.0% to 12.7%. One trial did not report the drop-outs.

[b] Inverted funnel plot very suggestive of publication bias. Many of the included studies are of small size, and all are funded by industry.

[c] Event rate corresponds to the median event rate in the included studies.

[d] CI interval includes values suggesting significant benefit and no effect.

Table S7—*[Section 2.5.1] Evidence Profile: Fondaparinux vs LMWH for Initial Anticoagulation of Acute DVT*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With LMWH	With Fondaparinux	Relative Effect (95% CI)	Risk With LMWH	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	33/1,107 (3.0)	41/1,098 (3.7)	RR 1.25 (0.8-1.97)	30 per 1,000	7 more per 1,000 (from 6 fewer to 29 more)
Recurrent VTE (critical outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	45/1,107 (4.1)[f]	43/1,098 (3.9)[f]	RR 0.96 (0.64-1.45)	41 per 1,000[f]	2 fewer per 1,000 (from 15 fewer to 18 more)
Major bleeding (critical outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	13/1,107 (1.2)[g]	12/1,098 (1.1)[g]	RR 0.93 (0.43-2.03)	12 per 1,000[g]	1 fewer per 1,000 (from 7 fewer to 12 more)

Bibliography: Büller et al.[25] INR = international normalized ratio. See Table S1 and S2 legends for expansion of other abbreviations.

[a] Fondaparinux 7.5 mg (5.0 mg in patients weighing < 50 kg and 10.0 mg in patients weighing > 100 kg) SC once daily for at least 5 d and until VKAs induced an INR > 2.0.
Enoxaparin 1 mg/kg of body weight SC bid for at least 5 d and until VKAs induced an INR > 2.0.

[c] All patients had acute symptomatic DVT.

[d] Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Analysis excluded 0.6% of randomized patients. Not stopped early for benefit.

[e] CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f] Five fatal VTE in fondaparinux group and five fatal VTE in LMWH group.

[g] Twelve patients in the fondaparinux group and 13 in the LMWH group had a major bleeding during the initial period (7 d). Of these, two in the fondaparinux group and none in the LMWH group were fatal.

Table S8—*[Section 2.5.2] Evidence Profile: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Bid	With LMWH Once	Relative Effect (95% CI)	Risk With Bid	Risk Difference With LMWH Once (95% CI)
Mortality (important outcome)											
1,261 (3 studies), 3 mo	No serious risk of bias[c]	Serious[d]	No serious indirectness	Serious[e]	Undetected	Low[c-e] due to inconsistency, imprecision	20/647 (3.1)	20/614 (3.3)	RR 1.05 (0.57-1.94)	31 per 1,000	2 more per 1,000 (from 13 fewer to 29 more)
Recurrent VTE (critical outcome)											
1,261 (3 studies), 3 mo	No serious risk of bias[c]	Serious[f]	No serious indirectness	Serious[e]	Undetected	Low[c,e,f] due to inconsistency, imprecision	32/647 (4.9)	26/614 (4.2)	RR 0.86 (0.52-1.42)	49 per 1,000	7 fewer per 1,000 (from 24 fewer to 21 more)
Major bleeding (critical outcome)											
1,522 (5 studies), 10 d	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[c,e] due to imprecision	9/772 (1.2)	10/750 (1.3)	RR 1.13 (0.48-2.66)	12 per 1,000	2 more per 1,000 (from 6 fewer to 20 more)

Bibliography: van Dongen et al.[26] See Table S1, S2, and S5 legends for expansion of other abbreviations.

[a] The five included studies used four brands of LMWH (enoxaparin, tinzaparin, dalteparin, and nadroparin). In Merli et al, enoxaparin 1 mg/kg bid was compared with 1.5 mg/kg once daily. Holmström[27] et al adjusted the dose to anti-Xa levels, which resulted in different daily doses after a number of days. In the remaining studies, the dose of the once-daily administration was double the dose of the twice-daily administration (equal total daily dose).

[b] Of the five included studies, one included patients with PE and DVT, and four included only patients with DVT. All studies addressed the initial management of VTE.

[c] All included studies concealed allocation. Two studies had a double-blind design, and two others were single blind. One study did not mention blinding. ITT likely used in all studies. Participants were lost to follow-up in only two studies (0.3% and 2.2%).

[d] $I^2 = 37\%$; point effect estimate in favor of bid dose in Merli et al[16] and in favor of once-daily dose in Charbonnier et al.[28]

[e] Imprecision judged relative to no difference.

[f] $I^2 = 65\%$; point effect estimate in favor of bid dose in Merli et al[16] and in favor of once-daily dose in Charbonnier et al.[28]

Table S9—*[Section 2.7] Evidence Profile: Home Treatment vs Hospital Treatment of Acute DVT*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Hospital Treatment	With Home Treatment	Relative Effect (95% CI)	Risk With Hospital Treatment	Risk Difference With Home Treatment (95% CI)
Mortality (important outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	Serious[f]	Undetected	Low[a,b,e,f] due to indirectness, imprecision	39/851 (4.6)	28/857 (3.3)	RR 0.72 (0.45-1.15)	46 per 1,000	13 fewer per 1,000 (from 25 fewer to 7 more)
Recurrent VTE (critical outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	No serious imprecision	Undetected	Moderate[a,b,e] due to indirectness	63/851 (7.4)	39/857 (4.6)	RR 0.61 (0.42-0.9)	74 per 1,000	29 fewer per 1,000 (from 7 fewer to 43 fewer)
Major bleeding (critical outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	Seriousf	Undetected	Moderate[a,b,e,g] due to indirectness	18/851 (2.1)	12/857 (1.4)	RR 0.67 (0.33-1.36)	21 per 1,000	7 fewer per 1,000 (from 14 fewer to 8 more)
Quality of life (important outcome)											
0 (3 studies[h]), 3 mo	No serious risk of bias	No serious inconsistency[i]	Serious[j]	Seriousk	Undetected	Low[i-k] due to indirectness, imprecision	…	…	Not pooled	See comment[h-k]	See comment[h-k]

Bibliography: Othieno et al[29]; included studies.[13,14,30-33] Quality of life.[13,34,35] See Table S1 and S2 for expansion of abbreviations.

[a] Four studies had partial hospital treatment of many in the home arm: Koopman et al (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm), Levine et al (2.1 vs 6.5 d), Boccalon et al (1 vs 9.6 d), and Ramacciotti et al (3 vs 7 d). In Daskalopoulos et al, there was no hospital stay at all in the home group. Chong et al did not report duration of hospital stay.

[b] Only one study (Boccalon et al) used LMWH in both treatment arms. Remaining studies used UFH in the inpatient arm and LMWH in the outpatient arm.

[c] Studies included in the systematic review should have recruited patients whose home circumstances were adequate.

[d] All studies included patients with lower-extremity DVT and excluded patients with suspected or confirmed PE. Studies also excluded patients who were pregnant.

[e] Out of six studies, allocation was clearly concealed in three (unclear in remaining three). Outcome adjudicators were blinded in the two largest studies (unclear in remaining). Four reported loss to follow-up (was significant in only a small study). ITT analysis was conducted in four (unclear in remaining two). No study was stopped early for benefit. Overall, the judgment was that these limitations would not warrant downgrading of quality because it has already been downgraded by at least one level based on other factors.

[f] The CI includes both values suggesting benefit and harm.

[g] Judged as precise based on the narrow CI around absolute effect.

[h] Bäckman et al[34] reported evaluation of health-related quality of life using the EQ-5D. They found no differences in mean quality-of-life scores or in the proportion of patients showing improvement in self-rated health state. Koopman et al evaluated health-related quality of life using the Medical Outcome Study Short Form-20 and an adapted version of the Rotterdam Symptom Checklist. The changes over time were similar in both groups except that the patients receiving LMWH had better scores for physical activity ($P = .002$) and social functioning ($P = .001$) at the end of the initial treatment. The authors did not report enough data to assess precision and clinical significance of results. O'Brien et al[35] assessed changes in quality of life using the Medical Outcome Study Short Form-36 in 300 patients participating in Levine et al.[14] They found that, the change in scores from baseline to day 7 was not significantly different between the treatment groups for seven of the eight domains. The one exception was the domain of social functioning, where a greater improvement was observed for the outpatient group.

[i] Potential inconsistency as Bäckman et al[34] showed no effect, whereas Koopman et al[13] and O'Brien et al[35] showed potential benefit.

[j] Two of the three studies had partial hospital treatment of many in the home arm: Koopman et al[13] (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm) and Levine et al (2.1 vs 6.5 d).

[k] Not able to evaluate but imprecision is possible. Taken together with the potential inconsistency, we downgraded the quality of evidence by one level.

Table S10—*[Section 2.9] Evidence Profile: Catheter-Directed Thrombolysis vs No Catheter-Directed Thrombolysis for Extensive Acute DVT of the Leg*[ab]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Catheter-Directed Thrombolysis	With Catheter-Directed Thrombolysis	Relative Effect (95% CI)	Risk With No Catheter-Directed Thrombolysis	Risk Difference With Catheter-Directed Thrombolysis (95% CI)
Mortality (important outcome)											
153 (2 studies), 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	3/76 (3.9)[e]	0/77 (0)	RR 0.14 (0.01-2.71)	39 per 1,000[e]	34 fewer per 1,000 (from 39 fewer to 67 more)
Nonfatal recurrent VTE (critical outcome)											
153 (1 study), 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	1/76 (1.3)	0/77 (0)	RR 0.35 (0-8.09)	48 per 1,000[f]	31 fewer per 1,000 (from 48 fewer to 340 more)
Nonfatal major bleeding (critical outcome)											
153 (2 studies), 7 d	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	0/76 (0)	1/77 (1.3)[g]	RR 2.00 (0.19-19.46)	29 per 1,000[f,h]	29 more per 1,000 (from 23 fewer to 535 more)
Postthrombotic syndrome (critical outcome; assessed with: complete lysis on venography (Elsharawy et al); patency on ultrasound and air plethysmography (Enden et al))											
138 (2 studies), 2 y	No serious risk of bias[c]	No serious inconsistency	Serious[i]	No serious imprecision	Undetected	Moderate[c,i] due to indirectness	49/70 (70)	23/68 (33.8)	RR 0.46 (0-0.79)	588 per 1,000[j]	318 fewer per 1,000 (from 123 fewer to 588 fewer)[k]

(Continued)

Table S10—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Catheter-Directed Thrombolysis	With Catheter-Directed Thrombolysis	Relative Effect (95% CI)	Risk With No Catheter-Directed Thrombolysis	Risk Difference With Catheter-Directed Thrombolysis (95% CI)
Quality of life (important outcome; measured with the Medical Outcome Survey Short Form-12, Health Utilities Index MARK version 2/3 questionnaires; better indicated by lower values)											
98 (1 study[l]), 16 mo	No serious risk of bias[m,n]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low[m,n]	30	68	...		See footnote[o]

Bibliography: Elsharawy et al,[36] Enden et al,[37] Comerota et al.[38] CDT = catheter-directed thrombolysis; PTS = postthrombotic syndrome. See Table S1 legend for expansion of other abbreviations.

[a] All patients were anticoagulated per protocol, but the intervention group received CDT in addition to anticoagulation.

[b] In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for < 14 d, good functional status, life expectancy ≥ 1 y) who have a low risk of bleeding.

[c] Allocation was concealed in Enden et al and unclear in Elsharawy et al. Outcome assessor blinded in both studies. Follow-up rates were 87% in Enden et al and 100% in Elsharawy et al. None of the studies was stopped early for benefit.

[d] CI includes values suggesting both benefit and harm.

[e] Three control patients died of cancer.

[f] Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[39]

[g] In the Enden et al study, one patient had "durable and partial impairment of sensibility of the foot" immediately after receiving CDT, and nine patients had minor bleeding complications.

[h] Most of bleeding events occur during the first 7 d.

[i] Surrogate outcome: absence of patency at 6 mo in Enden et al study; absence of complete lysis at 6 mo in Elsharawy et al study.

[j] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[k] Severe PTS: assuming the same RR of 0.46 and a baseline risk of 13.8%, the absolute reduction is 75 fewer severe PTS per 1,000 (from 29 fewer to 138 fewer) over 2 y.

[l] Camerota et al.[38]

[m] Participation rate was 65%.

[n] Recall was used to measure quality of life prior to the thrombotic event; we did not consider these measurements.

[o] At the initial follow-up (mean, 16 mo), patients treated with CDT reported a trend toward a higher mental summary scale ($P = .087$) and improved Health Utilities Index ($P = .078$). They reported better overall role physical functioning ($P = .046$), less stigma ($P = .033$), less health distress ($P = .022$), and fewer overall symptoms ($P = .006$) compared with patients who were treated with anticoagulation alone.

Table S11—*[Section 2.9] CDT vs No CDT for Extensive Acute DVT of the Leg: Clinical Description and Results (All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Semba et al[41]/1994	Prospective registry	21 patients (27 limbs) with iliofemoral DVT ≤ 14 d (20) or > 14 d (7) duration	4.9 million units urokinase (mean) infused over 30 h (mean), followed by heparin and then warfarin for 8-12 wk Adjunctive therapy: limbs with residual stenoses > 50% received angioplasty (2) or stenting (14)	Clot lysis, complications	3 mo	Significant lysis: 18/25[a] (72%) Partial lysis: 5/25 (20%) No lysis: 2/25 (8%) Complications: 1 small hematoma at puncture site, no intervention/ transfusion
Verhaeghe et al[42]/1997	Prospective study	24 patients with iliofemoral DVT ≤ 14 d (16) or > 14 d (8) duration	3 mg/h rt-PA (mean 86 mg) infused with 1,000 U/h IV heparin, followed by heparin, adjusted to APTT Adjunctive therapy: hydrodynamic thrombectomy (3) and stents (9)	Clot lysis, bleeding	13 mo (mean)	Significant lysis: 19/24 (79%) Partial lysis: 5/24 (21%) Bleeding: 6/24 (25%) Patency: 3 mo: 84% 1 y: 78%
Bjarnason et al[43]/1997	Prospective registry	77 patients (87 limbs) with iliofemoral DVT ≤ 14 d (69) or > 14 d (18) duration	2,000-2,500 units/kg per h urokinase infused for 75 h (mean) with 5,000 International Units bolus heparin plus infusion adjusted to aPTT Adjunctive therapy: angioplasty (52 limbs), stent (38), AVF (15), surgical thrombectomy (13), mechanical thrombectomy (4), surgical bypass (3)	Clot lysis, PE, bleeding	1 y	Early results: Significant lysis: 69/87 (79%) Iliac (63%) Femoral (40%) No lysis: 18/87 (21%) PE: 1 (1%) Bleeding: major, 5/77 (6%); minor, 11/77 (14%) Patency at 1 y: Iliac: 63% Femoral, 40%

(Continued)

Table S11—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Mewissen et al[44]/1999 (National Multicenter Registry)	Prospective multicenter registry	287 patients (312 infusions) with lower limb DVT ≤ 10 d (188) or > 10 d (99) duration	7.8 million units urokinase (mean) infused for 53.4 h (mean) in 297 limbs In 6 limbs, only systemic infusion (no CDT) Adjunctive therapy: stents (104), systemic infusion (54)	Clot lysis, PE, bleeding, death	1 y	Early results: 50%-100% lysis: 258/312 (83%) <50% lysis: 54/312 (17%) PE: 6/473[b] (1%) Bleeding: 54/473[b] (11%) Death: 2/473[b] (< 1%) Patency at 1 y: Iliac: 64% Femoral: 47%
AbuRahma et al[45]/2001	Prospective study	51 patients (51 limbs) with iliofemoral DVT given choice between conventional therapy (heparin + warfarin) orlysis + angio/stent (if needed). Lysis offered only to patients with DVT ≤ 14 d duration and no contraindications	Anticoagulation: 33 patients given 1,000-2000 units/h heparin infusion for 5-7 d.	Clot lysis, PE, bleeding	Anticoag: 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: 18 patients given loading dose 4,500 units urokinase followed by 4,500 units/kg per h for 24-48 h or 4-8-mg bolus of rt-PA followed by 2-4-mg/h infusion Adjunctive therapy: patients with residual stenosis > 50% received stents (10)		CDT: 6 mo?	CDT: 30-d significant lysis: 15/18 (83%) 6-mo patency: 15/18 (83%) Bleeding: 2/18 (11%)
Elsharawy et al[36]/2002)	RCT, single center	35 patients with DVT < 10 d duration randomized to CDT or anticoagulation alone	CDT: 18 patients received ~1 million units SK pulse-spray for 1 h, followed by 100,000 units/h SK infusion until complete lysis, no change in 12 h, or complication Adjunctive therapy: angioplasty/stent (1)	Clot lysis, PE, bleeding	1 wk and 6 mo	CDT, 1 wk Complete lysis: 11/18 (61%) No lysis: 0 (0%) PE: 0 Bleeding: 0 Anticoagulation, 1 wk: Complete lysis: 0/17 (0%) No lysis: 17/17 (100%) PE: 1/17 (6%) Bleeding: 0

(Continued)

Table S11—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Anticoagulation: 17 patients received 5,000 units heparin bolus, followed by heparin adjusted to aPTT			CDT, 6 mo Complete lysis: 13/18 (72%) No lysis: 0 (0%) Anticoagulation, 6 mo Significant lysis:2/17 (12%) No lysis: 7/17 (41%)
Enden et al[37]/2009 (CaVenT)	RCT, multicenter	Iliofemoral DVT < 21 d duration	CDT: tPA 0.01 mg/kg per h, maximum of 20 mg/24 h for 4 d. Treated in four referral centers Anticoagulation alone: usual practice, administered locally	Clot lysis, PE, bleeding (PTS at 24 mo pending)	1 wk and 6 mo	CDT, 1 wk ≥50%lysis: 44/50 (68%) PE: 0 Major bleeding: 1/50 Anticoagulation, 1 wk: Lysis not assessed PE: 0 Major bleeding: 0 (puncture site nerve damage: 0) CDT, 6 mo Iliofemoral patency: 32/50 (64%) Anticoagulation, 6 mo Iliofemoral patency: 19/53 (36%)

Early prospective observational studies with < 20 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines.[46] AVF = arteriovenous fistula; CaVenT = Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase. See Table S2, S4, S5, and S10 legends for expansion of other abbreviations.

[a] Twenty-five of 27 limbs treated with CDT; two could not be crossed with the guidewire.

[b] Calculated from total number of patients in Venous Registry.

Table S12—*[Section 2.9] CDT vs No CDT for Extensive Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to follow-up
Semba et al[41]/1994	N/A	N/A	N/A	N/A
Verhaeghe et al[42]/1997	N/A	N/A	N/A	N/A
Bjarnason et al[43]/1997	N/A	N/A	N/A	N/A
Mewissen et al[44]/1999	N/A	N/A	N/A	N/A
AbuRahma et al[45]/2001	N/A	N/A	N/A	N/A
Elsharawy et al[36]/2002	Computer-designated cards	PN	N for patients, caregivers, and probably data analysts. Y for vascular imaging	0
Enden et al[37]/2009	Computer-designated cards	Y	No for patients and caregivers. Yes for vascular imaging.	One loss to follow-up (CDT), five withdrawals, five postrandomization exclusions

N = no; N/A = not applicable; Y = yes. See Table S10 legend for expansion of other abbreviation.

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Table S13—*[Section 2.10] Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg: Clinical Description and Results (Randomized Trials That Compared Systemic Thrombolytic Therapy With No Thrombolytic Therapy)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Browse et al[52]/1968	RCT, single center	10 patients with lower-extremity DVT confirmed by phlebography	Lysis: 600,000 units SK plus 100 mg hydrocortisone for first hour, then continued every 6 h for 3 d (5 patients) Anticoagulation: 4-6 hourly doses of heparin 5,000 units for 48 h followed by warfarin (5 patients)	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[53]/1968	RCT, single center	16 patients with DVT	Thrombolysis: SK 200,000 units over 90 min, then 100,000 units as maintenance dose for 22.5 h; heparin 500 mg given during 24 h, plus prednisone (8 patients) Anticoagulation: Heparin plus prednisone (8 patients)	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[54]/1969	RCT, single center	30 patients with DVT of <4 d	Thrombolysis: SK 500,000 units IV over 30 min; 900,000 units every 6 h $\times 5$ d (10 patients)	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%) Note: (1 patient excluded from treatment)

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Arvin: Arvin loading dose 80 units IV over 6 h; 80 units over 15 min; 40-80 units every 6 h × 5 d (10 patients) Anticoagulation: Heparin 10,000 units IV over 5 min, then 10,000-15,000 units every 6 h × 5 d (10 patients)			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)
Tsapogas et al[55]/1973	RCT, single center	34 patients with DVT of < 5 d	Thrombolysis: titrated initial dose of SK IV, then SK 100,000 units/h maintained and adjusted up to 72 h IV heparin for 1 wk 6-12 h post SK (19 patients) Anticoagulation: Heparin IV into affected limb, 7,000 units bolus then 1,500 units/h adjusted; continued for 7 d (15)	Clot lysis, PE, bleeding	7 d	Thrombolysis: Complete/partial lysis: 10/19 (53%) No lysis: 9/19 (47%) PE: 0 Minor bleeding: 3 (16%) Anticoagulation: Complete/partial lysis: 1/15 (7%) No lysis: 14/15 (93%) PE: 1/15 (7%) Bleeding: 0
Duckert et al[56]/1975	Prospective study	134 patients with acute or subacute DVT	Thrombolysis: initial dose SK calculated according to tolerance injected over 15-30 min; maintenance dose at 30 mL/h was two-thirds of first dose (92 patients) Anticoagulation: 5,000 units heparin for initial dose followed by 25,000 units/24 h infusion (42 patients).	Clot lysis, PE, bleeding	~7 d	Thrombolysis: Significant lysis: 39/92 (42%) Partial lysis: 23/92 (25%) No lysis: 30/92 (33%) PE: 7 (8%) Major bleeding: 58 (62%) Minor bleeding: 24 (26%)s Anticoagulation: Significant lysis: 0/42 (0%) Partial lysis: 4/42 (10%) No lysis: 38/42 (90%) PE: 5/42 (12%) Major bleeding: 2/42 (5%) Minor bleeding: 4/42 (10%)

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Porter et al[57]/1975	RCT, single center	50 patients with DVT < 14 d duration	Thrombolysis: SK 250,000 units IV over 30 min, then 100,000 units/h titrated for 72 h followed by IV heparin titrated over 7 d (23 patients) Anticoagulation: IV heparin 150 units/kg loading dose then titrated for 10 d (26 patients)	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[58]/1977	RCT, single center	24 patients with DVT	Thrombolysis: initial dose of 250,000 units SK for 20 min, followed by 100,000 units/h for 72 h (12 patients) Anticoagulation: initial dose heparin 150 units/kg IV, 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
Arnesen et al[59]/1978	RCT, single center	42 patients with proximal DVT of < 5 d.	Thrombolysis: loading dose of SK 250,000 units IV, then 100,000 International Units/h IV for 72-96 h (21 patients) Anticoagulation: heparin 15,000 International Units IV bolus, then total of 30,000 International Units IV infusion for 72-90 h (21 patients)	Clot lysis, PE, bleeding	21 d-6 y	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%)

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Elliot et al[60]/1979	RCT, single center	51 patients with clinical history of DVT of < 8 d	Thrombolysis: loading dose of SK 600,000 units infused over 30 min, followed by 100,000/h for 3 d; heparin for 4 d following SK (26 patients) Anticoagulation: heparin 10,000 units IV initially, followed by 10,000 units IV daily for a 6-h infusion to maintain clotting time of 2.5-3 times normal for 7 d (25 patients)	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[a] (60%) Treatment 2 Symptom-free: 2/21[b] (9%)
Watz et al[61]/1979	Prospective study	35 patients with DVT	Thrombolysis: initial dose of SK 250,000 units in 30 min, followed by maintenance 100,000 units/h (18 patients) Anticoagulation: heparin 45,000 units daily with warfarin (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%) Minor bleeding: 3/18 (12%) Anticoagulation: Significant lysis: 1/17 (6%) Partial lysis: 5/17 (29%) No lysis: 11/17 (65%) PE: 1/17 (6%) Minor bleeding: 2/17 (12%)

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Kiil et al[62]/1981	RCT, single center	20 patients with DVT of < 72 h	Thrombolysis: urokinase 200,000 units IV for 24 h; after 18 h, heparin loading dose of 15,000 units, then 40,000 units/d for 5 d (11 patients) Anticoagulation: heparin 40,000 units/day 4 for 6 d (9 patients)	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[63]/1982	Follow-up to RCT of Arnesen (1978)	35/42 patients from RCT	Phlebography and clinical examination by blinded evaluators	Normal legs, PTS symptoms	6.5 y	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[49]/1986	RCT, single center	36 patients with calf DVT of < 7 d	Thrombolysis: SK 50,000 International Units IV over 15 min, then 100,000 International Units over 12 h for up to 7 d, titrated; given with heparin 5,000 International Units IV over 12 h (17 patients) Anticoagulation: heparin 5,000 International Units IV for 15 min then 30,000 International Units/d, titrated over 7 d (19 patients)	Clot lysis, bleeding, PE	5 y	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[51]/1989	Prospective cohort study (A) and multicenter RTC (B)	32 patients with DVT of < 10 d	Study A: open-label study with rt-PA 100 mg over IV 8 h (day 1), 50 mg rt-PA over 8 h (day 2); 10% dose as bolus (11 patients)	Clot lysis, bleeding	72 h	Note: Authors assigned veins a relative value reflecting degree of thrombosis (maximum, 40 units: complete thrombosis). The unit scores reflect the reduction in thrombosis postlysis.

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Study B: rt-PA 100 mg: IV of 100 mL containing rt-PA 100 mg infused over 8 h (day 1), IV of 100 mL containing 50 mg rt-PA infused over 8 h (day 2); 10% dose as bolus (8 patients) 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 (6 patients) Placebo: IV of 100 mL containing placebo infused over 8 h on both days 1 and 2 (7 patients) Co-treatment: heparin 5,000 units IV bolus then continuous infusion 1,000 units/h for up to 72 h			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
Goldhaber et al[64]/1990	RCT, multicenter	64 patients (65 randomizations) with DVT of < 14 d	rt-PA: rt-PA 0.05 mg/kg per h IV for 24 h, then heparin 100 units/kg bolus, then 1,000 units/h, adjusted (36 patients) rt-PA + heparin: rt-PA as in group 1 plus heparin concomitantly (17 patients) Anticoagulation: heparin 100 units/kg bolus, then 1,000 units/h (12 patients)	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 + 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: 5/65 venograms not analyzed

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Turpie et al[50]/1990	RCT, multicenter	83 patients with DVT of <7 d	Phase 1: Lysis + heparin: two-chain rt-PA 0.5 mg/kg IV for 4 h (12 patients)	Clot lysis, bleeding	24-48 h	Phase 1: Lysis + heparin: ≥50% lysis: 7/12 (58%) <50% lysis: 2/12 (17%) No lysis: 3/12 (25%) Bleeding: 4/12 (33%)
			Placebo + heparin (12 patients)			Placebo + heparin: <50% lysis: 2/12 (17%) No lysis: 10/12 (83%) Bleeding: 1/12 (8%)
			Phase 2: Lysis + heparin: one-chain rt-PA 0.5 mg/kg IV for 8 h and repeated in 24 h (29 patients)			Phase 2: Lysis + heparin: ≥50% lysis: 6/29 (21%) <50% lysis: 7/29 (24%) No lysis: 15/29 (52%) Bleeding: 1/29 (3%)
			Placebo + heparin (30 pts)			Placebo + heparin ≥50% lysis: 2/30 (7%) <50 lysis:5/30 (17%) No lysis: 23/30 (77%) Bleeding: 1/30 (3%)
			Cotreatment: heparin 5,000-unit IV bolus then 30,000 units/24 h, adjusted for 7-10 d			
Schweizer et al[65]/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 given concomitantly; warfarin day 7-12 mo	7 d: clot lysis, bleeding 1 y: PTS symptoms	7 d and 1 y	rt-PA: Complete lysis: 6/22 (27%) Bleeding: 1/22 (5%) PTS symptoms: 14/22 (64%)
			Urokinase 100,000 International Units/hr IV into pedal vein continuously 7 d; heparin IV 7 d; plasminogen monitored; warfarin day 7-12 mo			Urokinase: Complete lysis: 11/22 (50%) Bleeding: 1/22 (5%) PTS symptoms: 9/22 (41%)

(Continued)

Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Anticoagulation: heparin IV adjusted for 7 d; warfarin day 1-12 mo			Anticoagulation: Complete lysis: 0 Bleeding: 0 PTS Symptoms: 15/22 (68%)
Schweizer et al[66]/2000	RCT, multicenter	250 patients with DVT of < 9 d	rt-PA: locoregional rt-PA 20 mg/day for 4 h through pedal vein for 4-7 d; IV heparin given simultaneously at 1,000 International Units/h, adjusted Urokinase: locoregional urokinase 100,000 International Units infused continuously; fibrinogen and plasminogen monitored; IV heparin given concomitantly Systemic SK: 3 million units/d for 6 h with heparin for up to 7 d. Premedications: hydrocortisone 100 mg, ranitidine 50 mg, clemastine 2 mg Systemic urokinase: 5 million International Units/d for 4 h up to 7 d; IV heparin given concomitantly Anticoagulation: heparin IV, adjusted. Cotreatment: bed rest, compression bandages, compression therapy, warfarin for 12 mo	Clot lysis, bleeding, mortality	1 y	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 SK: 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%)

See Table S1, S2, and S11 legends for expansion of abbreviations.

[a] Four deaths, other causes, two lost to follow-up.

[b] Four deaths, two PEs, two other causes.

Table S14—*[Section 2.10] Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg: Methods*

Author/Year	Randomization	Allocation concealment	Blinding	Loss to follow-up
Browse et al[52]/1968	N/A	N/A	N/A	0
Robertson et al[53]/1968	Patients given consecutive code numbers and divided into equal groups of 2—not truly randomized	Labels on SK and heparin coded	Y, data assessors; unclear for patients, caregivers, analysts	0
Kakkar et al[54]/1969	Sequential sealed envelope	Adequate	Y, patients No, caregivers, assessors, analysts	0
Tsapogas et al[55]/1973	Sealed envelope	Adequate	Not blinded	0
Duckert et al[56]/1975	N/A	N/A	N/A	N/A
Porter et al[57]/1975	Assigned at random to one of two groups	N/A	N/A	N/A
Marder et al[58]/1977	Assigned at random to one of two groups. Five-day follow-up venograms were not performed in 3 of the SK patients, so an additional 3 patients were added to SK group in nonrandomized fashion.	Unclear	Not blinded	23
Arnesen et al[59]/1978	Assigned at random to either group by sealed envelope	Adequate	Y, radiologic assessors No, patients, caregivers, analysts	0
Elliot et al[60]/1979	Assigned at random to one of two groups	Unclear	Y, assessors N, patients, caregivers, analysts	N/A
Watz et al[61]/1979	N/A	N/A	N/A	N/A
Kiil et al[62]/1981	Assigned at random to either group	Unclear	Y, assessors, analysts N, patients, caregivers	0
Arnesen et al[63]/1982	N/A	N/A	Evaluator blinded	7
Schulman et al[49]/1986	Assigned at random to either group by sealed envelope	Adequate	Single blind	0
Verhaeghe et al[51]/1989	Assigned at random to one of three groups	Unclear	Y, patients, assessors N, caregivers, analysts	0
Goldhaber et al[64]/1990	Assigned at random to one of three groups through sealed envelope	2:2:1 allocation scheme	Not blinded	0
Turpie et al[50]/1990	Assigned at random to one of two groups in each phase of study	Unclear	Y, patients, assessors N, caregivers, analysts	37
Schweizer et al[65]/1998	Assigned at random to one of three groups	Adequate	Y, assessors N, patients, caregivers, analysts	1
Schweizer et al[66]/2000	Assigned at random to one of five groups	Unclear	Single blind—not sure who	12

Y = yes. See Table S5 and S12 legends for expansion of other abbreviations.

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Table S15—*[Section 2.10] Evidence Profile: Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemic Lysis	With Systemic Lysis	Relative Effect (95% CI)	Risk With No Systemic Lysis	Risk Difference With Systemic Lysis (95% CI)
Mortality (important outcome)											
688 (5 studies), 3 mo[a]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness[c,d]	Very serious[e]	Undetected	Low[b-e] due to imprecision	5/233 (2.1)	4/455 (0.9)	RR 0.86 (0.27-2.68)	21 per 1,000	3 fewer per 1,000 (from 16 fewer to 36 more)
Nonfatal recurrent VTE (critical outcome)											
687 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness[d]	Very serious[e]	Undetected	Low[d,e,g] due to imprecision	2/233 (0.9)	10/454 (2.2)	RR 1.28 (0.25-6.68)	48 per 1,000[h]	13 more per 1,000 (from 36 fewer to 273 more)
Nonfatal major bleeding (critical outcome)											
688 (10 studies), 3 mo[f]	No serious risk of bias[i]	No serious inconsistency	No serious indirectness[c,d]	Serious	Undetected	Moderate[c,d,i] due to imprecision	10/234 (4.3)	38/454 (8.4)	RR 1.84 (0.94-3.59)	29 per 1,000[h,j]	24 more per 1,000 (from 2 fewer to 75 more)

(Continued)

Table S15—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemic Lysis	With Systemic Lysis	Relative Effect (95% CI)	Risk With No Systemic Lysis	Risk Difference With Systemic Lysis (95% CI)
Postthrombotic syndrome (critical outcome)											
678 (2 studies), 2 y[k]	Serious[l,m]	No serious inconsistency	No serious indirectness[d3]	Serious[e4]	Undetected	Low[d,e,l,m] due to risk of bias, imprecision	24/230 (10.4)	27/448 (6)	RR 0.71 (0.49-1.04)	588 per 1,000[n]	171 fewer per 1,000 (from 300 fewer to 24 more)[o]
Quality of life not measured											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Watson et al.[47] We excluded Elsharawy et al[36] from the analysis because it used catheter directed thrombolysis.[36] We identified no studies published since the search date of the systematic review. See Table S1, S10, and S11 legends for expansion of abbreviations.

[a] Range of follow-up in included studies, 1 to 72 mo.

[b] Allocation concealed in three of five studies. Follow-up inadequate in one of five (Common et al[48]). Excluding this study from the analysis does not change the effect estimate. All studies had blinded outcome assessors. None of the studies used a placebo control.

[c] The population of one study (Schulman et al[49]) consisted of patients with calf vein thrombosis.

[d] Interventions varied across studies with regard to agent (eg, tPA, SK, urokinase), dose, use of the pedal vein administration, duration of treatment, and concomitant drugs (eg, steroids). However, we did not downgrade for indirectness given that there is no standard regimen, and all analyses showed no heterogeneity in results.

[e] CI included both no effect and a potentially significant effect.

[f] Range of follow-up in included studies, 1 to 30 d.

[g] Allocation concealed in two of three studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used a placebo control.

[h] Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[39i]Allocation concealed in seven of 10 studies. Follow-up inadequate in one 10 studies (Common et al[48]). Excluding this study from the analysis does not affect the effect estimate. All studies had blinded outcome assessors. Two studies used placebo (Turpie et al; [50]Verhaeghe et al[51]).

[j] Only 4% of all major bleeding events were intracranial bleeds.

[k] Range of follow-up in included studies: 1 to 6 y.

[l] Allocation concealed in two of two studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used placebo control.

[m] No use of a standardized validated tool reported.

[n] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[o] Severe PTS: assuming the same RR of 0.71 and a baseline risk of 13.8%,[40] the absolute reduction is 40 fewer severe PTS per 1,000 (from 70 fewer to 6 more) over 2 y.

Table S16—*[2.11] Evidence Profile: Surgical Thrombectomy Vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg*[a]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Surgical Thrombectomy	With Surgical Thrombectomy	Relative Effect (95% CI)	Risk With No Surgical Thrombectomy	Risk Difference With Surgical Thrombectomy (95% CI)
Mortality not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Nonfatal recurrent VTE (critical outcome)											
51 (1 study), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness[c]	Very serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	1/27 (3.7)[d]	0/24 (0)	RR 0.37 (0.02-8.75)	48 per 1,000[d,e]	30 fewer per 1,000 (from 47 fewer to 372 more)
Nonfatal major bleeding (critical outcome)											
51 (1 study), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected	See comment	0/27 (0)	0/24 (0)[f]	Not estimable	See comment	…
PTS (critical outcome)											
51 (1 study), 2 y	Serious[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Low[g,h] due to risk of bias, imprecision	25/27 (92.6)	14/24 (58.3)	RR 0.63 (0.44-0.9)[i]	588 per 1,000[j]	218 fewer per 1,000 (from 59 fewer to 329 fewer)[k]
Quality of life not measured											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Plate et al.[67] See Table S1, S5, and S10 legends for expansion of abbreviations.

[a] The study included patients with DVT with symptoms of leg swelling not exceeding 7 d and a proximal extension of the thrombus above the inguinal ligament, but not into the vena cava.

[b] Not clear whether allocation was concealed. No blinding reported. Not clear whether analysis was ITT. Follow-up rate 88% at 6 mo. Study not stopped early for benefit.

[c] CI includes values suggesting either harm or benefit.

[d] One event, which was a symptomatic PE.

[e] Baseline risks for nonfatal recurrent VTE derived from Douketis et al.[39]

[f] No severe bleeding complications were recorded in either group. Three patients in thrombectomy group developed local wound hematoma.

[g] In addition to other study limitations, this outcome was assessed by those who did the surgery and anticoagulation. No standardized tool was used. One surgical patient had an amputation secondary to venous gangrene and was not counted in the PTS assessment.

[h] Few number of events. This warrants rating down the quality of evidence by a second level when considered along with study limitations.

[i] The RR is based on the 6-mo data.

[j] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[k] Severe PTS: assuming the same RR of 0.63 and a baseline risk of 13.8% over 2 y,[40] the absolute reduction is 51 fewer severe PTS per 1,000 (from 14 fewer to 77 fewer) over 2 y.

Table S17—*[Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Clinical Description and Results (All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Plate et al[67]/1984	RCT, multicenter	58 patients with acute iliofemoral venous thrombosis	Medical: 5,000-unit bolus heparin followed by 500 units/kg per 24 h adjusted to aPTT, and oral anticoagulation (31 patients) Surgical: operative venous thrombectomy with temporary AVF plus anticoagulation as above (27 patients)	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%, $P < .005$) Iliofemoral patency: 16/21 (76%, $P < .025$) Valve competence: 13/23, (52% $P < .05$) (venous gangrene in 1 patient)
Einarsson et al[68]/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 preoperatively and postoperatively 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[69]/1986		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%
Plate et al[70]/1990	Five-year follow-up to RCT (Plate, 1984[67])	41/58 patients (22 medical, 19 surgical) available for evaluation at 5 y	Prior treatment: Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation	PTS sequelae, iliac patency, venous pressure	5 y	Medical: PTS sequelae: 6/22 (27%) Iliac patency: 11/22 (50%) Venous pressure: 60 mm Hg (mean)

(Continued)

Table S17—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
						Surgical: PTS sequelae: 2/19 (11%) Iliac patency: 15/19 (78%) Venous pressure: 43 mm Hg (mean, $P < .05$)
Neglén et al[71]/1991	Prospective registry	48 patients with iliofemoral DVT of 1-14 d	Operative venous thrombectomy with temporary AVF (closed 6-12 wk postoperative) Adjunctive therapy: transvenous percutaneous dilatation of severe iliac stenosis (3 patients)	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%
Plate et al[72]/1997	Ten-year follow-up to RCT (Plate, 1984 [10] and 1990 [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 y	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)

Early prospective observational studies with <20 patients and retrospective studies are described in Table 5 of the eighth edition of these guidelines.[46] See Table S1, S2, S4, S10, and S11 legends for expansion of abbreviations.

Table S18—*[Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Plate et al[67]/1984	ND	PN	N, patients, caregivers, assessors, and data analysts	7
Einarsson et al[68]/1986	N/A	N/A	N/A	N/A
Einarsson et al[69]/1986	N/A	N/A	N/A	N/A
Plate et al[70]/1990	N/A	N/A	N/A	17
Neglén et al[71]/1991	N/A	N/A	N/A	N/A
Plate et al[72]/1997	N/A	N/A	N/A	28

See Table S5 and S12 legends for expansion of abbreviations.

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Table S19—*[Section 2.13] Evidence Profile: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Vena Cava Filters	With Vena Cava Filters	Relative Effect (95% CI)	Risk With No Vena Cava Filters	Risk Difference With Vena Cava Filters (95% CI)
Mortality (important outcome)											
400 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	103/200 (51.5)	98/200 (49.0)	RR 0.95 (0.78-1.16)[e]	515 per 1,000	26 fewer per 1,000 (from 113 fewer to 82 more)
Symptomatic PE (critical outcome)											
304 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[c,f] due to imprecision	24/159 (15.1)	9/145 (6.2)	RR 0.41 (0.2-0.86)[g]	151 per 1,000	89 fewer per 1,000 (from 21 fewer to 121 fewer)
Recurrent DVT (important outcome)											
310 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[c,f] due to imprecision	41/150 (27.3)	57/160 (35.6)	RR 1.3 (0.93-1.82)[h]	273 per 1,000	82 more per 1,000 (from 19 fewer to 224 more)
Major bleeding (important outcome)											
337 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	31/168 (18.5)	26/169 (15.4)	RR 0.83 (0.52-1.34)[i]	185 per 1,000	31 fewer per 1,000 (from 89 fewer to 63 more)

(Continued)

Table 19—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Vena Cava Filters	With Vena Cava Filters	Relative Effect (95% CI)	Risk With No Vena Cava Filters	Risk Difference With Vena Cava Filters (95% CI)
PTS (important outcome)											
308 (1 study), 8 y	Serious[j]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Low[d,j] due to risk of bias, imprecision	107/153 (69.9)	109/155 (70.3)	RR 0.87 (0.66-1.13)	699 per 1,000	91 fewer per 1,000 (from 238 fewer to 91 more)
Complications (important outcome)											
379 (1 study), 2 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[f] due to imprecision	0/186 (0)	0/193 (0)	…	…	…[k]
Quality of life not reported											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Decousus et al,[8] The PREPIC Investigators.[73] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a] Four types of permanent vena cava filters were used: Vena Tech LGM (B. Braun Melsugen AG), titanium Greenfield (Boston Scientific Corporation), Cardial (C.R. Bard, Inc), and Bird's Nest (Cook Group Incorporated).

[b] Anticoagulation consisted of LMWH or UFH initially (according to a 2 × 2 factorial design) followed by oral anticoagulation for at least 3 mo.

[c] Allocation concealed. Data collectors and outcome adjudicators blinded. ITT analysis. Data missing for 4% at 2 y and 1% at 8 y. Enrollment was stopped at 400 instead of targeted 800 due to slow recruitment.

[d] CI includes both negligible effect and appreciable benefit or appreciable harm.

[e] RR, 1.0 (95% CI, 0.29-3.4) at 12 d; RR, 1.08 (95% CI, 0.73-1.58) at 2 y.

[f] Small number of events.

[g] RR, 0.23 (95% CI, 0.05-1.05) at 12 d (both symptomatic and asymptomatic PE). RR, 0.54 (95% CI, 0.21-1.41) at 2 y (symptomatic PE)

[h] RR, 1.78 (95% CI, 1.09-2.94) at 2 y.

[i] RR, 1.5 (95% CI, 0.54-4.14) at 12 d. RR, 0.74 (95% CI, 0.41-1.36) at 2 y.

[j] No standardized validated tool used to measure PTS.

[k] No complications directly related to the filter or its insertion reported in the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) trial.[8] Mismetti et al[74] (prospective study) reported an incidence of 3.2% (excluding filter tilting and puncture site hematoma) among 220 patients receiving retrievable vena cava filter for secondary prevention of VTE, whereas while Athanasoulis et al[75] (retrospective study) reported an incidence of 0.3% for major complications among 1,731 patients receiving vena cava filters predominantly for secondary prevention of VTE.

Table S20—*[Section 2.14] Evidence Profile: Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Delayed Ambulation	With Early Ambulation	Relative Effect (95% CI)	Risk With Delayed Ambulation	Risk Difference With Early Ambulation (95% CI)
Mortality (important outcome)											
385 (4 studies), 3 mo[c]	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	Undetected	Low[d,e] due to risk of bias, imprecision	2/186 (1.1)	3/199 (1.5)	RR 1.3 (0.23-7.55)	11 per 1,000	3 more per 1,000 (from 8 fewer to 70 more)
PE (critical outcome; assessed with symptomatic or asymptomatic PE)											
385 (4 studies), 4-12 d	Serious[d]	No serious inconsistency	No serious indirectness[f]	Serious[e]	Undetected[g]	Low[d-g] due to risk of bias, imprecision	22/186 (11.8)	27/199 (13.6)	RR 1.16 (0.66-2.05)	118 per 1,000	19 more per 1,000 (from 40 fewer to 124 more)
Quality of life (important outcome; measured with quality of life questionnaire in chronic limb venous insufficiency [CIVIQ]; better indicated by lower values)											
53 (1 study), 2 y	Serious[h]	No serious inconsistency	Serious[i]	No serious imprecision	Undetected	Low[h,i] due to risk of bias, indirectness	17	36	-	See footnote[j]	
PTS (important outcome; assessed with Villata-Prandoni score [value >5])											
37 (1 study) 2 y	Serious[h]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Low[e,h] due to risk of bias, imprecision	9/11 (81.8)	14/26 (53.8)	RR 0.66 (0.42-1.03)	Moderate	
										400 per 1,000	136 fewer per 1,000 (from 232 fewer to 12 more)

Bibliography: Kahn et al,[76] Aissaoui et al.[77] Included studies.[78-82] See Table S1, S2, S5, and S10 legends expansion of other abbreviations.

[a] In two of four eligible trials, all patients received early compression therapy (bandages or stockings). In the two other trials, only patients randomized to early ambulation received early compression therapy.

[b] Two of four eligible studies excluded patients with symptomatic PE; in the third study, 24% of participants had symptomatic PE at baseline. It was not clear whether the fourth study excluded patients with symptomatic PE.

[c] Three studies reporting acute phase mortality reported no deaths.

[d] Concealment of allocation reported in one of four studies; blinding of outcome assessors reported in two of four studies; ITT analysis reported in two of four studies. Follow-up 97%-100%. In two of four trials, only patients randomized to early ambulation received early compression therapy (bandages or stockings). In the two other trials, all patients received early compression therapy.

[e] CI includes both values of clinically significant benefit and values of clinically significant harms.

[f] PE assessed as both symptomatic and asymptomatic PE.

[g] Funnel plot reported as not asymmetrical by Aissaoui et al.[77]

[h] Concealment of allocation not reported, outcome assessors not blinded for this outcome; 70% follow-up rate; compression stockings used on patients with early mobilization but in patients with delayed mobilization.

[i] No explanation was provided.

[j] Psychologic and overall somatic quality of life did not differ significantly between the treatment groups, whereas DVT-related items, especially those reflecting the ease of locomotion, showed significantly greater improvement with compression than with bed rest ($P < .001$ for bandages, $P < .05$ for stockings).

Table S21—*[Section 2.14] Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Schellong et al[82]/1999	RCT, single center	126 patients with acute proximal DVT	Ambulation: leg elevation until day 2, then ambulation and compression (64 patients) Bed rest for 8 d with leg elevation and compression (62 patients)	PE by V̇/Q̇ scan	10 d	Ambulation: PE: 10/59 (17%) Bed Rest: PE: 14/63 (22%)
Partsch et al[81]/2000	RCT, multicenter	45 patients with proximal DVT < 14 d duration	Ambulation + bandages: inelastic Unna boot bandages plus walking exercises (15 patients) Ambulation + stockings: elastic compression stockings plus walking exercises (15 patients) Bed rest, no compression, LMWH (15 patients)	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 with group C PE, group A: 2/15 (13%) PE, group B: 1/15 (7%) PE, group C: 1/15 (7%)
Aschwanden et al[78]/2001	RCT, single center	129 patients with acute DVT	Ambulation ≥ 4 h/d for 4 d under supervision, LMWH (69 patients) Bed rest for 4 d (60 patients)	New PE between baseline and day 4 by V̇/Q̇ 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 et al[83]/2001	Prospective study	1,289 patients with acute DVT	All treated with LMWH, compression, and immediate ambulation	PE on V̇/Q̇ scan at 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; follow-up scans were performed in 1,256/1,289 patients
Blättler et al[79]/2003	RCT	53 patients with proximal DVT	Ambulation + bandages: firm inelastic bandages, ambulation (18 patients) Ambulation + stockings: elastic compression stockings, ambulation (18 patients)	Walking distance, well-being, and DVT-related quality of life, leg pain by visual analog scale, edema, clinical scores, thrombus progression	9 d	Well-being/quality of life: Improved with stockings ($P < .05$), bandages ($P < .01$) Leg pain: Decreased faster during first 4 d w/ bandages and stockings vs bed rest ($P < .01$); near absence of pain at 9 d achieved with bandages only

(Continued)

Table S21—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Bed rest only (17 patients)			Edema: Marked reduction in leg size with bandages and stockings vs bed rest ($P < .001$) Clinical scores: Improved with bandages and stockings vs bed rest ($P < .001$) Thrombus progression: Improved with bandages and stockings vs bed rest ($P < .01$) PE: No difference between groups
Partsch et al[84]/2004	2-y follow-up to RCT (77)	37 patients followed up 2 y post-RCT	Anticoagulation and bed rest vs anticoagulation and ambulation with compression bandages or stockings	PTS assessment (Villalta-Prandoni scale)	2 y	PTS scores: Ambulatory group (mean score, 5.1) had improved outcome vs bed rest group (mean score, 8.2; $P < .01$)
				Pain assessment by visual analog scale and modified Lowenberg test		Pain: Lower pain levels in mobile group vs bed rest (ns)
				Thrombus regression		Thrombus extension: No difference in thrombus regression of thrombus remnants between groups
Trujillo-Santos et al[85]/2005	Prospective study	2,650 patients with acute DVT (2,038 [77%]) or PE (612 [23%])	DVT group, bed rest or ambulation: 1,050 (52%) patients received bed rest, and 988 (48%) ambulated. All received LMWH. PE group, bed rest or ambulation: 385 (63%) patients received bed rest, and 227 (37%) ambulated. All received LMWH.	Symptomatic, confirmed PE during first 15 d of therapy	3 mo	DVT group, bed rest: PE: 7/1050 (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%)
Jünger et al[80]/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%)

ns = not significant; $\dot{V}/\dot{Q}$ = ventilation/perfusion. See Table S2, S5, and S10 legends for expansion of other abbreviations.

Table S22—*[Section 2.14] Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Schellong et al[82]/1999	Patients randomized to 1 of 2 study groups	Unclear	Y, assessors N, patients, caregivers, analysts	4
Partsch et al[81]/2000	Patients randomized to 1 of 3 study groups by sealed envelope	Unclear	Y, assessors N, patients, caregivers, analysts	0
Aschwanden et al[78]/2001	Patients randomized to 1 of 2 study groups	Sealed envelope	Not blinded	5
Partsch et al[83]/200	N/A	N/A	N/A	N/A
Blättler et al[79]/2003	Patients randomized to 1 of 3 study groups by sealed envelope	Not specified	Y, assessors N, patients, caregivers, analysts	0
Partsch et al[84]/2004	N/A	N/A	N/A	21
Trujillo-Santos et al[85]/2005	N/A	N/A	N/A	N/A
Jünger et al[80]/2006	Patients randomized to 1 of 2 study groups by sealed envelope	Unclear	Y, analysts N, patients, caregivers, assessors	

See Table S5 and S12 legends for expansion of abbreviations.

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Table S23—*[Sections 3.1.1-3.1.4] Evidence Profile: Four or Six Weeks vs Three or Six Months as Minimum Duration of Anticoagulation for VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall quality of Evidence	With Control	With 4 or 6 wk vs 3 or 6 mo of Anticoagulation	Relative Effect (95% CI)	Risk With Control	Risk Difference With 4 or 6 wk vs 3 or 6 mo of Anticoagulation (95% CI)
Recurrent VTE (critical outcome)											
2,185 (5 studies[c]), 1-2 y[d]	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision[g]	Undetected	High[e-g]	70/1,090 (6.4)	127/1,095 (11.6)	RR 1.83 (1.39-2.42)	64 per 1,000	53 more per 1,000 (from 25 more to 91 more)
Major bleeding (critical outcome)											
2,185 (5 studies), 1-2 y[d]	No serious risk of bias	No serious inconsistency[f]	No serious indirectness	No serious imprecision	Undetected	High[f]	13/1,090 (1.2)	7/1,095 (0.6)	RR 0.54 (0.22-1.32)	12 per 1,000	5 fewer per 1,000 (from 9 fewer to 4 more)
Mortality (important outcome)											
2,098 (5 studies), 1-2 y[d]	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision[h]	Undetected	High[e,f,h]	55/998 (5.5)	57/1,100 (5.2)	RR 0.97 (0.68-1.38)	55 per 1,000	2 fewer per 1,000 (from 18 fewer to 21 more)

Bibliography: Kearon et al,[86] Pinede et al,[87] Schulman et al,[88] Levine et al,[89] British Thoracic Society.[90] See Table S1, S5, and S2 legends for expansion of abbreviations.

[a] Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al, 6 wk vs 3 mo for Pinede et al, and 4 wk vs 3 mo for the other three studies.

[b] Populations varied among studies: first provoked isolated distal DVT, proximal DVT or PE provoked in Kearon et al; first isolated distal DVT in Pinede et al; first isolated distal DVT, proximal DVT, or PE in Schulman et al; proximal DVT (21% had cancer) in Levine et al; and DVT or PE (29% not objectively confirmed) in British Thoracic Society.

[c] Timing of randomization relative to the start of treatment varied across studies: Pinede et al, Schulman et al, and British Thoracic Society randomized at diagnosis; Kearon et al and Levine et al randomized to stop or to continue treatment of 2 more months after the initial 4 wk of treatment.

[e] Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al, Pinede et al). In one study (British Thoracic Society), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appeared to have used effective randomization concealment, ITT analysis, and appears to have a low unexplained drop-out frequency.

[f] No heterogeneity with $I^2 = 0\%$.

[g] No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.

[d] Follow-up was for ~1 y in all studied except for Schulman et al in which it was 2 y.

[h] Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

Table S24—*[Sections 3.1.1-3.1.4] Comparison of Durations of Anticoagulant Therapy for DVT and PE: Clinical Description and Results*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Short (4 or 6 wk) vs intermediate (3 or 6 mo) durations of anticoagulation							
Kearon et al[86]/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 on warfarin.
	VKA (INR 2.0-3.0) For 2 more mo.	81/81	11 mo	3/81 (4%) RR 0.6 (0.1-2.5)	0/81 RR 1.0 (0.0-51.6)	1/81 (1%) RR 3.1 (0.1-74.4)	
Pinede et al[87]/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 (0.3-10.0)	3/92 RR 3.4 (0.4-33.4)		
Schulman et al[88]/1995 (DURAC 1)	VKA (INR 2.0-2.85) for 1.5 mo	443/443	2 y	80/443 (18%)	1/443	22/443 (5%)	First VTE: DVT (distal or proximal) or PE. Only asked about bleeding while on VKAs.
	VKA (INR 2.0-2.85) for 6 mo	454/454		43/454 (9%) RR 0.5 (0.4, 0.7)	5/454 (1%) RR 4.9 (0.6-41.6)	17/454 (4%) RR (0.7-1.4)	
Levine et al[89]/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 (0.2-1.4)	1/109 (1%) RR 2.9 (0.1-70.2) (within 2 mo of randomization)	9/109 (8%) RR 1.0 (0.4-2.5)	
British Thoracic Society et al[90]/1992	VKA (INR 2.0-3.0) For 1 mo	358/358	1 y	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 y	14/354 (4%) RR 0.5 (0.3-0.9)	4/354 (1%) RR 0.8 (0.2-3.0)	28/354 (8) RR 1.1 (0.6-1.8)	All bleeds were on VKA. Only 1 recurrent VTE among 116 patients with postoperative VTE.

(Continued)

Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Different intermediate durations (6 or 12 mo vs 3 mo) of anticoagulation							
Campbell et al[91]/2007	VKA (INR 2.0.0-3.5) for 3 mo	369/396	1 y	31/369 (8%)	0/369 (during 3 mo. treatment)	15/369 (4%)	Population: DVT or PE; proportion with calf DVT not known. Only bleeding during treatment is reported; 20% of VTE outcomes were not objectively verified.
	VKA (INR 2.0-3.5) for 6 mo	380/414	1 y	29/380 (8%) RR0.9 (0.6-1.5)	8/380 (2%) (during 6 mo. treatment) RR 16.5 (1.0-285)	19/369 (5%) RR 1.3 (0.6-2.5)	
Agnelli et al[92]/2003 (WODIT PE)	VKA stopped	91/91	2.6 y (mean)	11/91 (12%)	1/91 (1%)	7/91 (8%)	Population: first unprovoked PE. Treated for ≥3 mo. Among the 4 groups, only 1 recurrent VTE while on VKA.
	VKA (INR 2.0-3.0) for 9 more mo	90/90	2.9 y (mean)	11/90 (12%) RR 1.0 (0.5-2.2)	2/90 (2%) RR 2.0 (0.5-21.9)	8/90 (9%) RR 1.16 (0.4-3.0)	
	VKA stopped	70/70	2.8 y (mean)	7/70 (10%)	0/70 (0%)	0/70 (0%)	Population: first provoked PE. Treated for ≥3 mo (see above)
	VKA (INR 2.0-3.0) for 3 more mo	75/75	2.9 y (mean)	4/75 (5%) RR 0.5 (0.2-1.7)	1/75 (1%) RR 1.9 (0.1-56)	4/75 (5%) RR 8.4 (0.5-153)	
Agnelli et al[93]/2001 (WODIT DVT)	VKA stopped	133/133	3.2 y (mean)	21/133 (16%)	2/133 (2%)	7/133 (5%)	Population: first unprovoked proximal DVT treated for 3 mo. One patient had recurrent VTE on VKA. Bleeding in the intervention group was while on VKA.
	VKA (INR 2.0-3.0) for 9 mo	134/134	3.1 y (mean)	21/134 (16%) RR 1.0 (0.6-1.7)	4/134 (3%) RR 2.0 (0.4-10.7)	7/134 (5%) RR 1.0 (0.4-2.8)	
Pinede et al[87]/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 (0.6-1.9)	7/269 (3%)) RR 1.4 (0.4-4.4)		
Siragusa et al[94]/2008 (DACUS)	VKA stopped	92/92	1.8 y	27/92 (29%)	1/92 (1%)	Not specified (total of 3 non-VTE/bleed deaths)	Population: first proximal DVT (provoked, 24%; unprovoked, 76%) treated for 3 mo and residual DVT on baseline ultrasound

(Continued)

Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
			Indefinite vs intermediate durations of anticoagulation (INR ~2.0-3.0)				
Palareti et al[95]/2006 (PROLONG)	Remain off (stop) VKA	103/105	1.4 y (mean)	18/120 (15%)	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 patient. 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	(maximum, 1.5 y)	2/103 (2%) RR 0.1 (0.0-0.4)	1/120 (1%) RR 2.6 (0.1-62.6)	1/120 (1%) RR 0.9 (0.1-13.6)	
Kearon et al[96]/1999 (LAFIT)	VKA stopped (placebo)	83/83	10 mo (mean)	17/83 (20%)	0/83	3/83 (4%)	Population: first unprovoked proximal DVT or PE (5% had previous provoked VTE). The recurrent VTE in the VKA patient was after stopping VKA.
	VKA (INR 2.0-3.0) for 2 more years	79/79	(maximum, 2 y)	1/79 (1%) RR 0.1 (0.0-0.5)	3/79 (4%) RR 7.4 (0.4-140)	1/79 (1%) RR 0.3 (0.0-3.3)	
Schulman et al[97]/1997 (DURAC 2)	VKA (INR 2.0-2.85) for 6 mo	111/111	4 y	23/111 (2%)	3/111 (3%)	16/111 (14%)	Second VTE: DVT (distal or proximal) or PE. All recurrent VTE in the indefinite VKA group were after stopping VKAs. Bleeding during the first 6 mo of VKA in 1 of 6 mo group and 6 of indefinite group (only asked about bleeding while on VKAs).
	VKA (INR 2.0-2.85) indefinitely	116/116		3/116 (3%) RR 0.1 (0.0-0.4)	10/116 (9%) RR 3.2 (0.9-11.3)	10/116 (9%) RR 0.6 (0.3-1.3)	
Farraj et al[98]/2004	VKA (INR 2.0-3.0) for 6 mo	32/36	3 y	7/32 (22%)	2/32 (6%)	0/32	In total: 2 VTE after 24 mo (24 mo group); 1 VTE on therapy (24 mo group)
	VKA (INR 2.0-2.85) for 24 mo	32/36		3/32 (3%) RR 0.4 (0.1-1.5)	2/32 (6%) RR 1.0 (0.2-6.7)	0/32	

(Continued)

Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Fixed vs flexible duration, depending on presence of residual thrombosis on follow-up ultrasound (INR 2.0-3.0)							
Prandoni et al[99]/2009 (AESOPUS)	VKA stopped if provoked and 3 more months if unprovoked	268/268	33 mo	46/268 (17%)	2/268 (1%)	11/268 (4%)	Population: first provoked (43%) or unprovoked (57%) proximal DVT treated for 3 mo. One VTE in each group while on VKAs. The flexible group was treated for a mean of 4 mo (provoked) and 5 mo (unprovoked) longer.
	Stopped if no residual vein thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked	270/270		32/270 (12%) RR 0.7 (0.4-1.1)	4/270/255 (1%) RR 2.0 (0.4-10.8)	4/255 (6%) RR 1.5 (0.7-3.2)	
Indefinite vs intermediate durations of anticoagulation (INR ~1.5-2.0, after initial INR 2.0-3.0 in both groups)							
Ridker et al[100]/2003 (PREVENT)	VKA stopped or not restarted (placebo)	253/253	2.1 y (mean)	37/253 (15%)	2/253 (1%)	8/253 (3%)	Population: unprovoked DVT (distal or proximal) or PE (first episode in 38%). Eight recurrent VTE in the VKA group after stopping VKAs.
	VKA INR 1.5-2.0	255/255	(maximum, 4.3 y)	14/255 (5%) RR 0.4 (0.2-0.7)	5/255 (2%) RR 2.5 (0.5-12.7)	4/255 (2%) RR 0.5 (0.1-1.6)	
Low intensity (INR 1.5-1.9) vs conventional intensity (INR 2.0-3.0)							
Kearon et al[101]/2003 (ELATE)	VKA INR 1.5-1.9	369/369	2.4 y (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 VTE in INR 1.5-1.9 and three in the INR 2.0-3.0 group after stopping VKAs.
	VKA INR 2.0-3.0 (blinded)	369/369		6/369 (2%)RR 0.4 (0.1-0.9)	8/369 (2%) RR 0.9 (0.3-2.3)	8/369 (2%) RR 0.5 (0.2-1.2)	

AESOPUS = Ultrasound Findings to Adjust the Duration of Anticoagulation; DACUS = Duration of Anticoagulation based on Compression UltraSonography; DOTAVK = Durée Optimale du Traitement AntiVitamines K; DURAC = Duration of Anticoagulation; ELATE = Anticoagulation for Thrombo-Embolism; LAFIT = Long-term Anticoagulation for a First episode of Idiopathic venous Thromboembolism; PREVENT = Prevention of Recurrent Venous Thromboembolism; SOFAST = First Acute Secondary Thrombosis; WODIT DVT = Warfarin Optimal Duration Italian Trial in patients with DVT; WODIT PE = Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism. See Table S1, S2, and S7 legends for expansion of other abbreviations.

Table S25—*[Sections 3.1.1-3.1.4] Comparison of Durations of Anticoagulant Therapy for DVT and PE: Methodologic Quality*

Author/Year (Acronym)	Intervention	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Kearon et al[86]/2004 (SOFAST)	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more mo	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	Placebo: 0/84 VKA: 0/81	ITT	Stopped early because of slow recruitment.
Pinede et al[87]/2001 (DOT AVK)	VKA (INR 2.0-3.0) for 1.5 and 3 mo VKA (INR 1.0-3.0) for 3 and 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Stopped early because of slow recruitment. Patient withdrawals: 4 in short- and 16 in long-duration groups. Total of 22 patients dropped out.
Schulman et al[88]/1995 (DURAC 1)	VKA (INR2.0-2.85) for 1.5 mo VKA (INR 2.0-2.85) for 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Other: PN Data Analysts: PN	Total of 44 patients dropped out during follow-up but partial follow-up achieved	ITT	Five patient were excluded because protein C found after randomization.
Levine et al[89]/1995	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more mo.	RCT	CY	Patients: CY Caregivers: CY Adjudications: VTE, CY Data Analysts: PN	Placebo: 1/105 VKA: 6/109 (did not complete 11-mo follow-up)	ITT	Two placebo and 4 warfarin patients withdrew consent shortly after randomization.
British Thoracic Society et al[90]/1992	VKA (INR 2.0-3.0) For 1 mo VKA (INR 2.0-3.0) for 3 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN	No VKA: 27/354 VKA: 30/358	ITT	Forty-four randomized patients excluded centrally as did not satisfy entry criteria.
Campbell et all[91]/2007	VKA (INR 2.0.0-3.5) for 3 mo VKA (INR 2.0-3.5) for 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN	3- mo VKA: 6/369 6- mo VKA: 4/380	ITT	Sixty-one randomized patients excluded centrally as did not satisfy entry criteria. Stopped early because of low recruitment.
Agnelli et al[92]/2003 (WODIT PE)	VKA stopped VKA (INR 2.0-3.0) for 9 more mo.	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Two patients in the control groups and 2 patients in the intervention groups crossed over. Five patients in the intended group did not stop VKA. Four patients in the control groups restarted VKAs.
Agnelli et al[93]/2001 (WODIT DVT)	VKA stopped VKA (INR 2.0-3.0) for 9 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Trial stopped early for lack of adequate benefit. Four patients in the intervention and 2 patients in the control group crossed over.

(Continued)

Table S25—*Continued*

Author/Year (Acronym)	Intervention	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Siragusa et al[94]/2008 (DACUS)	VKA stopped VKA (INR 1.0-3.0) for 9 mo.	RCT	PY	Patients: CN Caregivers: CN Adjudications: PY Data Analysts: PN	None	ITT	Not known whether the many postenrollment exclusions were postrandomization. Trial stopped early because recurrent VTE was higher than expected.
Palareti et al[95]/2006 (PROLONG)	Remain off (stop) VKA Restart indefinitely VKA (INR 2.0-3.0) (not blinded)	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	No VKA: < 3/105 VKA: 0/122	ITT	Four patients excluded because lupus anticoagulant found after randomization.
Kearon et al[96]/1999 (LAFIT)	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more y	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	None	ITT	Trial stopped early because of overall benefit. After recurrent VTE, patients were not followed. resulting in shorter follow-up and potential for underestimation of bleeding in the no-VKA group.
Schulman et al[97]/1997 (DURAC 2)	VKA (INR 2.0-2.85) for 6 mo VKA (INR 2.0-2.85) indefinitely	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Other, PN Data Analysts: PN	Total of 14 patients dropped out during follow-up, but partial follow-up achieved	ITT	Actual mean duration of VKA was 7.7 mo in 6-mo group and 42.7 mo in indefinite (48 mo) group.
Prandoni et al[99]/2009 (AESOPUS)	VKA stopped if provoked and 3 more mo if unprovoked Stopped if no residual vein thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Data Analysts: PY	4 subjects in each group	ITT	
Ridker et al[100]/2003 (PREVENT)	VKA stopped or not restarted (placebo) VKA INR 1.5-2.0	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	Not specified Probably low or nil	ITT	Trial stopped early because of overall benefit. Number of crossovers not described.
Farraj et al[98]/2004	VKA (INR 2.0-3.0) for 6 mo VKA (INR 2.0-2.85) for 24 mo	RCT	PY	Patients: CN Caregivers: CN Data Collectors: PN. Adjudicators: PN Data Analysts: PN	0/32 0/32 (see comments)	ITT	Four postrandomization exclusions for each group because of poor compliance.
Kearon et al[101]/2003 (ELATE)	VKA INR 1.5-1.9 VKA INR 2.0-3.0 (blinded)	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	INR 1.5-1.9: ≤ 1/369 INR 1.5-1.9: ≤ 1/369	ITT	Crossover to INR 2.0-3.0 in 21 patients

See Table S1, S2, S7, and S24 legends for expansion of abbreviations.

Table S26—*[Sections 3.1.1-3.1.4] Evidence Profile: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With 3 mo	With 6 or 12 mo	Relative Effect (95% CI)	Risk With 3 mo	Risk Difference With 6 or 12 mo (95% CI)
Recurrent VTE (critical outcome)											
2,061 (6 studies), 1-3 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d,e]	Undetected	Moderate[d-e] due to imprecision	118/1,025 (11.5)	105/1,036 (10.1)	RR 0.89 (0.69-1.14)	115 per 1,000	13 fewer per 1,000 (from 36 fewer to 16 more)
Major bleeding (critical outcome)											
2,061 (6 studies), 1-3 y	No serious risk of bias[f]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[f]	9/1,025 (0.9)	24/1,036 (2.3)	RR 2.49 (1.2-5.16)	9 per 1,000	13 more per 1,000 (from 2 more to 37 more)
Mortality (important outcome[g])											
1,331 (5 studies), 1-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[d] due to imprecision	29/663 (4.4)	38/668 (5.7)	RR 1.3 (0.81-2.08)	44 per 1,000	13 more per 1,000 (from 8 fewer to 47 more)

Bibliography: Pinede et al,[87] Campbell et al,[91] Agnelli et al,[93] Agnelli et al,[92] Siragusa.[94] See Table S1, S2, and S5 legends for expansion of abbreviations.

[a] Timing of randomization relative to the start of treatment and length of treatment in the non-3-mo group varied across studies: Pinede et al and Campbell et al randomized at diagnosis, and Agnelli et al randomized after the initial 3 mo of treatment to stop, or continue, treatment. The longer duration of treatment was 6 mo in Pinede, Campbell, and Agnelli et al (2003) (provoked PE), and 12 mo in Agnelli (2001) and Agnelli (2003) (unprovoked PE).

[b] Study populations varied across studies: Pinede et al enrolled provoked and unprovoked proximal DVT and PE; Campbell et al enrolled provoked and unprovoked isolated distal DVT, proximal DVT and PE; Agnelli et al (2003) had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); and Agnelli et al (2001) enrolled unprovoked proximal DVT.

[c] Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Campbell et al, Pinede et al), and one stopped because of lack of benefit (Agnelli et al [2001]). In one study (Campbell), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were not blinded in any study. Adjudicators of outcomes were blinded in all but one study (Campbell). All studies used effective randomization concealment and ITT analysis and appear to have a low unexplained drop-out frequency.

[d] CIs include both values suggesting no effect and values suggesting either benefit or harm.

[e] Low number of events and a total number of participants $<2,000$.

[f] One study may have confined the assessment of bleeding to when subjects were receiving anticoagulant therapy, which could have inflated the increase in bleeding associated with the longer duration of therapy (Campbell et al).

[g] Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

Table S27—*[Sections 3.1.1-3.1.4] Extended Anticoagulation vs No Extended Anticoagulation for Different Groups of Patients With VTE and Without Cancer*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
Mortality (important outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency[c]	No serious indirectness	Serious[d,e]	Undetected	Moderate[c-e] due to imprecision	38/599 (6.3)	16/585 (2.7)	RR 0.57 (0.31-1.03)	63 per 1,000	27 fewer per 1,000 (from 44 fewer to 2 more)
Recurrent VTE at 1 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	102/599 (17)	21/585 (3.6)	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
										10 per 1,000	10 per 1,000
										First VTE provoked nonsurgical/first unprovoked distal DVT[f-j]	
										50 per 1,000	44 fewer per 1,000 (from 31 fewer to 45 fewer)
										First unprovoked VTE[f-j]	
										100 per 1,000	88 fewer per 1,000 (from 62 fewer to 91 fewer)
										Second unprovoked VTE[f-j]	
										150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
Major bleeding at 1 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	Undetected	Moderate due to imprecision	7/599 (1.2%)	21/585 (3.6%)	RR 2.63 (1.02-6.76)	Low risk of bleeding[k,l]	
										3 per 1,000	5 more per 1,000 (from 0 more to 17 more)
										Moderate risk of bleeding[k,l]	
										6 per 1,000	10 more per 1,000 (from 0 more to 35 more)
										High risk of bleeding[k,l]	
										12 per 1,000	20 more per 1,000 (from 0 more to 69 more)

(Continued)

Table S27—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
Recurrent VTE at 5 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	102/599 (17%)	21/585 (3.6%)	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
										30 per 1,000	26 fewer per 1,000 (from 19 fewer to 27 fewer)
										First VTE provoked nonsurgical/first unprovoked distal DVT[f-j]	
										150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
										First unprovoked VTE[f-j]	
										300 per 1,000	264 fewer per 1,000 (from 186 fewer to 273 fewer)
										Second unprovoked VTE[f-j]	
										450 per 1,000	396 fewer per 1,000 (from 279 fewer to 409 fewer)
Major bleeding at 5 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	Undetected	Moderate due to imprecision	7/599 (1.2%)	21/585 (3.6%)	RR 2.63 (1.02-6.77)	Low risk of bleeding[k,l]	
										15 per 1,000	24 more per 1,000 (from 0 more to 87 more)
										Moderate risk of bleeding[k,l]	
										30 per 1,000	49 more per 1,000 (from 1 more to 173 more)
										High risk of bleeding[k,l]	
										60 per 1,000	98 more per 1,000 (from 1 more to 346 more)
Burden of anticoagulation not reported											

(Continued)

Table S27—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
…	…	…	…	…	…	…	…	…	…	See comment[m]	See comment[m]
PTS not reported											
…	…	…	…	…	…	…	…	…	…	See comment[n]	See comment[n]

Bibliography: Schulman et al (DURAC 2),[97] Kearon et al (LAFIT),[96] Farraj,[98] Palareti (PROLONG).[95] See Table S1, S2, S7, and S10 legends for expansion of abbreviations.

[a]Studies vary in follow-up duration (10 mo to 3 y) and in duration of time-limited VKA (3 to 6 mo).

[b]We excluded Ridker et al (PREVENT)[100] because target INR was 1.75 (low intensity), which has been shown in an RCT to be less effective than a target of 2.5.

[c]$I^2 = 0\%$.

[d]CI includes both values suggesting no effect and values suggesting either appreciable harms or appreciable benefit.

[e]Small number of events. Decision to rate down also takes into account that two studies were stopped early for benefit.

[f]Annual risk of VTE recurrence after discontinuing oral anticoagulation therapy in patients with first VTE provoked by surgery: 1% (Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med*. 2010;170(19):1710-1716); we assumed a 0.5% yearly risk thereafter (3% over 5 y).

[g]Annual risk in patients with first VTE provoked by non surgical factor: about 5% the first year (Iorio et al); we assumed 2.5% yearly thereafter (15% over 5 y).

[h]Annual risk in patients with first episode of unprovoked VTE: 9.3% over 1 y in Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179(5):417-426; 11.0% over 1 y, 19.6% over 3 y, and 29.1% over 5 y in Prandoni et al (2007). We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).

[i]Annual risk in patients with second episode of unprovoked VTE: we assumed an RR of 1.5 compared with a first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).

[j]Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier 2010).

[k]Annual risk of major bleeding is based on three risk levels: low, intermediate, and high. The corresponding 0.3%, 0.6%, and 1.2% risks are estimates based on control arms of included studies (see Table 3).

[l]Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al) (no data available for after discontinuing oral anticoagulation therapy).

[m]Burden of anticoagulation: endured by all patients who continue extended-duration anticoagulation (100%) and applies to patients who stop anticoagulation (no extended-duration anticoagulation) who subsequently experience a recurrent VTE (5%, 10%, 15% at 1 y; 15%, 30%, 45% at 5 y).

[n]Baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (VETO [Venous Thrombosis Outcomes study]; *Ann Intern Med*. 2008) and threefold (Prandoni. *Ann Intern Med*. 2004) to 10-fold (Van Dongen. *J Thromb Haemost*. 2005) increase in PTS.

Table S28—*[Section 3.3] Evidence Profile: LMWH vs VKA for Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With VKA	With LMWH	Relative Effect (95% CI)	Risk With VKA	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
2,496 (7 studies), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	202/1,231 (16.4)	204/1,265 (16.1)	RR 0.96 (0.81-1.13)	164 per 1,000	7 fewer per 1,000 (from 31 fewer to 21 more)
Recurrent VTE (critical outcome)											
2,727 (8 studies), 6 mo	Serious[f]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[f] due to risk of bias	105/1,349 (7.8)	67/1,378 (4.9)	RR 0.62 (0.46-0.84)	No cancer[g]	
										30 per 1,000	11 fewer per 1,000 (from 5 fewer to 16 fewer)
										Nonmetastatic cancer[g]	
										80 per 1,000	30 fewer per 1,000 (from 13 fewer to 43 fewer)
										Metastatic cancer[g]	
										200 per 1,000	76 fewer per 1,000 (from 32 fewer to 108 fewer)
Major bleeding (critical outcome)											
2,737 (8 studies), 6 mo	No serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious[i]	Undetected	Moderate[h,i] due to imprecision	53/1,351 (3.9%)	45/1,386 (3.2%)	RR 0.81 (0.55-1.2)	No cancer or nonmetastatic cancer[j]	
										20 per 1,000	4 fewer per 1,000 (from 9 fewer to 4 more)
										Metastatic cancer[j]	
										80 per 1,000	15 fewer per 1,000 (from 36 fewer to 16 more)

(Continued)

Table S28—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With VKA	With LMWH	Relative Effect (95% CI)	Risk With VKA	Risk Difference With LMWH (95% CI)
Burden of anticoagulation (important outcome)[k]											
…	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not applicable	High	Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits	LMWH: daily injection, no dietary interactions, no frequent blood testing/monitoring	…	…	
PTS (important outcome; assessed with self-reported leg symptoms and signs)											
100 (1 study), 2 y	Serious[l]	No serious inconsistency	Serious[m]	No serious imprecision	Undetected	Low[l,m] due to risk of bias, indirectness	31/44 (70.5%)	34/56 (60.7%)	RR 0.85 (0.77-0.94)	Moderate[n] 200 per 1,000	30 fewer per 1,000 (from 12 fewer to 46 fewer)

Bibliography: Included studies: Deitcher et al,[102] Hull et al,[103] Hull et al,[104] Lee et al,[105] Lopaciuk et al,[106] Lopez-Beret et al,[107] Meyer G et al,[108] Romera et al[109] Two of these studies enrolled only patients without cancer,[104,107] 3 enrolled only patients with cancer[108,102,105], and 3 enrolled both patients with and without cancer[103,106,109] (separate data provided for cancer and non-cancer patients in one study[103,110]). Excluded studies (less than 50% of therapeutic dose LMWH during extended phase): Pini et al,[111] Das et al,[112] Gonzalez-Fajardo et al,[113] Veiga et al,[114] Kakkar et al,[115] (Cesarone 2003 Circ abstract). PTS data from: Hull et al.[104] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a]Limited to LMWH regimens that used ≥50% of the acute treatment dose during the extended phase of treatment.

[b]The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al [2007]) in which patients randomized to LMWH received initially the same LWMH, whereas patients randomized to VKA received initially UFH.

[c]Two of these studies enrolled only patients without cancer, three enrolled only patients with cancer, and three enrolled both patients with and without cancer (separate data provided for cancer and non-cancer patients in one study).

[d]One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

[e]CI includes both no effect and harm with LMWH.

[f]None of the studies were blinded, although the diagnosis of recurrent VTE has a subjective component and there could be a lower threshold for diagnosis of recurrent VTE in VKA-treated patients because switching the treatment of such patients to LMWH is widely practiced. At the same time, there is reluctance to diagnose recurrent VTE in patients who are already on LMWH because there is no attractive alternative treatment option.

[g]Risk of recurrent VTE: low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate corresponds to patients with local or recently resected cancer (based on average rate across the six studies in this analysis and appears to be consistent with Prandoni et al [particularly if low risk is increased to 4%]), and high to patients with locally advanced or distant metastatic cancer (Prandoni et al[116]).

[h]No study was blinded; diagnosis of major bleeding has a subjective component.

[i]The 95% CIs for the RR for major bleeding includes a potentially clinically important increase or decrease with LMWH and may vary with the dose of LMWH used during the extended phase of therapy.

[j]Risk of bleeding: low corresponds to patients without risk factor for bleeding (ie, >75 y, cancer, metastatic disease; chronic renal or hepatic failure; platelet count <800,000; requires antiplatelet therapy; history of bleeding without a reversible cause) (Table 2) (based on Prandoni et al[116] and Beyth et al,[117] adjusted to a 6-mo time frame).

[k]Hull et al reported no significant difference in quality of life but suggested greater satisfaction with LMWH over VKA (questionnaire did not directly assess the burden of injections).

[l]Patients and investigators not blinded. Self-reported leg symptoms and signs after 3 mo of treatment.

[m]The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

[n]Baseline risk assumes that patients all wear pressure stockings. Control event rate comes from observational studies in review by Kahn et al,[118] adjusted to 2-y time frame.

Table S29—*[Section 3.3] Evidence Profile: Rivaroxaban vs LMWH and VKA Therapy for Short- and Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With LMWH and VKA Therapy	With Rivaroxaban	Relative Effect (95% CI)	Risk With LMWH and VKA Therapy	Risk Difference With Rivaroxaban (95% CI)
Death (important outcome)											
3,449 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[e,f] due to imprecision	49/1,718 (2.9)	38/1,731 (2.2)	HR 0.67 (0.44-1.02)	29 per 1,000	9 fewer per 1,000 (from 16 fewer to 1 more)
Recurrent VTE (critical outcome)											
3,449 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[g]	Undetected	Moderate[e,g] due to imprecision	51/1,718 (3)[h]	36/1,731 (2.1)[h]	HR 0.68 (0.44-1.04)	30 per 1,000[h]	9 fewer per 1,000 (from 17 fewer to 1 more)
Major bleeding (critical outcome)											
3,429 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[g]	Undetected	Moderate[e,g] due to imprecision	19/1,711 (1.1)[i]	13/1,718 (0.8)[i]	HR 0.68 (0.34-1.38)[j]	11 per 1,000[i]	4 fewer per 1,000 (from 7 fewer to 4 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits	Rivaorxaban: daily medication, no dietary interactions, no frequent blood testing/monitoring	…	…	…

Bibliography: Einstein DVT.[119] HR = hazard ratio. See Table S1, S2, S5, and S7 legends for expansion of other abbreviations.

[a]Rivaroxaban 15 mg bid for 3 wk and then 20 mg/d for a total of 3 (12%), 6 (63%), or 12 (25%) months.

[b]Enoxaparin 1 mg/kg bid for ~8 d and then VKA therapy targeted to INR 2.5 for 3, 6, or 12 mo.

[c]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs (unprovoked, 62%; cancer, 6%; previous VTE, 19%).

[d]Follow-up was prespecified to be 3 mo (12%), 6 mo (63%), or 12 mo (25%).

[e]Allocation was concealed. Patients, providers, and data collectors were not blinded, but outcome adjudicators were blinded. ITT analysis; 1.0% loss to follow-up. Not stopped early for benefit.

[f]CI includes values suggesting benefit or no effect; relatively low number of events.

[g]CI includes values suggesting benefit and harm.

[h]One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.

[i]Bleeds contributing to death: one in the rivaroxaban group and five in the warfarin group.

[j]Calculated from reported data.

Table S30—*[Section 3.3] Evidence Profile: Rivaroxaban vs Placebo for Extended Anticoagulation of VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Rivaroxaban	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Rivaroxaban (95% CI)
Mortality (important outcome)											
1,196 (1 study), 6 or 12 mo[c]	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	2/594 (0.34)	1/602 (0.17)	RR 0.49 (0.04-5.4)[f]	3 per 1,000	2 fewer per 1,000 (from 3 fewer to 15 more)
Recurrent VTE (critical outcome)											
1,196 (1 study), 6 or 12 mo[c]	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[d]	42/594 (7.1)[g]	8/602 (1.3)[g]	HR 0.18 (0.09-0.39)	71 per 1,000[g]	58 fewer per 1,000 (from 43 fewer to 64 fewer)
Major bleeding (critical outcome)											
1,188 (1 study), 6 or 12 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[d,h] due to imprecision	0/590 (0)[i]	4/598 (0.7)[i]	RR 4.9 (0.58-42)[f]	[i]	7 more per 1,000 (from 3 more to 16 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	…		Rivaroxaban: daily medication, no dietary interactions, no frequent blood testing/ monitoring	…	…
PTS (important outcome) not reported											
…	…	…	…	…	…	…	…	…	…	…	[j]

Bibliography: Einstein DVT.[119] See Table S1, S2, S5, S10, and S29 legends for expansion of abbreviations.

[a]Rivaroxaban 20 mg/d for 6 or 12 mo after initial long-term therapy.

[b]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE (unprovoked, 73%; cancer, 5%; previous VTE, 19%).

[c]Follow-up was prespecified to be 6 mo (60%) or 12 mo (40%).

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. ITT analysis; 0.2% loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting benefit or no effect; relatively low number of events.

[f]Calculated from reported data with addition of one event to each event rate as event rate 0 in control group.

[g]One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.

[h]CI includes values suggesting benefit and harm.

[i]Bleeds contributing to death: none in the rivaroxaban group and none in the warfarin group.

[j]PTS: baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (Kahn et al[40]). There is threefold (Prandoni et al[120]) to 10-fold (van Dongen et al[121]) increase in PTS with recurrent VTE in the ipsilateral leg.

Table S31—*[Section 3.3] Dabigatran vs VKA Therapy for Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Warfarin	With Dabigatran	Relative Effect (95% CI)	Risk With Warfarin	Risk Difference With Dabigatran (95% CI)
Death (important outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	21/1,265 (1.7)	21/1,274 (1.6)	HR 0.98 (0.53-1.79)	17 per 1,000	0 fewer per 1,000 (from 8 fewer to 13 more)
Recurrent VTE (critical outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	24/1,265 (1.9)[f]	30/1,274 (2.4)[f]	HR 1.01 (0.65-1.84)	19 per 1,000[f]	0 more per 1,000 (from 7 fewer to 16 more)
Major bleeding (critical outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	24/1,265 (1.9)[g]	20/1,274 (1.6)[g]	HR 0.82 (0.45-1.48)	19 per 1,000[g]	3 fewer per 1,000 (from 10 fewer to 9 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits	Dabigatran: daily medication, No dietary restrictions, no frequent blood testing/monitoring	…	…	…

Bibliography: Schulman et al.[122] See Table S2, S5, and S29 legends for expansion of abbreviations.

[a]Dabigatran 150 mg bid taken orally for 6 mo after an initial treatment with LMWH or IV UFH.

[b]Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 mo after an initial treatment with LMWH or IV UFH.

[c]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE.

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Modified ITT analysis; 1.1% loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]One fatal VTE in dabigatran group and three fatal VTEs in warfarin group.

[g]One fatal major bleeding event in dabigatran group and one fatal major bleeding event in warfarin group.

Table S32—*[Section 4.1] Elastic Stocking for Prevention of PTS: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Brandjes et al[127]/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 (98 patients)	Cumulative incidence of mild to moderate and severe PTS	3 and 6 mo, then every 6 mo to a median of 76 mo	Compression stockings: Mild-moderate PTS: 20% (RR, 0.42; 95% CI 0.27-0.66; $P < .001$) Severe PTS: 11% (RR, 0.49; 95% CI, 0.25-0.95; $P < .001$) Control group: Mild-moderate PTS: 47% Severe PTS: 23%
Ginsberg et al[124]/2001	RCT	47 asymptomatic patients with valvular incompetence 1 y post-DVT	Compression stockings: below-knee elastic compression stockings 20-30 mm Hg (24 patients) Placebo: placebo stocking (23 patients)	PTS symptoms	57 mo (mean)	Compression stockings: PTS symptoms: 0% Placebo: PTS symptoms: 4%
Prandoni et al[120]/2004	RCT	180 patients with first episode of symptomatic, acute proximal DVT	Compression stockings: below-knee elastic compression stockings 30-40 mm Hg (90 patients) Control group: no intervention (90 patients)	Cumulative incidence of mild to moderate and severe PTS	3-5 y	Compression stockings: PTS symptoms: 25% (CI, 15.6%-33.4%) Control group: PTS symptoms: 49% (CI, 38.7%-59.4%)
Partsch et al[84]/2004	2-y follow-up to RCT	37 symptomatic patients with acute DVT followed long term	All anticoagulated with LMWH followed by oral anticoagulation Inelastic bandages + early ambulation (13 patients) Elastic stockings (30 mm Hg) + early ambulation (13 patients) Bed rest for 9 d, no compression (11 patients)	Overall leg pain Leg circumference PTS score (Villalta-Prandoni)	2 y	Leg pain: No difference between groups Calf circumference: No difference between groups PTS score: Significantly better outcome with ambulation and bandaging or stockings compared with bed rest ($P < .01$)
Ashwanden et al[130]/2008	RCT, single center	169 first or recurrent proximal DVT without PTS after 6 mo of compression stockings	Compression stockings: below-knee, 26-36 mm Hg (84 patients) Control group: stopped stockings (85 patients)	PTS shin changes (≥ C4 on CEAP)	0-7 y (mean, 3 y)	PTS compression stockings: 13% Control group: 20% HR: 0.8 (95 % CI, 0.3-1.3)

See Table S1, S2, S5, S10, and S29 legends for expansion of other abbreviations.

Table S33—*[Section 4.1] Elastic Stocking for Prevention of PTS: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Brandjes et al[127]/1997	Y	Y (sealed envelopes)	Patients: N Caregivers: N Assessors: Y Data analysis: PY	Intervention group: 4 lost to follow-up, 19 died Control group: 2 lost to follow-up, 18 died
Ginsberg et al[124]/2001	Y	Probably, but not specified	Patients: Y Caregivers: Y Assessors: Y data analysis: PY	Intervention: lost to follow-up not reported, 3 died Control group: lost to follow-up not reported
Prandoni et al[120]/2004	Y	Y	Patients: N caregivers: N Assessors: Y Data analysis: PY	Intervention: 2 lost to follow-up, 6 died Control group: 13 lost to follow-up
Ashwanden et al[130]/2008	Y	Y	Patients: N Caregivers: N Assessors: N Data analysis: N	Intervention: 19 (described) Control group: 13 (described)

See Table S5 legend for expansion of abbreviations.

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Table S34—*[Section 4.1] Evidence Profile: Elastic Compression Stockings vs No Elastic Compression Stockings To Prevent PTS of the Leg*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Elastic Compression Stockings	With Elastic Compression Stockings	Relative Effect (95% CI)	Risk With No Elastic Compression Stockings	Risk Difference With Elastic Compression Stockings (95% CI)
PTS (critical outcome; assessed with Villalta Score)											
421 (2 studies), 2 y	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[c] due to risk of bias	91/211 (43.1)[d]	41/210 (19.5)	RR 0.46 (0.34-0.63)[e]	479 per 1,000[d,f]	259 fewer per 1,000 (from 177 fewer to 316 fewer)[g]
Recurrent VTE (critical outcome)											
374 (2 studies), 5 y	No serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious[i]	Undetected	Moderate[h,i] due to imprecision	26/188 (13.8)	26/186 (14)	RR 1.01 (0.61-1.67)[e]	210 per 1,000[j]	2 more per 1,000 (from 82 fewer to 141 more)
Quality of life (important outcome)											
0 (0[k])							…	…	…	See comment[k]	…

Bibliography: Kolbach et al.[123] We excluded Ginsberg et al[124] and Belcaro et al[125] because they respectively randomized patients 7 and 12 mo after their DVT rather than at the time of the acute DVT. We also excluded Arpaia et al[126] because they randomized patients to receive stockings at the time of diagnosis of DVT vs 2 wk later.[126] See Table S1 and S5 legends for expansion of abbreviations.

[a]Brandjes[127] used graded elastic compression stockings (40 mm Hg of pressure at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf); stockings were applied 2 to 3 wk after the first episode of proximal DVT. Prandoni[120] used flat-knitted stockings (30-40 mm Hg of pressure at the ankle); stockings were started at hospital discharge an average of 1 wk after admission. In both studies, stockings were used for 2 y.

[b]Prandoni[120] excluded patients with recurrent ipsilateral DVT, preexisting leg ulcers, or signs of CVI, bilateral thrombosis, a short life expectancy, or a contraindication for use of stockings (eg, advanced-stage peripheral arterial insufficiency). Brandjes et al excluded patients with short life, paralysis of the leg, bilateral thrombosis, leg ulcers, or extensive varicosis.

[c]Patients were not blinded to the treatment assignment, and outcomes were partly based on subjective report of symptoms.

[d] In Prandoni,[120] most events occurred during the first 6 mo: the cumulative incidence of PTS in the control group was 40% after 6 mo, 47% after 1 y, and 49% after 2 y.

[e] The effect estimate shown here results from a meta-analysis (Mantel-Haenszel fixed-effects model) of the two relevant trials. A fixed-effects model was chosen because of the small number of studies available.

[f]This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates the PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[g]Severe PTS: assuming the same RR of 0.46 and a baseline risk of 8.1% over 2 y, the absolute reduction is 44 fewer severe PTS per 1,000 (from 30 fewer to 53 fewer) over 2 y.

[h]We did not rate down the quality of evidence for recurrent VTE for the lack of blinding because this a more objective outcome than PTS.

[i]CI includes both negligible effect and appreciable benefit or appreciable harm.

[j]This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE (Heit[128]) and 29.1% confirmed VTE (Prandoni[129]).

[k]This is an important outcome that should be considered in future studies.

Table S35—*[Section 4.2.1] Evidence Profile: Compression Stockings vs No Compression Stockings for Patients With PTS*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Compression Stockings	With Compression Stockings	Relative Effect (95% CI)	Risk With No Compression Stockings	Risk Difference With Compression Stockings (95% CI)
Symptomatic relief (critical outcome; assessed with treatment success[d])											
115 (2 studies), 12-26 mo	Serious[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected[g]	Low[e-g] due to risk of bias, imprecision	33/57 (57.9)	32/58 (55.2)	RR 0.96 (0.70-1.31)	579 per 1,000	23 fewer per 1,000 (from 174 fewer to 179 more)
Quality of life not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Recurrent VTE not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported[h]											
…	…	…	…	…	…	…	…	…	…	…	…

Bibliography: Ginsberg 2001[124]; Frulla. 2005[131] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a]Ginsberg et al: graduated compression stockings, 30-40 mm Hg (calf or thigh length, depending on symptoms). Patients were encouraged to wear stockings as much as possible during waking hours. Frulla (2005): below-knee graded elastic compression stockings (ECS) (30-40 mm Hg at the ankle). Patients in both arms of the study received hydroxyethylrutosides (HR) (we considered the ECS + HR vs HR comparison).

[b]Ginsberg et al: placebo stockings (calf or thigh length, depending on symptoms).

[c]Ginsberg et al included patients with PTS 1 y after chronic, typical proximal DVT. Frulla (2005) included patients with clinical symptoms and signs suggestive of PTS.

[d]Ginsberg et al reported treatment failure (defined a priori based on any of five clinical criteria, including symptoms and ulcer development). Treatment success refers to the absence of treatment failure. Frulla used the Villalta scale.

[e]Ginsberg et al: Adequacy of sequence generation and allocation concealment were unclear; patients and outcome assessors were adequately blinded; unclear whether analysis followed the ITT principle; unclear whether follow-up was complete. Frulla (2005): outcome assessors were blinded; follow-up was complete. ITT principle was adhered to, but sequence generation and allocation concealment were unclear, and patients were not blinded.

[f]Very small number of patients.

[g]Publication bias not detected but not ruled out given that we identified only one small study partially supported by industry (provision of graduated compression stockings).

[h]Indirect evidence from the CLOTS1 (Clots in Legs Or sTockings after Stroke) trial suggests that compression stockings is associated with an RR of 4 for skin complications.

[i]Absence of ulcer included in the treatment success outcome in Ginsberg et al.

Table S36—*[Section 4.2.2] Evidence Profile: Intermittent Compression Device vs No Intermittent Compression Device for Patients With Severe PTS*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Intermittent Compression Device	With Intermittent Compression Device	Relative Effect (95% CI)	Risk With No Intermittent Compression Device	Risk Difference With Intermittent Compression Device (95% CI)
Symptomatic relief (critical outcome; measured with symptom score (includes scoring of pain, swelling, and limitation of activity); range of scores, 10-70; better indicated by higher values)											
82 (2 studies[d]), 8 wk	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness[g]	Serious[h]	Undetected[i]	Moderate[e-i] due to imprecision	41[d]	41[d]	…	The mean symptomatic relief in the control groups was 0	The mean symptomatic relief in the intervention groups was 0.41 SDs higher (0.02 lower to 0.85 higher)
Quality of life (critical outcome; measured with VEINES-QOL; range of scores, 0-100; better indicated by higher values)											
0 (1 study[d,j]), 8 wk	No serious risk of bias[k]	No serious inconsistency	No serious indirectness[g]	Serious[h]	Undetected[d,l]	Moderate[f-h,k,l] due to imprecision	…	0	…	The mean quality of life in the control groups was 50.2	The mean quality of life in the intervention groups was 2.3 higher (1.04 lower to 5.64 higher)

(Continued)

Table S36—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Intermittent Compression Device	With Intermittent Compression Device	Relative Effect (95% CI)	Risk With No Intermittent Compression Device	Risk Difference With Intermittent Compression Device (95% CI)
Recurrent VTE not reported[m]											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported[n]											
…	…	…	…	…	…	…	…	…	…	…	…

Bibliography: Ginsberg 1999,[132] O'Donnell, 2008.[133] See Table S1, S5, and S10 legends for expansion of other abbreviations.

[a]Ginsberg et al: Extremity pump used bid for 20 min each session; 50 mm Hg (therapeutic pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device to wear for most of the day for 8 wk.

[b]Ginsberg et al: Extremity pump used bid for 20 min each session; 15 mm Hg (placebo pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device with no connection between motor and planar sheet for 8 wk.

[c]Patients with previous DVT with symptoms of severe PTS.

[d]Crossover RCTs.

[e]In both studies, sequence generation was adequate; patients were blinded. Analysis adhered to ITT principle, and there were no missing outcome data. In Ginsberg et al (but not in O'Donnell et al), outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[f]$I^2 = 0\%$.

[g]Some concerns with indirecteness given relatively short follow-up (8 wk).

[h]Very small number of patients. CI includes both values suggesting no effect and values suggesting a beneficial effect.

[i]Publication bias not detected but not ruled out given that we identified only two small studies with one (Ginsberg et al) partially supported by industry (provision of devices).

[j]O'Donnell et al.

[k]Sequence generation was adequate; patients were blinded; analysis adhered to ITT principle; and there were no missing outcome data. However, outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[l]Publication bias not detected but not ruled out given that we identified only one small study.

[m]O'Donnell et al indicated no cases of recurrent VTE by the end of this study but judged the follow-up period to be short.

[n]O'Donnell et al indicated that one patient in the control group developed a venous ulceration. Three other participants developed nonserious skin-related side effects. Indirect evidence from the CLOTS1 (Clots in Legs Or sTockings after Stroke) trial suggests that compression stockings are associated with an RR of 4 for skin complications: Common side effects are attributed to Venowave were heat sensation, skin irritation, and increased sweating.

Table S37—*[Section 4.3] Evidence Profile: Venoactive Medication vs No Venoactive Medication for Patients With PTS*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Venoactive Medication	With Venoactive Medication	Relative Effect (95% CI)	Risk With No Venoactive Medication	Risk Difference With Venoactive Medication (95% CI)
Symptomatic relief (critical outcome; assessed with PTS score (Villalta scale) < 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al; improved tiredness of the leg at 8 wk in de Jongste et al[c])											
163 (2 studies)	No serious risk of bias[d]	Serious[e]	No serious indirectness	Serious[f]	Undetected[g]	Low[d-g] due to inconsistency, imprecision	39/82 (47.6)	44/81 (54.3)	RR 1.14 (0.85-1.52)	476 per 1,000	67 more per 1,000 (from 71 fewer to 247 more)
Quality of life not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Recurrent VTE not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Side effects (critical outcome)											
203 (2 studies)	No serious risk of bias[d]	No serious inconsistency[h]	No serious indirectness	Serious[f]	Undetected[g]	Moderate[d,f-h] due to imprecision	5/82 (6.1%)	13/121 (10.7%)	RR 2.04 (0.76-5.51)	61 per 1,000	63 more per 1,000 (from 15 fewer to 275 more)

Bibliography: Frulla 2005[131] de Jongste 1989.[134] See Table S1, S5, and S10 legends for expansion of abbreviations.

[a]Included studies assessed rutosides; we excluded Monreal et al[135] because it compared two venoactive medications.

[b]Patients with PTS and history of DVT in PTS leg.

[c]Investigators assessed other symptoms (pain, heaviness, swelling feeling, restless legs, and cramps) but did not report a composite score. The symptom we chose to report showed the most benefit; the effect estimates for the other symptoms ranged from 0.8 to 1.4, and none was statistically significant.

[d]In both studies, sequence generation and allocation concealment were unclear. Both studies blinded outcome assessors and had complete follow-up. Although de Jongste et al blinded patients, they did not adhere to the ITT principle and did not use a validated scale to measure symptomatic relief. Although Frulla (2005) adhered to the ITT principle, it did not blind patients.

[e]$I^2 = 77\%$.

[f]Small number of patients. CI including both values suggesting harms and values suggesting benefits.

[g]Publication bias not detected but not ruled out given that we identified only two small studies, and it was unclear whether they were funded by industry.

[h]$I^2 = 7\%$.

Table S38—*[Section 5.4] Evidence Profile: Fondaparinux vs IV UFH for Initial Anticoagulation of Acute PE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With UFH	With Fondaparinux	Relative Effect (95% CI)	Risk With UFH	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	48/1,110 (4.3)	57/1,103 (5.2)	RR 1.20 (0.82-1.74)	43 per 1,000	9 more per 1,000 (from 8 fewer to 32 more)
Recurrent VTE (critical outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	56/1,110 (5.0)[f]	42/1,103 (3.8)[f]	RR 0.75 (0.51-1.12)	50 per 1,000[f]	13 fewer per 1,000 (from 25 fewer to 6 more)
Major bleeding (critical outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	26/1,110 (2.3)[g]	22/1,103 (2.0)[g]	RR 0.85 (0.49-1.49)	23 per 1,000[g]	4 fewer per 1,000 (from 12 fewer to 11 more)

Bibliography: Büller et al.[136] See Table S1, S2, S4, and S7 legends for expansion of abbreviations.

[a]Fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing < 50, 50 to 100, or > 100 kg, respectively) SC once daily given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

[b]UFH continuous IV infusion (ratio of the aPTT to a control value, 1.5-2.5) given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

[c]All patients had acute symptomatic hemodynamically stable PE.

[d]Allocation was concealed. Patients, providers, and data collectors not blinded. Outcome adjudicators were blinded; 0.6% of randomized patients were lost to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]Sixteen fatal VTE in fondaparinux group and 15 fatal VTE in UFH group.

[g]Fourteen patients in the fondaparinux group and 12 in the LMWH group had a major bleeding during the initial period (6-7 d). Of these, one in the fondaparinux group and one in the UFH group were fatal.

Table S39—*[Section 5.5] Evidence Profile: Early Discharge vs Standard Discharge in the Treatment of Acute PE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Standard Discharge	With Early Discharge	Relative Effect (95% CI)	Risk With Standard Discharge	Risk Difference With Early Discharge (95% CI)
Mortality (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	6/228 (2.6)	4/243 (1.6)	RR 0.58 (0.17-1.97)	26 per 1,000	11 fewer per 1,000 (from 22 fewer to 26 more)
Nonfatal recurrent PE (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	2/228 (0.9)	3/243 (1.2)	RR 1.23 (0.25-6.03)	9 per 1,000	2 more per 1,000 (from 7 fewer to 44 more)
Major bleeding (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	1/228 (0.4)	4/243 (1.6)	RR 2.74 (0.45-16.71)	4 per 1,000	8 more per 1,000 (from 2 fewer to 69 more)
Quality of life not reported											
…	…	…	…	…	…	…		…	…	…	…

Bibliography: Otero et al,[137] Aujesky et al.[138] See Table S1, S2, and S5 legends for expansion of abbreviations.

[a]Mean length of hospital stay: 3.4 (SD 1.1) vs 9.3 (SD 5.7) in Otero et al and 0.5 (SD 1.0) vs 3.9 (SD 3.1) in Aujesky et al.

[b]The two RCTs included only patients with low risk: risk classes I or II on the Pulmonary Embolism Severity Index in Aujesky et al[139]; low risk on clinical prediction rule by Uresandi et al[140] in Otero et al.

[c]Otero et al: allocation concealed, no patients lost to follow-up, ITT analysis, no blinding of outcome assessors reported, study stopped early because the rate of short-term mortality was unexpectedly high in the early discharge group (2 [2.8%] vs 0 [0%]). Aujesky et al: unclear whether allocation was concealed, three (1%) patients had missing outcome data, ITT analysis, outcome adjudicators blinded, no early stoppage.

[d]CI includes both values suggesting no effect and values suggesting appreciable harm or appreciable benefit.

Table S40—*[Section 5.6.1] Evidence Profile: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemically Administered Thrombolytic Therapy	With Systemically Administered Thrombolytic Therapy	Relative Effect (95% CI)	Risk With No Systemically Administered Thrombolytic Therapy	Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)
Mortality (critical outcome)											
847 (12 studies), 30 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[g]	Undetected[h]	Low[e-h] due to risk of bias and imprecision	26/423 (6.1)	15/424 (3.5)	RR 0.7 (0.37-1.31)	Low[i,j]	
										11 per 1,000	3 fewer per 1,000 (from 7 fewer to 3 more)
										High[i,j]	
										89 per 1,000	27 fewer per 1,000 (from 56 fewer to 28 more)
Recurrent PE (important outcome)											
801 (9 studies), 30 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[g]	Undetected[h]	Low[e-h] due to risk of bias and imprecision	30/404 (7.4)	18/397 (4.5)	RR 0.7 (0.4-1.21)	57 per 1,000	17 fewer per 1,000 (from 34 fewer to 12 more)
Major bleeding (critical outcome)											
847 (12 studies), 10 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[k]	Undetected[h]	Moderate[e,f,h,k] due to risk of bias and imprecision	24/423 (5.7)	38/424 (9)	RR 1.63 (1-2.68)[l]	Low[m]	
										1 per 1,000	1 more per 1,000 (from 0 more to 2 more)

(Continued)

Table S40—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemically Administered Thrombolytic Therapy	With Systemically Administered Thrombolytic Therapy	Relative Effect (95% CI)	Risk With No Systemically Administered Thrombolytic Therapy	Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)
										High[m]	
										62 per 1,000	39 more per 1,000 (from 0 more to 104 more)

Bibliography: Nine earlier studies[141-149] extracted from three systematic reviews (Dong et al,[150] Wan et al,[151] Agnelli et al[152]) and two recently published studies (Becattini C et al,[153] Fassulo et al[154]). See Table S1 and S2 legends for expansion of abbreviations.

[a]Included studies used different thrombolytic agents with varying doses and durations of administration; no statistical heterogeneity was noted.

[b]Thrombolysis was in addition to anticoagulation (most of the studies used heparin followed by warfarin; three studies used warfarin only).

[c]One study included exclusively patients with hemodynamic compromise (shock); six excluded them, whereas the rest either included a number of such patients or did not specify related eligibility. criteria. Of studies not restricted to patients with hemodynamic compromise (n = 11), only three were clearly restricted to patients with right ventricular dysfunction; the rest either did not specify related eligibility criteria or included both patients with and without right ventricular dysfunction. As a result, it was not possible to perform reliable categorization of studies to conduct subgroup analyses based on the presence or absence of right ventricular dysfunction or hemodynamic compromise.

[d]Studies included patients at low risk of bleeding.

[e]Report of methodologic quality was poor in most studies. Of the 12 eligible studies, allocation was concealed in five, three were single blinded (outcome assessor), six were double blinded, and three were not blinded. Most studies did not report on missing outcome data. None of the studies was stopped early for benefit. For the increase in bleeding with thrombolytic therapy, quality of evidence is increased from low to moderate because there is high quality evidence of this association in patients with myocardial infarction and the indirectness of this evidence to patients with PE is minor.

[f]$I^2 = 0\%$.

[g]CI includes values suggesting both benefit and no effect or harm; small number of events.

[h]Inverted funnel plots suggested possible publication bias in favor of thrombolytics.

[i]Recurrent PE stratification based on the simplified Pulmonary Embolism Severity Index validated in the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) cohort.[155]

[j]Some studies suggest that the baseline risk of mortality in patients with hemodynamic instability is high as 30% (Wood et al).[156] In that case, the absolute number of death associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).

[k]CI includes values suggesting both harm and no effect; small number of events.

[l]Indirect evidence from studies of thrombolysis for myocardial infarction and acute stroke provide more-precise estimates of increase major bleeding with thrombolytics use.

[m]Major bleeding risk stratification derived from the RIETE cohort.[157] The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of major bleeds with thrombolysis would be 20 per 1,000 (from 0 more to 52 more).

Table S41—*[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Clinical Description and Results*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
			SK + heparin vs heparin				
Tibbutt et al[148]/1974	SK 600,000 units intrapulmonary followed by 100,000 units for 72 h	SK: 11/13 (84.6%)	72 h	SK: 0/11	SL: 1/11 (9.1%)	SK: 0/11	All hydrocortisone 100 mg and at 60 h of treatment warfarin initial dose 25 mg for 6 mo.
	Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h	Heparin: 12/17 (70.6%)		Heparin: 0/12	Heparin: 1/12 (8.3%) RR 0.92 (0.06-12.95)	Heparin: 0/12	Seven patients who failed to complete the treatment regimen were excluded from the analysis.
							Patients reporting major bleeding required a blood transfusion.
							Some 6-mo follow-up data available
Ly et al[146]/1978	SK 250,000 units followed by 100,000 units/h for 72 h	SK: 14/14	10 d	SK: 1/14 (7.1%)	SK: 4/14 (28.6%)	SK: 1/14 (7.1%)	Primary outcome was angiographic reperfusion.
	Heparin 15,000 units followed by 1,250 units/h for 7 d	Heparin: 11/11		Heparin: 2/11 (18.2%) RR 2.55 (0.26-24.56)	Heparin: 2/11 (18.2%) RR 0.64 (0.14-2.86)	Heparin: 2/11 (18.2%) RR 2.55 (0.26-24.56)	Five of the 25 patients received nonrandomized therapy. Uncertain if deaths were in patients who were randomized or not randomized.
Dotter et al[143]/1979	SK 250,000 units followed by 100,000 units/h for 18-72 h	SK: 15/15	In hospital	SK: 0/15	SK: 3/15 (20.0%)	SK: 1/15 (6.7%)	All: warfarin/VKA. Primary outcome was angiographic reperfusion (not clearly stated).
	Heparin 1,500 units per kg for 2-7 d	Heparin: 16/16		Heparin: 1/16 (6.3%) RR 2.82 (0.12-64.39)	Heparin: 4/16 (25.0%) RR 1.25 (0.33-4.68)	Heparin: 2/16 (12.5%) RR 1.88 (0.19-18.60)	
Jerjes-Sanchez et al[145]/1995	SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h	SK: 4/4	In hospital	SK: 0/4 (0%)	SK: 0/4 (0%)	SK: 0/4 (0%)	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 SK patients had not.
	Heparin 10,000 units followed by 1,000 units/h	Heparin: 4/4		Heparin: 4/4 (100%) RR 9.00 (0.64-126.85)	Heparin: 0/4 (0%)	Heparin: 4/4 (100%) RR 9.00 (0.64-126.85)	

(Continued)

Table S41—*Continued*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
			Urokinase vs heparin				
UPET Study Group et al[141]/1970	Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h	Urokinase 82/82	2 wk	Urokinase: 12/82 (14.6%)	Urokinase: 37/82 (45.1%)	Urokinase: 6/82 (7.3%)	All: heparin for a minimum of 5 d. The major bleeding reported includes moderate + severe bleeding.
	Heparin: infusion of 75 units/lb followed by 10 units/lb per h	Heparin: 78/78		Heparin: 15/78 (19.2%) RR 1.31 (0.66-2.63)	Heparin: 21/78 (26.9%) RR 0.60 (0.39-0.92)	Heparin: 7/78 (8.9%) RR 1.23 (0.43-3.49)	Angiographic follow-up data available up to 12 mo.
Marini et al[147]/1988	High dose: urokinase 3,300,000 units over 12 h	High-dose urokinase: 10/10	7 d	High-dose urokinase: 0/10	High-dose urokinase: 0/10	High-dose urokinase: 0/10	Primary outcome was lung scan perfusion.
	Low dose: urokinase 800,000 units over 12 h daily for 3 d	Low-dose urokinase: 10/10		Low-dose urokinase: 0/10	Low-dose urokinase: 0/10	Low-dose urokinase: 0/10	Thrombolysis arms did not receive heparin.
	Heparin 30,000 units/d for 7 d followed by OAC	Heparin: 10/10		Heparin: 0/10	Heparin: 0/10	Heparin: 0/10	All patients: OACs continued for 1 y.
			rt-PA (alteplase) + heparin vs heparin				
Dalla-Volta et al[142]/1992	rt-PA 10 mg followed by 90 mg over 2 h	rt-PA alteplase: 20/20	30 d	rt-PA alteplase: 1/20 (5.0%)	rt-PA alteplase: 3/20 (15.0%)	rt-PA alteplase: 2/20 (10.0%)	Primary outcome was angiographic reperfusion.
	Heparin 10,000 units followed by 1,750 units/h for 7-10 d	Heparin: 16/16		Heparin: 0/16 RR 2.43 (0.11-55.89)	Heparin: 2/16 (12.5%) RR 1.20 (0.23-6.34)	Heparin: 0/16 RR 4.05 (0.21-78.76)	
Goldhaber et al[158]/1993	rt-PA alteplase 100 mg over 2 h followed by heparin 1,000 units/h	rt-PA: 46/46	In hospital 14-21 d	rt-PA: 0/46	rt-PA: 3/46 (6.5%)	rt-PA: 0/46	Primary outcome was echocardiographic right ventricular function.
	Heparin 5,000 units followed by 1,000 units/h	Heparin: 55/55		Heparin: 5/55 (9.1%) RR 0.11 (0.01-1.91)	Heparin: 1/55 (1.8%) RR 3.59 (0.39-33.33)	Heparin: 2/55 (3.6%) RR 0.24 (0.01-4.84)	
Konstantinides et al[159]/2002	Alteplase 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h	Alteplase: 118/118	30 d	Alteplase: 4/118 (3.4%)	Alteplase: 1/118 (0.8%)	Alteplase: 4/118 (3.4%)	Primary outcome was death or need for escalation of therapy (later decision could be made after unblinding).
	Heparin 5,000 units followed by 1,000 units/h + placebo	Heparin + placebo: 138/138		Heparin + placebo: 4/138 (2.9%) RR 1.17 (0.30-4.57)	Heparin + placebo: 5/138 (3.6%) RR 0.23 (0.03-1.97)	Heparin + placebo: 3/138 (2.2%) RR 1.56 (0.36-6.83)	

(Continued)

Table S41—*Continued*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
Levine et al[160]/1990	rt-PA 0.6mg/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 5,000 units followed by 30,000/d	Placebo: 25/25		Placebo: 0/25	Placebo: 0/25	Placebo: 0/25 RR 2.29 (0.10-54.06)	
PIOPED Investigators[144]/1990	rt-PA 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 + heparin (doses determined by physician)	Placebo: 4/4		Placebo: 0/4	Placebo: 0/4 RR 1.50 (0.07-30.59)	Placebo: 0/4	Heparin doses determined by attending physician in both groups One death occurred 19 d after treatment
Fasullo et al[154]/2011	Alteplase 100 mg over 2 h	Alteplase: 37/37	10 d	Alteplase: 0/37	Alteplase: 2/37 (5.4%)	Alteplase: 0/37	All had right ventricular dysfunction. Primary outcome was echocardiographic changes.
	Placebo + heparin 5,000 units followed by 1,000 units/h	Placebo: 35/35		Placebo: 3/35 (8.5%)	Placebo: 1/35 (2.9%)	Placebo: 5/35 (14.2%)	Three recurrent PE were fatal. One additional fatal and nonfatal PE in heparin arm by 180 d. No fatal or intracranial bleeds.
			Tenectaplase + heparin vs heparin				
Becattini et al[153]/2010	Tenectaplase: ~2 mg/kg bolus	Tenectaplase: 28/28	30 d	Tenectaplase: 2/28	Tenectaplase: 2/28	Tenectaplase: 0/28	All had right ventricular dysfunction. Primary outcome was echocardiographic changes.
	Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)	Placebo: 32/32		Placebo: 1/32	Placebo: 1/32	Placebo: 1/32	No fatal PE or major bleeding; one intracranial bleed (tenectaplase).

CTA = Committee on Thrombolytic Agents; OAC = oral anticoagulant; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; UPET = Urokinase Pulmonary Embolism Trial. See Table S1, S2, and S11 legends for expansion of other abbreviations.

Table S42—*[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Methodologic Quality*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
			SK + heparin vs heparin				
Tibbutt et al[148]/1974	SK 600,000 units intrapulmonary followed by 100,000 units for 72 h	RCT	PY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK: 0/11 (0%)	Per protocol	All hydrocortisone 100 mg and at 60 h of treatment, warfarin initial dose 25 mg for 6 mo.
	Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h				Heparin: 0/12 (0%)		Seven patients who failed to complete the treatment regimen were excluded from the analysis.
Lyet al[146]/1978	SK 250,000 units followed by 100,000 units/h for 72 h	RCT	CY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK: 0/14 (0%)	As treated	Included 5 nonrandomized patients, and uncertain if deaths occurred in those who were randomized or not randomized.
	Heparin 15,000 U followed by 1250 U/h for 7days				Heparin: 0/11 (0%)		
Dotter et al[143]/1979	SK 250,000 units followed by 100,000 units/h for 18-72 h	RCT	PY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK plus heparin: 0/15 (0%)	ITT	
	Heparin 1,500 units per kg for 2-7 d				Heparin: 0/16 (0%)		
Jerjes-Sanchez et al[145]/1995	SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h	RCT	CY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK + heparin: 0/4 (0%)	ITT	
	Heparin 10,000 units followed by 1,000 units/h				Heparin: 0/4 (0%)		
			Urokinase vs heparin				
UPET Study Group[141,149]/1970	Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h Heparin: infusion of 75 units/lb followed by 10 units/lb per h	RCT	CY	Patients: CY Caregivers: CN Data Collectors: CY Adjudicators: CY Data Analysts: CY	Urokinase: 0/82 (0%) Heparin: 0/78 (0%)	As treated	

(Continued)

Table S42—*Continued*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
Marini et al[147]/1988	High dose: urokinase 3,300,000 units over 12 h	RCT	PY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	High-dose urokinase: 0/10 (0%)	ITT	
	Low dose: urokinase 800,000 units over 12 h daily for 3 d				Low-dose urokinase: 0/10 (0%)		
	Heparin 30,000 units/d for 7 d followed by OAC				Heparin: 0/10 (0%)		
			rt-PA (alteplase) + heparin vs heparin				
Dalla-Volta et al[142]/1992	rt-PA (alteplase) 10 mg followed by 90 mg over 2 h	RCT	PY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	rt-PA: 0/20 (0%)	ITT	
	Heparin 10,000 units followed by 1,750 units/h for 7-10 d				Heparin: 0/16 (0%)		
Goldhaber et al[158]/1993	rt-PA 100 mg over 2 h followed by heparin 1,000 units/h	RCT	CY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	rt-PA: 0/46 (0%)	ITT	
	Heparin 5,000 units followed by 1,000 units/h				Heparin: 0/55 (0%)		
Konstantinides et al[159]/2002	rt-PA (alteplase) 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h	RCT	CY	Patients: PY Caregivers: CN Data Collectors: PY Adjudicators: PN Data Analysts: PY	rt-PA: 0/118 (0%)	ITT	All: UFH 5,000 units.
	Heparin 5,000 units followed by 1,000 units/h				UFH: 0/138 (0%)		
Levine et al[160]/1990	rt-PA 0.6 mg/kg over 2 min	RCT	PY	Patients: CY Caregivers: CY Data Collectors: CY Adjudicators: CY Data Analysts: CY	rt-PA: 0/33(0%)	ITT	All: UFH initial bolus of 5,000 units followed by continuous infusion at starting dose of 30,000 for the first 24 h.
	Placebo + heparin 5,000 units followed by 30,000/d				Heparin: 0/25(0%)		

(Continued)

Table S42—*Continued*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
PIOPED Investigators[144]/1990	rt-PA 40-80mg at 1 mg/min	RCT	PY	Patients: CY Caregivers: CY Data Collectors: PY Adjudicators: PY Data Analysts: PY	rt-PA: 0/9(0%)	ITT	All: heparin doses determined by attending physician.
	Placebo plus heparin (doses determined by physician)				Heparin: 0/4(0%)		
Fasullo et al[154]/2011	Alteplase 100 mg over 2 h	RCT	CY	Patients: CY Caregivers: CY Data Collectors: PY Adjudicators: CY Data Analysts: PY	rt-PA: 0/37	ITT	Primary outcome was echocardiographic changes.
	Placebo + heparin 5,000 units followed by 1,000 units/h				Heparin: 0/35		
			rt-PA (alteplase) + heparin vs heparin				
Becattini et al[153]/2010	Tenectaplase: ~2 mg/kg bolus	RCT	CY	Patients: CY Caregivers: CY Data Collectors: CY Adjudicators: CY Data Analysts: PY	Tenectaplase: 0/28(0%)	ITT	Primary outcome was echocardiographic changes.
	Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)				Heparin: 0/30(0%)		

See Table S1, S2, S5, S11, and S41 legends for expansion of other abbreviations.

Table S43—*[Section 8.1] Evidence Profile: Fondaparinux vs Placebo for Acute SVT*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Fondaparinux	With Fondaparinux	Relative Effect (95% CI)	Risk With No Fondaparinux	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e,f]	Undetected	Moderate[d-g] due to imprecision	1/1,500 (0.1)	2/1,502 (0.1)	RR 1.99 (0.18-21.87)	4 per 1,000[h]	4 more per 1,000 (from 3 fewer to 83 more)
VTE (critical outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[d]	22/1,500 (1.5)	4/1,502 (0.3)	RR 0.18 (0.06-0.53)	33 per 1,000[h]	27 fewer per 1,000 (from 16 fewer to 31 fewer)
SVT recurrence (important outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[f,g]	Undetected	High[d] due to imprecision	26/1,500 (1.7)	8/1,502 (0.5)	RR 0.31 (0.14-0.68)	19 per 1,000[h]	13 fewer per 1,000 (from 6 fewer to 16 fewer)
Major bleeding (critical outcome)											
2,987 (1 study), 47 d	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e,i]	Undetected	Moderate[d,e,i] due to imprecision	1/1,488 (0.1)	1/1,499 (0.1)	RR 0.99 (0.06-15.86)[e]	1 per 1,000	0 fewer per 1,000 (from 1 fewer to 10 more)
Quality of life not measured											
…	…	…	…	…	…	…		…	…	…	…

Bibliography: CALISTO study by Decousus et al.[161] CALISTO = Comparison of ARIXTRA™ in lower LImb Superficial Thrombophlebitis with placebo; SVT = superficial vein thrombosis. See Table S1 and S5 legends for expansion of other abbreviations.

[a]Fondaparinux 2.5 mg for 45 d.

[b]Patients in the two treatment groups benefited from close clinical monitoring with adequate diagnostic procedures in the event of new and persistent symptoms.

[c]Patients with infusion-related SVT were excluded if from CALISTO.

[d]Allocation concealed. Outcome adjudicators, steering committee, patients, providers, and data collectors blinded. Follow-up rate was 98%. ITT analysis for efficacy outcomes. Not stopped early for benefit.

[e]CI includes values suggesting large benefit and values suggesting large harm.

[f]We rated down by only one level because the low event rate and large sample size.

[g]Small number of events.

[h]Baseline risk derived from a large prospective cohort study.[162]

[i]The upper limit of the CI for absolute effect (10 more bleeds) is not low enough to suggest a clear balance of benefits vs harms.

Table S44—*[Section 8.1] Superficial Vein Thrombosis Treatment: Clinical Description and Results (Randomized Trials Comparing Treatments)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
STENOX Study[163] Group/2003	Parallel RCT, multicenter	436 patients with ultrasound-confirmed acute symptomatic SVT (≥ 5 cm length) of the lower extremity	Enoxaparin 40 mg SC daily Enoxaparin 1.5 mg/kg SC daily Tenoxicam, 20 mg po daily Placebo once daily All given 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 bleeding 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 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* = ns for all comparisons of active treatment vs placebo SVT recurrence/extension day 12: Placebo: 33/112 (29.5%) Enoxaparin 40 mg: 9/110 (8.3%); RR 0.28 (95% CI, 0.14-0.55) Enoxaparin 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 3 mo: Placebo: 5/112 (4.5%) (PE 0) Enoxaparin 40 mg: 6/110 (5.7%); (PE 2); RR 1.22 (95% CI, 0.38-3.89) Enoxaparin 1.5mg/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* = ns for all comparisons of active treatment vs placebo SVT recurrence/extension 3 mo: Placebo: 37/112 (33.0%) Enoxaparin 40 mg: 16/110 (14.5%); RR 0.44 (95% CI, 0.26-0.74)

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
						Enoxaparin 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 bleeding: 0 Death: 0
Titon et al[164] /1994	Parallel RCT, multicenter	117 patients with ultrasound-confirmed SVT of the lower extremities	Nadroparin fixed dose, 6,150 anti-Xa International Units daily	Echocardiographic extension of thrombus at day 7 and at 8 wk	8 wk	Day 7 extension of thrombus: Fixed-dose nadroparin: 1/38 (2.6%)
			Nadroparin 31.5 anti-Xa International Units/kg SC daily	Changes in symptoms and clinical signs (warmth, flushing, edema, pain on palpation)		Weight-based nadroparin: 2/40 (5%); RR 1.90 (95% CI, 0.18-20.1)
			Naproxen 500 mg po daily	DVT		Naproxen: 1/39 (2.6%); RR 0.97 (95% CI, 0.06-15.02)
			Treatments given for 6 d	PE		P = ns
			All patients wore compression stockings for 7 d	Major bleeding		8-wk 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 (95% CI) 0.19 (0.01-3.73) No DVT, PE, or major bleeding 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≤ .01 in favor of nadroparin vs naproxen; this difference was maintained at 8 wk
Prandoni for Vesalio Investigators Group[165]/2005	Parallel RCT, multicenter	164 patients with ultrasound-confirmed acute SVT of the greater saphenous vein	High-dose weight-adjusted nadroparin (190 anti-Xa International Units/kg for 10 d followed by 95 anti-Xa International Units/kg for 20 d)	Composite outcome of asymptomatic or symptomatic SVT extension, asymptomatic or symptomatic DVT, symptomatic PE at 3 mo	3 mo	3 mo follow-up:

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
				Improvement in clinical symptoms and signs at 1 mo		
			Low-dose nadroparin (2,850 anti-Xa International Units for 30 d)	Major bleeding		SVT High dose: 2/83 (2.4%) (1 occurred while on treatment) Low dose: 5/81 (6.2%) (all occurred while on treatment) RR 2.56 (95% CI, 0.51-12.83)
				Death		
			No placebo group NSAIDS and aspirin use discouraged			VTE High dose: 4/83 (4.8%) (3 symptomatic events; 1 [PE] occurred while on 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 bleeding: 0 Death: 0
Marchiori et al[166]/2002	Parallel RCT, single center	60 patients with ultrasound-confirmed first acute SVT of greater saphenous vein	Low-dose UFH (5,000 International Units bid SC for 4 wk)	VTE	6 mo	VTE during treatment period: Low dose: 4/30 (13.3%) (3 asymptomatic DVT, 1 PE)
				Extension/Recurrence of thrombosis		
			High-dose UFH (12,500 International Units for 1 wk then 10,000 International Units for 3 wk)	Major bleeding		High dose: 0/30 (0%); RR 0.11 (95% CI, 0.01-1.98; P = ns)
				HIT		
				Death		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 = ns)
			Use of concomitant systemic or local antiinflammatory drugs permitted but use not described			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 = ns) 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 = ns)

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
						No major bleeding, HIT, or death in any group
Belcaro et al[167]/1999	Parallel RCT, multicenter	562 patients with ultrasound-confirmed SVT and large varicose veins or venous incompetence	A. Elastic compression stockings alone B. Elastic compression stockings and simple flush ligation C. Elastic compression stockings and complete stripping and perforator ligation D. Elastic compression stockings and low-dose SC heparin E. Elastic compression stockings and LMWH 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: A: 32/78 (41%) B: 11/78 (14.1%); RR 0.34 (95% CI, 0.19-0.63) C: 0/70; RR 0.02 (95% CI, 0.00-0.27) D: 4/71 (5.6%); RR 0.14 (95% CI, 0.05-0.37) E: 4/76 (5.2%); RR 0.13 (95% CI, 0.05-0.35) F: 5/71 (7.0%); RR 0.17 (95% CI, 0.07-0.42) $P < .05$ for groups C, D, E, F vs A or B Extension at 6 mo: A: 13/78 (16.7%) B: 6/78 (7.7%); RR 0.46 (95% CI, 0.18-1.15) C: 1/70 (1.4%); RR 0.09 (95% CI, 0.01-0.64) D: 2/71 (2.8%); RR 0.17 (95% CI, 0.04-0.72) E: 1/76 (1.3%); RR 0.08 (95% CI, 0.01-0.59) F: 5/71 (7%); RR 0.42 (95% CI, 0.16-1.13) *P* not stated New DVT at 3 mo: A: 6/78 (7.7%) B: 2/78 (2.5%); RR 0.33 (95% CI, 0.07-1.60) C: 2/70 (2.8%); RR 0.37 (95% CI, 0.08-1.78) D: 0/71 (0%); RR 0.08 (95% CI, 0.0-1.47) E: 0/76 (0%); RR 0.08 (95% CI, 0.0-1.38) F: 0/71 (0%); RR 0.08 (95% CI, 0.0-1.47) *P* = ns
Lozano et al[168]/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	Recurrence/extension of SVT VTE Complications of surgery	6 mo	Recurrent SVT Surgical group: 1/30 (3.3%) Enoxaparin group: 3/30 (10%); RR 3.0 (95% CI, 0.33-27.24)

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
			Outpatient enoxaparin 1 mg/kg bid for 1 wk then once daily for 3 wk	Major bleeding		VTE Surgical group: 2/30 (6.7%) (both symptomatic PE) Enoxaparin group: 0/30 (0%); RR 0.20 (95% CI, 0.01-4.0)
				Death		
			No placebo/control group	Costs		Wound infections: Surgical group: 2/30 (6.7%)
			All patients were instructed to wear elastic compression stockings and used acetaminophen for pain			Major bleeding: 0
						Death: 0
						Cost of treatment: Surgical group: $1,400/patient; mean, 1.6 d in hospital Enoxaparin group: $300/patient; 0 d in hospital
Sullivan et al[169]/2001	Systematic review of 6 studies (includes Belcaro (14 patients) and 5 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)	SVT progression	Surgical group: 4-6 mo	SVT progression: Surgical group: 18/148 (12%) Medical group: 10/71 (14%); RR 1.16 (95% CI, 0.56-2.38)
				DVT	Medical group: 6 d to 14 mo	DVT: Surgical group: 7/204 (3.4%) Medical group: 2/88 (2.2%) RR 0.66 (95% CI, 0.14-3.13)
				PE		PE: Surgical group: 2/98 (2.0%) Medical group: 0/17 (0%); RR 1.10 (95% CI, 0.06-21.98)
			Anticoagulation (IV heparin followed by VKA for 6 wks-6 mo) (n = 88)	Surgical complications Bleeding complications		Surgical complications: 6/78 (7.7%) (hematoma, seroma, infection) Bleeding complications: 0/17 (0%)

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Górski et al[170]/2005	Parallel RCT, multicenter	46 patients with ultrasound-confirmed SVT	Topical liposomal heparin spray gel (4 sprays of 458 International Units tid) Enoxaparin 40 mg SC once daily Treatment given for 7-14 d	Pain by visual analog scale (0-10) 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 article by reviewer Pain by visual analog scale, 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 assessment: Majority of patients (> 75%) reported good or very good treatment efficacy, no significant 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: 1/23 (4.3%); RR 0.30 (95% CI, 0.03-2.70) Adverse events: Allergic reaction in 1 patient in enoxaparin group Death: 0
Andreozzi et al[171]/1996	Parallel RCT, multicenter	56 patients with SVT of the lower limbs	A: Dermatan sulfate 100 mg SC once daily B: Dermatan sulfate 100 mg SC bid C: Dermatan sulfate 200 mg intramuscular once daily	Pain Increase in functional ability Local edema	30 d	Data extrapolated from graphs and figures in article by reviewer Resolution of pain, day 30: Group A: 47% Group B: 83% Group C: 79% *P* not stated

(Continued)

Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
			Treatment given for 30 d			Increase in ability to perform normal daily activities, day 30: Group A: 44% Group B: 67% Group C: 84% $P < .05$ groups B and C vs group A Local edema, day 30: Progressive improvement in all 3 groups; no significant differences between groups

The CALISTO study that compared fondaparinux with no fondaparinux is described in Table 28 and Table S42. HIT = heparin-induced thrombocytopenia; NSAID = nonsteroidal antiinflammatory drug; STENOX = Superficial Thrombophlebitis Treated by Enoxaparin. See Table S1, S2, S5, S21, and S43 legends for expansion of other abbreviations.

[a]Study design: RCT, cohort.

[b]Drugs: VKA, UFH, LMWH, NSAIDs, aspirin, topical treatments, surgery vs placebo, no treatment, each other or different durations or regimens of the same agent.

[c]Outcomes: extension of thrombus, symptomatic relief, DVT and PE, major bleeding, surgical complications, and death.

Table S45—*[Section 8.1] SVT Treatment: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up/ ITT
STENOX Study Group[163]/2003	Central randomization	Visually identical drugs and packaging; triple dummy design	Investigators, patients, and assessors blinded	9 lost to follow-up/ ITT
Titon et al[164]/1994	Randomized to one of three treatment groups; method of randomization not specified	Open label	Not blinded	8 lost to follow-up/ not specified
Prandoni for Vesalio group et al[165]/2005	Computer-generated random number sequence assigned to each patient to determine treatment group	Double dummy	Patients and adjudicators of outcome events blind	0 lost to follow-up/ ITT
Marchiori et al[166]/2002	Randomized to treatment group by computer-generated list	Not specified	Assessors blinded	0 lost to follow-up/ not specified
Belcaro et al[167]/1999	Not specified	Not blinded	Not blinded	118 lost to follow-up/not specified
Lozano et al[168]/2003	Method not specified	Not blinded	Not blinded	3 lost to follow-up/not specified
Sullivan et al[169]/2001	Review of six studies; includes one RCT (Belcaro [14 patients]) and five small case series	N/A	N/A	N/A
Andreozzi et al[170]/1996	Patients randomly assigned to one of three therapeutic groups (method not specified)	Open label	Not blinded	Not specified/not specified
Górski et al[171]/2005	Performed according to a prespecified randomization list; treatment allocated according to next number on list; no stratification was performed	Open trial	Not blinded	6 lost to follow-up/ITT

See Table S5, S12, S43, and S44 legends for expansion of abbreviations.

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Table S46—*[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Savage et al[172]/1999	Prospective cohort, two center	46 outpatients with UEDVT (includes 16 with CVC)	Dalteparin daily for 5-7 d (200 International Units/kg) and VKA with target INR of 2.0-3.0 Duration of VKA not provided	Symptomatic recurrence/extension of DVT PE Major bleeding Death	3 mo	Recurrence/extension DVT: 1/46 (2%) PE: 0/46 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay et al[173]/2003	Prospective cohort, single center	36 inpatients with UEDVT (includes 13 with CVC)	Nadroparin SC bid, 86 anti-Xa International Units/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 y	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 bleeding)
Prandoni et al[120]/2004	Prospective cohort, number of centers not stated	53 patients with first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death	Median of 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, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [numbers not provided])

(Continued)

Table S46—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Kovacs et al[174]/2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had CVC)	Dalteparin daily for 5-7 d (200 International Units/kg) and VKA to achieve target INR of 2.0-3.0	Recurrent VTE PE Major bleeding Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0/74 PE: 0/74 Major bleeding: 3/74 (4%) Death: 7/74 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0/74

CVC = central venous catheter; UEDVT = upper-extremity DVT. See Table S2, S7, and S41 legends for expansion of other abbreviations.

[a]Study design: prospective cohort studies.

[b]Drugs: IV UFH or LMWH followed by OACs.

[c]Outcomes: recurrent DVT and PE, major bleeding, total mortality, and early symptom relief.

Table S47—*[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up/ ITT
Savage et al[172]/1999	N/A	N/A	N/A	1 lost to follow-up/N/A
Karabay et al[173]/2003	N/A	N/A	N/A	0 lost to follow-up/N/A
Prandoni et al[120]/2004	N/A	N/A	N/A	2 lost to follow-up/N/A
Kovacs et al[174]/2006	N/A	N/A	N/A	0 lost to follow-up/N/A

See Table S12 and S46 legends for expansion of abbreviations.

Table S48—*[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 10 Patients)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Horne et al[175]/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	6 mo	Immediate patency: 10/18 (56%)
				Establishment of antegrade flow		Antegrade flow: 11/18 (61%)
				Bleeding events		Bleeds (all minor): 5/18 (28%)
Lee et al[176]/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%)

Early prospective observational studies with < 10 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines.[46] See Table S2, S10, S11, and S46 legends for expansion of abbreviations.

[a]Study design: retrospective and prospective cohort studies.

[b]Drugs: thrombolytic therapy compared with different types of lytic therapy or with anticoagulants.

[c]Outcomes: recurrent DVT and PE, vein patency, major bleeding, total mortality, and PTS of the arm.

Table S49—*[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Horne et al[175]/2000	No	N/A	N/A	Not specified
Lee et al[176]/2006	No	N/A	N/A	0 lost to follow-up

See Table S12 legend for expansion of abbreviation.

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Table S50—*[Section 9.3] Long-term Treatment of Acute UEDVT: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Intervention[a]	Outcomes[b]	Follow-up	Results
Savage et al[172]/1999	Prospective cohort, two center	46 outpatients with confirmed UEDVT (includes 16 with CVC)	Dalteparin 200 International Units/kg daily for 5-7 d 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 bleeding Death	3 mo	Recurrence/extension: 1/46 (2%) PE: 0 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay et al[173]/2003	Prospective cohort, single center	36 inpatients with confirmed UEDVT (includes 13 with CVC)	Nadroparin SC bid, 86 anti-Xa International Units/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 y	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 bleeding) PTS: 0
Martinelli et al[177]/2004	Case-control study with prospective follow-up of cases, single center	98 patients with primary UEDVT (none with CVC)	VKA for mean 6 mo (77 patients), heparin SC (14 patients), or antiplatelet agents (7 patients) for ≤ 3 mo	Recurrent VTE after anticoagulants stopped	Median of 5.1 y	Recurrent VTE: 12/98 (12%) overall (all UEDVT) Annual incidence recurrent VTE: 2.4% (95% CI, 1.2%-4.0%) (results not provided by treatment group)
Prandoni et al[178]/2004	Prospective cohort, number of centers not stated	53 patients with confirmed first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE	Median of 48 mo	Results not presented according to initial treatment with UFH vs LMWH

(Continued)

Table S50—*Continued*

Author/Year	Type of Publication	Participants	Intervention[a]	Outcomes[b]	Follow-up	Results
				Death PTS		Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 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 y Cumulative incidence: 27.3%
Kovacs et al[174]/2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had CVC)	Dalteparin 200 International Units/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0	Recurrent VTE PE Major bleeding Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0 PE: 0 Major bleeding: 3 (4%) Death: 7 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0

Early prospective observational studies with < 20 patients, and retrospective studies, are described in Table 3 of the Eight edition of these guidelines[46] See Table S2, S7, S10, and S46 legends for expansion of abbreviations.

[a]Drugs: VKA, UFH, LMWH vs placebo, control or each other.

[b]Outcomes: recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm.

Table S51—*[Section 9.3] Long-term Treatment of Acute UEDVT: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Savage et al[172]/1999	N/A	N/A	N/A	1 lost to follow-up
Karabay et al[173]/2003	N/A	N/A	N/A	0 lost to follow-up
Martinelli et al[177]/2004	N/A	N/A	N/A	Not specified
Prandoni et al[178]/2004	N/A	N/A	N/A	2 patients lost to follow-up
Kovacs et al[174]/2007	N/A	N/A	N/A	0 lost to follow-up

See Table S12 and S46 legends for expansion of abbreviations.

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