Antithrombotic Therapy for Venous Thromboembolic Disease

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Harry R. Büller, MD, Chair; Giancarlo Agnelli, MD;
Russel D. Hull, MBBS, MSc, FCCP;
Thomas M. Hyers, MD, FCCP; Martin H. Prins, MD; and
Gary E. Raskob, PhD

This chapter about antithrombotic therapy for venous thromboembolic disease is part of the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004; 126:179S–187S*). Among the key recommendations in this chapter are the following: for patients with objectively confirmed deep vein thrombosis (DVT), we recommend short-term treatment with subcutaneous (SC) low molecular weight heparin (LMWH) or, alternatively, IV unfractionated heparin (UFH) [both Grade 1A]. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C+). In acute DVT, we recommend initial treatment with LMWH or UFH for at least 5 days (Grade 1C), initiation of vitamin K antagonist (VKA) together with LMWH or UFH on the first treatment day, and discontinuation of heparin when the international normalized ratio (INR) is stable and > 2.0 (Grade 1A). For the duration and intensity of treatment for acute DVT of the leg, the recommendations include the following: for patients with a first episode of DVT secondary to a transient (reversible) risk factor, we recommend long-term treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A). For patients with a first episode of idiopathic DVT, we recommend treatment with a VKA for at least 6 to 12 months (Grade 1A). We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A). We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) [Grade 1A] and against low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (Grade 1A). For the prevention of the postthrombotic syndrome, we recommend the use of an elastic compression stocking (Grade 1A). For patients with objectively confirmed nonmassive PE, we recommend acute treatment with SC LMWH or, alternatively, IV UFH (both Grade 1A). For most patients with pulmonary embolism (PE), we recommend clinicians not use systemic thrombolytic therapy (Grade 1A). For the duration and intensity of treatment for PE, the recommendations are similar to those for DVT.

(CHEST 2004; 126:401S–428S)

Key words: cancer; chronic thromboembolic pulmonary hypertension; deep vein thrombosis; heparin-induced thrombocytopenia; low molecular weight heparin; pulmonary embolism; thrombectomy; thrombolytic therapy; thrombophilia; thrombophlebitis; unfractionated heparin; vena cava filter; venous thromboembolism; vitamin K antagonist

Abbreviations: aPTT = activated partial thromboplastin time; CI = confidence interval; CTPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low molecular weight heparin; PE = pulmonary embolism; PTS = postthrombotic syndrome; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SC = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

This chapter will describe the effectiveness of antithrombotic agents, as well as devices or surgical techniques that are used in the treatment of patients with acute venous thromboembolism (VTE), a disease that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). In addition, the treatment of patients with acute upper-extremity DVT and two important complications of VTE, postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTPH), are discussed.

Table 1 describes the eligibility criteria for the studies considered in each section of the recommendations that follow. Trials on fondaparinux and ximelagatran are described in the chapter by Weitz et al in this Supplement, since neither of these were approved when the panel wrote these guidelines.

1.0 Treatment of DVT

1.1 Initial treatment of acute DVT of the leg

Anticoagulation is the main therapy for acute DVT of the leg. The objectives of anticoagulant therapy in the initial treatment of this disease are to prevent thrombus extension and early and late recurrences of DVT and PE. The evidence for the need for anticoagulation in patients with DVT is based on studies performed > 40 years ago. The first and only trial[1] evaluating heparin in patients with symptomatic PE that incorporated an untreated group was published in the 1960s. This trial[1]

Table 1—Question Definition and Eligibility Criteria: Treatment of VTE

Section	Population	Interventions or Exposure	Outcome	Methodology
1.1	Initial treatment of acute DVT of the leg	IV UFH, LMWH, and VKA	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
1.2	Initial treatment of acute DVT of the leg	IV UFH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
1.3	Initial treatment of acute DVT of the leg	SC UFH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
1.4	Initial treatment of acute DVT of the leg	LMWH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
1.5	Initial treatment of acute DVT of the leg	Systemically administered thrombolysis	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs and cohort studies
1.6	Initial treatment of acute DVT of the leg	Catheter-directed thrombolysis	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs and cohort studies
1.7	Initial treatment of acute DVT of the leg	Catheter extraction or fragmentation and surgical thrombectomy	Recurrent DVT and PE, total mortality, quality of life, and PTS	RCTs and cohort studies
1.8	Initial treatment of acute DVT of the leg	Vena caval interruption	Recurrent DVT and PE, total mortality, quality of life, and PTS	RCTs and cohort studies
1.9	Initial treatment of acute DVT of the leg	Nonsteroidal anti-inflammatory agents	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs and cohort studies
1.10	Initial treatment of acute DVT of the leg	New antithrombotic agents	Recurrent DVT and PE, total mortality, quality of life, and PTS	RCTs and cohort studies
1.11	Initial treatment of acute DVT of the leg	Immobilization	Recurrent DVT and PE, total mortality, quality of life, and PTS	RCTs and cohort studies
2.1	Long-term treatment of acute DVT of the leg	VKA	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
2.2	Long-term treatment of acute DVT of the leg	SC UFH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
2.3	Long-term treatment of acute DVT of the leg	LMWH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
3.1	Prophylaxis of PTS	Compression stockings	Symptomatic PTS	RCTs
3.2	Treatment of PTS	Physical measures	Symptomatic relief and ulceration	RCTs and cohort studies
3.3	Treatment of PTS	Drugs	Symptomatic relief and ulceration	
4.1	Initial treatment of acute PE	IV UFH or LMWH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and chronic pulmonary hypertension	RCTs
4.2	Initial treatment of acute PE	Systemically and locally administered thrombolytic drugs	Recurrent DVT and PE, total mortality, quality of life, and chronic pulmonary hypertension	RCTs and cohort studies
4.3	Initial treatment of acute PE	Catheter extraction or fragmentation	Recurrent DVT and PE, total mortality, quality of life, and chronic pulmonary hypertension	RCTs and cohort studies
4.4	Initial treatment of acute PE	Pulmonary embolectomy	Recurrent DVT and PE, total mortality, quality of life, and chronic pulmonary hypertension	RCTs and cohort studies
4.5	Initial treatment of acute PE	Vena caval interruption	Recurrent DVT and PE, total mortality, quality of life, and chronic pulmonary hypertension	RCTs and cohort studies
4.6	Initial treatment of acute PE	New antithrombotic agents	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and chronic pulmonary hypertension	RCTs and cohort studies
5.1	Long-term treatment of acute PE	VKA	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
5.2	Long-term treatment of acute PE	LMWH	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs
6.1	CTPH	Pulmonary thromboendarterectomy, VKA, and caval filter	Mortality, recurrent DVT and PE, and quality of life	RCTs and cohort studies
7.1	Superficial thrombophlebitis	Drugs	Extension of thrombus/symptomatic relief, symptomatic DVT and PE, major bleeding	RCTs and cohort studies
8.1	Initial treatment of acute upper-extremity DVT	IV UFH and LMWH	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies

Table 1—*Continued*

Section	Population	Interventions or Exposure	Outcome	Methodology
8.2	Initial treatment of acute upper-extremity DVT	Thrombolytic therapy	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies
8.3	Initial treatment of acute upper-extremity DVT	Catheter extraction, surgical thrombectomy, or superior vena caval filter	Recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm	RCTs and cohort studies
8.4	Long-term treatment of acute upper-extremity DVT	Anticoagulants	Recurrent DVT and PE, major bleeding, total mortality, quality of life, and PTS	RCTs and cohort studies
8.5	Long-term treatment of acute upper-extremity DVT	Elastic bandages	Recurrent DVT and PE total mortality, quality of life, and PTS	RCTs and cohort studies

showed a high mortality rate in untreated patients; PE detected at autopsy was the cause of death in the majority of these patients. Subsequent uncontrolled studies[2–4] confirmed that mortality was reduced when heparin was used to treat VTE, and reported a high mortality when patients did not receive anticoagulant therapy. Patients with DVT should be treated with anticoagulants as soon as the diagnosis is confirmed by objective testing. If the clinical suspicion is high and there is a delay before diagnosis can be confirmed by objective tests, then treatment should be started while awaiting confirmation. However, treatment should be continued only if the diagnosis is confirmed. Three options are available for the initial treatment of DVT: (1) body weight-adjusted low molecular weight heparin (LMWH) administered subcutaneous (SC) without monitoring, (2) IV unfractionated heparin (UFH), or (3) SC UFH administered with monitoring and subsequent dose adjustments.

Two randomized clinical trials in patients with proximal DVT reported that IV UFH administered for 5 to 7 days is as effective as UFH administered for more prolonged periods, provided that it is followed by adequate long-term anticoagulant therapy.[5,6] The efficacy and safety of this therapeutic approach is supported by subsequent studies. Shortening the duration of the initial heparin treatment has obvious appeal, as it reduces both the duration of hospital stay and the risk of heparin-induced thrombocytopenia. The currently recommended approach is to start heparin and vitamin K antagonists (VKAs) together at the time of diagnosis, and to discontinue heparin when the international normalized ratio (INR) is stable and > 2.0; this usually occurs after 5 to 7 days of heparin therapy.

There is no consensus on the optimal starting dose of VKA. Two trials[7,8] performed in hospitalized patients reported that a starting dose of 5 mg of the VKA warfarin, compared to 10 mg, is associated with less excessive anticoagulation and is less likely to cause a transient hypercoagulable state due to a faster fall in the plasma level of protein C than in the other vitamin K-dependent coagulation factors (see the chapter by Ansell et al in this Supplement). In contrast, another study[9] performed in outpatients failed to demonstrate an advantage of a start-

ing dose of 5 mg over 10 mg of warfarin. Thus, there is room for flexibility in selecting a starting dose. However, large loading doses of VKA should be avoided in patients who are at high risk of bleeding. The subsequent doses should be adjusted to maintain the INR at a target of 2.5 (range, 2.0 to 3.0).

Recommendations

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH or IV UFH or SC UFH (all **Grade 1A**).

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

1.1.3. In acute DVT, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).

1.1.4. We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (**Grade 1A**).

1.2 IV UFH for the initial treatment of DVT

Until recently, IV UFH has been the preferred initial treatment of DVT. UFH has an unpredictable dose response and a narrow therapeutic window, thereby making monitoring essential to ensure optimal efficacy and safety. It is generally accepted that a minimum level of heparin-induced anticoagulation must be reached and maintained to achieve an effective antithrombotic effect. The most widely used test for monitoring heparin therapy is the activated partial thromboplastin time (aPTT), which is a global coagulation test that not always correlates reliably with plasma heparin levels or with the antithrombotic activity of heparin. The aPTT response to heparin can be reduced by increased levels of various acute-phase reactant plasma proteins, including factor VIII. Moreover, the aPTT response is influenced by the coagulation timer and reagents used to perform the test.[10] Since many hospital laboratories are not able to monitor heparin levels directly and report

the results expeditiously, each laboratory should standardize the therapeutic range of the aPTT to correspond to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (see the chapter by Hirsh et al in this Supplement). In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, the so-called heparin-resistant patients, the dose of heparin should be adjusted by measuring the anti-Xa level because of a dissociation between the aPTT and heparin concentration.[11]

The starting dose of UFH for the treatment of DVT is either a bolus dose of 5,000 U, followed by a continuous infusion of at least 30,000 U for the first 24 h or a weight-adjusted regimen of 80U/kg bolus, followed by 18U/kg/h. Subsequent doses should be adjusted using a standard nomogram to rapidly reach and maintain an aPTT at levels corresponding to therapeutic heparin levels.[12–15] The requirement for an initial course of heparin in addition to VKAs as compared to starting treatment with VKAs alone was established in a randomized controlled trial (RCT),[16] which reported a threefold higher rate of recurrent VTE in patients receiving VKAs only.[15]

Intermittent IV injections of UFH are associated with a higher risk of bleeding than IV infusion and are not recommended.[17] Six randomized studies[18–23] compared bleeding and thromboembolic recurrence rates when heparin was administered by intermittent IV injection or by continuous heparin infusion. Two studies[18,19] reported that continuous heparin infusion was associated with a lower frequency of bleeding (1% and 0%, compared with 9% and 33%), and a third study[20] reported a trend toward reduced bleeding with continuous heparin, 5% compared with 10%. In the fourth study,[21] there was a trend in the other direction, while the two remaining studies[22,23] were too small to draw clear conclusions about recurrence rates. Patients receiving continuous IV heparin, however, also received a lower dose of heparin. Therefore, it is uncertain whether the difference noted in the rates of bleeding between patients randomized to continuous IV infusion or intermittent IV injection is related to the method of heparin administration or to differences in the total dose of UFH administered to the two groups.

Recommendations

1.2.1. If IV UFH is chosen, we recommend that it be administered by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).

1.2.2. In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, we recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).

1.3 SC UFH for the initial treatment of DVT

For the initial treatment of DVT, as an alternative to IV administration, UFH can be administered SC twice daily. The relative value of the IV and SC administration of UFH has been evaluated in eight clinical studies and reviewed in a meta-analysis.[24] SC UFH administered twice daily appeared to be more effective and at least as safe as IV UFH, provided that an adequate starting dose is administered, and this is followed by the administration of doses adjusted to achieve a therapeutic aPTT.

The usual regimen includes an initial IV bolus of 5,000 U followed by a SC dose of 17,500 U bid on the first day. When patients are receiving SC heparin, the aPTT should be drawn at 6 h after the morning administration and the dose of UFH adjusted to achieve a 1.5 to 2.5 prolongation.

Recommendations

1.3.1. In patients with acute DVT, we recommend that SC administered UFH can be used as an adequate alternative to IV UFH (**Grade 1A**).

1.3.2. For patients who receive SC UFH, we recommend an initial dose of 35,000 U/24 h SC, with subsequent dosing to maintain the aPTT in the therapeutic range (**Grade 1C+**).

1.4 LMWH for the initial treatment of DVT

LMWHs have more predictable pharmacokinetics and a greater bioavailability than UFH. Due to these pharmacologic features, body weight-adjusted doses of LMWH can be administered SC once or twice daily without laboratory monitoring in the majority of patients. However, in certain clinical situations, such as severe renal failure or pregnancy, dose adjustment might be required and, if so, can be achieved by monitoring plasma anti-Xa level. The most reasonable time to perform the anti-Xa assay is 4 h after the SC administration of a weight-adjusted dose of LMWH.

For twice-daily administration, a conservative therapeutic range is 0.6 to 1.0 IU/mL. The target range is less clear in patients treated with LMWH once a day, but a level between 1.0 IU/mL and 2.0 IU/mL seems to be reasonable.

A number of well-designed studies have compared the efficacy and safety of body weight-adjusted LMWH, administered SC without monitoring, with IV UFH administered with monitoring and subsequent dose adjustment.[25,26] The initial studies reported fewer recurrent events and less bleeding with LMWH, while the most recent studies showed comparable outcomes. Consequently, the meta-analysis[25] that only included the early studies reported that LMWH treatment results in fewer episodes of recurrence and bleeding than UFH. The most recent meta-analysis[26] included 13 randomized studies comparing IV heparin and LMWH for the initial treatment of acute DVT. Data were reported as pooled relative risk (RR) and 95% confi-

dence interval (CI). There was no statistically significant difference in risk between LMWH and UFH for recurrent VTE (RR in favor of LMWH, 0.85; 95% CI, 0.65 to 1.12), PE (RR, 1.02; 95% CI, 0.87 to 1.61), and major bleeding (RR, 0.63; 95% CI, 0.37 to 1.05). A statistically significant difference for risk of total mortality was observed in favor of LMWH (RR, 0.76; 95% CI, 0.59 to 0.90). The survival benefit was essentially accounted for by patients with malignancy. No apparent differences were observed in efficacy and safety among the different LMWHs.

In two randomized trials,[27,28] patients with symptomatic proximal DVT assigned to treatment with LMWH (enoxaparin twice daily or nadroparin twice daily) were encouraged to receive treatment at home, while those assigned to UFH were treated conventionally with a continuous infusion in the hospital. Out-of-hospital administration of LMWH in eligible patients was as effective and safe as UFH administered in the hospital. However, patients with symptomatic PE or previous venous thrombosis were excluded from these two studies, and only 33 to 69% of all patients with acute DVT were eligible to be treated as outpatients. More recently, 1,021 patients with DVT or PE were randomized to treatment with either SC LMWH (reviparin sodium twice daily) or IV adjusted-dose UFH for 8 days.[29] Again, patients receiving LMWH were encouraged to receive treatment at home. The mean hospital stay was 3 days shorter in patients assigned to LMWH, while rates of recurrent thromboembolism, bleeding, and death were similar in both groups.

Taken together, the results of the three studies[27–29] showed that patients with proximal venous thrombosis can be treated at home with LMWH and VKA initiated together. Treatment at home leads to cost savings and improved quality of life. In addition, selected patients can be discharged from the hospital early with a component of LMWH treatment at home. There have been several cohort studies[30,31] supporting the efficacy and safety of out-of-hospital treatment; these studies strongly support the view that replacing UFH with LMWH in the treatment of acute DVT is safe and cost-effective.

The large majority of the studies comparing LMWH treatment and UFH in the initial treatment of DVT evaluated a twice-daily weight-adjusted regimen. However, two studies[32,33] found once-daily administration as effective and safe as twice-daily dosing. Subgroup analysis suggested that the twice-daily dosing regimen might be more effective in patients with cancer.

In summary, the LMWHs used in these studies have been shown to be at least equivalent to IV UFH in the initial treatment of DVT. The major advantages of LMWH appear to be convenience of administration and cost savings associated with home therapy or early hospital discharge.

Recommendations

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

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

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

1.5 Systemically administered thrombolysis in the initial treatment of DVT

Theoretically, the use of thrombolytic agents to lyse venous thrombi and promptly relieve the vascular obstruction would seem a rational treatment approach for patients with DVT. However, the clinical relevance of achieving earlier relief of venous obstruction is uncertain, and thrombolytic treatment increases the risk of clinically relevant bleeding. In addition, the risk of death and early recurrence in these patients is low if anticoagulants are started promptly and in an appropriate dosage.

The relative value of thrombolytic and anticoagulant therapy for the initial treatment of proximal DVT has been a matter of discussion since the 1970s. Thrombolysis and heparin anticoagulation have been compared in several small trials. A pooled analysis was performed of six randomized trials comparing streptokinase and heparin in patients with acute DVT in which venography was used to confirm the diagnosis and the effect of therapy.[34] Thrombolysis was achieved 3.7 times more often among patients treated with streptokinase than among patients treated with heparin (95% CI, 2.5 to 5.7). Only three studies allowed a comparison to be made of major bleeding, which was 2.9 times more frequent with streptokinase (95% CI, 1.1 to 8.1).[34] More recent studies with urokinase and recombinant tissue-type plasminogen activator (tPA) reported similar findings. A meta-analysis[35] including the most recent studies reached conclusions similar to those of the previous overview.

The major argument for the use of thrombolytic therapy for the treatment of DVT is based on its potential to prevent the development of the PTS. This condition, which is a complication of the original DVT, is caused by permanent valvular incompetence and/or persistent venous obstruction. It is uncertain, however, whether the risk of PTS developing is reduced by treating the original DVT with thrombolytic therapy.

Who then, if anyone, should receive thrombolytic therapy for the treatment of acute DVT? A possible indication for thrombolysis is for patients with massive ileofemoral DVT of recent onset who, despite appropriate heparin therapy, are at risk of limb gangrene secondary to venous occlusion.

In conclusion, there is no evidence that supports the use of thrombolytic agents for the initial treatment of DVT in the large majority of patients. Furthermore, in patients with DVT, mortality from PE is very uncommon (approximately 1%) once anticoagulant therapy has been initiated.

Recommendations

1.5.1. In patients with DVT, we recommend **against** the routine use of IV thrombolytic treatment (**Grade 1A**).

1.5.2. In selected patients such as those with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, we suggest IV thrombolysis (**Grade 2C**).

1.6 Catheter-directed thrombolysis in the initial treatment of DVT

Catheter-directed thrombolysis has been proposed in patients with occlusive ileofemoral DVT to remove thrombus rapidly and restore venous drainage. The catheter is inserted in the popliteal or posterior tibial vein through an ultrasound-guided venipuncture. Urokinase and tPA are the thrombolytic agents most commonly used. The use of this approach is not supported by adequately designed studies. Catheter-directed thrombolysis has been reported to be associated with local and systemic bleeding,[36] and should be reserved essentially for limb salvage in individual cases after a careful assessment of its benefit/risk ratio compared to routine anticoagulation.

Recommendations

1.6.1. In patients with DVT, we recommend **against** the routine use of catheter-directed thrombolysis (**Grade 1C**).

1.6.2. We suggest that this treatment should be confined to selected patients such as those requiring limb salvage (**Grade 2C**).

1.7 Catheter extraction or fragmentation and surgical thrombectomy for the initial treatment of DVT

Surgical venous thrombectomy has been proposed for patients with proximal DVT < 40 years of age with posttraumatic, postoperative, or postpartum thrombosis.[37] Surgical thrombectomy is commonly complicated by a recurrence of thrombus formation.[38] A high percentage of patients require secondary dilatation and/or re-intervention and long-term anticoagulation. Venous thrombectomy cannot be recommended in the vast majority of patients with proximal DVT. It could be considered in selected patient with phlegmasia cerulea dolens.

Recommendations

1.7.1. In patients with DVT, we recommend **against** the routine use of venous thrombectomy (**Grade 1C**).

1.7.2. In selected patients such as patients with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, we suggest venous thrombectomy (**Grade 2C**).

1.8 Vena caval interruption for the initial treatment of DVT

The interruption of the inferior vena cava is achieved by the placement of a filter; vena-caval ligation is now rarely used. Many types of filters are available, but there are no controlled studies comparing their relative efficacy and safety in preventing PE. Therefore, the superiority of one type of filter over another remains unclear. An inferior vena caval filter can be inserted through the internal jugular vein or the femoral vein and advanced into place in the inferior vena cava, usually below the renal veins, using fluoroscopic guidance. Suprarenal placement of filter, if required, has been shown to be safe and effective. A new promising development with these devices are removable vena cava filters.

Placement of an inferior vena caval filter is indicated when there is a contraindication to, or complication of, anticoagulation in patients with proximal vein thrombosis. Less frequent indications include recurrent thromboembolism despite adequate anticoagulation, heparin-induced thrombocytopenia, chronic recurrent PE with pulmonary hypertension, and the concurrent performance of surgical pulmonary embolectomy or pulmonary endarterectomy.

Resumption of anticoagulation is recommended as soon as possible after insertion of a filter because the filter alone is not an effective treatment of DVT. Most of the studies reporting on caval filter are uncontrolled case series and many of them are weakened by incomplete reporting of patient outcomes. In the only randomized study[39] of filter placement in patients who were also all treated with anticoagulants, the device did not prolong early or late survival in patients after a first episode of VTE, although it did reduce the rate of PE. This benefit was offset by a tendency for more recurrent DVT in those patients who received a filter.

Recommendations

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

1.8.2. We suggest the placement of an inferior vena caval filter in patients with a contraindication for, or a complication of anticoagulant treatment (**Grade 2C**), as well as in those with recurrent thromboembolism despite adequate anticoagulation (**Grade 2C**).

1.9 Nonsteroidal anti-inflammatory agents for the initial treatment of DVT

There is limited evidence for the efficacy of nonsteroidal anti-inflammatory agents for the treatment of acute DVT. Nielsen et al[40] randomized 90 patients with venographically proven DVT but without clinical signs of PE into two different treatment regimens to compare the safety and efficacy of continuous VKA treatment vs non-VKA treatment. In the VKA group, patients were actively mobilized and wore compression stockings; in

the non-VKA group, patients were treated with the nonsteroidal anti-inflammatory agent phenylbutazone for 10 days. Thus, this study compared early mobilization and VKA against phenylbutazone after initial treatment with IV heparin. Venography was repeated after 30 days. A perfusion-ventilation lung scan was performed on days 1 to 2, 10, and 60. In 59 patients, a repeat venography was performed: 29 procedures in the VKA-plus-compression stockings group, and 30 procedures in the phenylbutazone group. In distal veins, the investigators observed regression in nine patients and eight patients, respectively (4.4% absolute RR in favor of VKA; 95% confidence limit, 27.5 to − 18.7%); in proximal veins, they observed regression in five patients and eight patients, respectively (10.9% in favor of VKA; 95% confidence limit, 32.0 to − 10.1%). No difference in the frequency of abnormal lung scan results was found after 10 days (0.8% in favor of VKA; 95% confidence limit, 21.5 to − 19.9%) or after 60 days (3.3% in favor of phenylbutazone treatment; 95% confidence limit, 21.8 to − 28.5%). In the VKA group, the incidence of bleeding complications was 8.3%. No side effects of phenylbutazone were found. Compared to phenylbutazone, there was no statistically significant beneficial effect of VKA and compression stocking treatment in actively mobilized patients on DVT progression. However, the number of patients in the study was small and the CIs wide.

Recommendation

1.9.1. For the initial treatment of DVT, we recommend **against** the use of nonsteroidal anti-inflammatory agents (**Grade 2B**).

1.10 New antithrombotic agents for the initial treatment of DVT

Two new anticoagulants have been evaluated in phase 3 clinical trials for the treatment of DVT. Fondaparinux, a synthetic selective anti-factor Xa, was evaluated in one phase II study[41] and in a large phase III study in the initial treatment of DVT.[96] Ximelagatran has been compared with LMWH followed by VKA in one large randomized, blinded, double-dummy study. Since none of these compounds have been registered for this indication, no recommendations are made (see chapter by Weitz et al in this Supplement).

1.11 Immobilization

Traditionally, strict bed rest for several days has been recommended in combination with anticoagulation in patients with DVT to avoid thrombi from breaking off and causing PE. Although bed rest was common when IV infusion of UFH was used for the initial treatment of DVT, with the introduction of LMWHs and its use in ambulatory patients, the need for immobilization has been challenged. In two randomized studies[42,43] with limited sample sizes, bed rest as an additional measure to anticoagulation was not shown to reduce the incidence of silent PE as detected by lung scanning. Further, in another small randomized study,[44] the rate of resolution of pain and swelling was significantly faster when patients were managed with early ambulation and leg compression compared to bed rest. The safety of using a compression bandage combined with walking exercise was assessed in a cohort of 1,289 patients with acute DVT nearly all treated with LMWH.[45] A low incidence of recurrent and fatal PE was observed in the study,[45] thereby suggesting that mobile patients with DVT do not require bed rest.

Recommendation

1.11.1. For patients with DVT, we recommend ambulation as tolerated (**Grade 1B**).

2.0 Long-term Treatment of Acute DVT of the Leg

Patients with acute DVT require long-term anticoagulant treatment to prevent a high frequency (15 to 50%) of symptomatic extension of thrombosis and/or recurrent venous thromboembolic events.[46–48] This observation applies to patients with proximal vein thrombosis (popliteal, femoral, or iliac vein thrombosis) and also to patients with thrombosis confined to the deep veins of the calf. The need for long-term anticoagulant treatment of DVT is supported by three lines of evidence from randomized clinical trials: (1) a randomized trial[46] in which no long-term anticoagulant treatment was administered to patients with symptomatic calf vein thrombosis, which documented a 20% rate of symptomatic extension and/or recurrence of thrombosis despite initial treatment with IV UFH for several days; (2) a randomized trial[47] that evaluated SC low-dose UFH (5,000 U bid) as an alternative to oral VKA for long-term treatment, in which the low-dose UFH regimen proved ineffective and resulted in a high rate (47%) of recurrent VTE; and (3) randomized trials[49–51] in which a reduced duration of treatment (4 to 6 weeks) resulted in a clinically important increase in recurrent thromboembolic events by comparison to the conventional duration of treatment for 3 months.

Treatment with VKA is the preferred approach for long-term treatment in most patients with DVT of the legs. Treatment with adjusted doses of UFH[52] or therapeutic doses of LMWH is indicated for selected patients in whom VKA are contraindicated (*eg*, pregnancy) or impractical, or in patients with concurrent cancer, for whom LMWH regimens have been shown to be more effective and safer.[53–56]

Recent evidence from clinical research has provided data on a number of unresolved issues related to the long-term treatment of patients with DVT of the leg. These issues are as follows: (1) the optimal duration of long-term anticoagulant treatment, (2) the optimal intensity of the anticoagulant effect with VKA, and (3) the relative effectiveness and safety of alternative approaches to long-term VKA treatment, including LMWH and the

new anticoagulants idraparinux (a long-acting injectable pentasaccharide), and the oral direct thrombin inhibitor ximelagatran.

The optimal duration of long-term treatment for patients with DVT has been the subject of extensive clinical research in recent years.[49,51,57–62] Most of the studies have evaluated different durations of treatment using VKA (see section 2.1 below). In general, the results indicate that patients can be classified into five different subgroups with regard to optimal duration of long-term anticoagulant treatment. These subgroups are as follows: (1) first-episode DVT secondary to a transient risk factor[49–51,57]; (2) first-episode DVT and concurrent cancer[53–57]; (3) first-episode idiopathic DVT (defined as DVT occurring in the absence of a known identifiable risk factor)[59–62]; (4) first-episode DVT associated with a prothrombotic genotype or a prognostic marker of an increased risk of recurrent thromboembolism[63–71] (this subgroup includes patients with a deficiency of antithrombin III, protein C, or protein S; or those with a prothrombotic gene mutation [eg, factor V Leiden or prothrombin 20210]; or those with antiphospholipid antibodies, homocysteinemia, or factor VIII levels above the ninetieth percentile of normal; or patients with persistent residual thrombosis on repeated testing with compression ultrasonography); and (5) recurrent DVT (two or more episodes of VTE).[58] Recommendations about the appropriate duration of long-term anticoagulant treatment are provided in section 2.1 below for each of the above patient subgroups.

2.1 VKAs for the long-term treatment of DVT

Long-term treatment with adjusted doses of a VKA such as warfarin or acenocoumarol is highly effective for preventing recurrent VTE.[46,47] Laboratory monitoring of the anticoagulant effect and dose adjustment in the individual patient is required due to wide interpatient variation in the anticoagulant response, and the influence of drug interactions and diet on the anticoagulant effect of VKA. It is current standard practice to monitor the anticoagulant effect of VKA using the prothrombin time, and to report the results as the INR.

Intensity of anticoagulant effect

The preferred intensity of the anticoagulant effect of treatment with VKA has been established by the results of randomized trials.[61,62,72,73] Most recently, Kearon et al[62] reported a randomized, blinded trial comparing low-intensity warfarin therapy (target INR, 1.5 to 1.9) with standard-intensity warfarin therapy (INR, 2.0 to 3.0) for the extended treatment of patients with unprovoked VTE. All patients had completed at least 3 months of standard-intensity warfarin therapy before randomization. The average follow-up was 2.3 years. The incidences of objectively documented recurrent VTE were 1.9%/yr among the 370 patients in the low-intensity group, and 0.6%/yr among the 369 pa-

tients in the standard-intensity group (hazard ratio, 3.3; 95% CI, 1.2 to 9.1). The incidences of major bleeding were 0.96%/yr in the low-intensity group and 0.93%/yr in the standard-intensity group; the corresponding incidences of all bleeding (major and minor) were 4.9%/yr and 3.6%/yr, respectively. Thus, low-intensity warfarin treatment was less effective than standard-intensity therapy (INR, 2.0 to 3.0), and did not provide a safety advantage.[62] The observed incidence of recurrent VTE of 1.9%/yr in the low-intensity group is similar to the incidence of 2.6%/yr reported in a recent study[61] that compared low-intensity warfarin therapy (INR, 1.5 to 2.0) with placebo (the latter had an incidence of recurrent VTE of 7.2%/yr). Taken together, the results of these two randomized trials[61,62] indicate that although low-intensity warfarin therapy is more effective than placebo, it is less effective than standard-intensity therapy (INR, 2.0 to 3.0), and does not reduce the incidence of bleeding complications.

Additional important evidence regarding the intensity of anticoagulant therapy with VKA is provided by a recent randomized trial by Crowther et al,[73] who compared standard-intensity warfarin therapy (INR, 2.0 to 3.0) with high-intensity warfarin therapy (INR, 3.1 to 4.0) for the prevention of recurrent thromboembolism in patients with persistently positive antiphospholipid antibodies and a history of thromboembolism (venous or arterial). The average follow-up was 2.7 years. Recurrent thromboembolism occurred in 2 of 58 patients (3.4%) receiving standard-intensity therapy, compared with 6 of 56 patients (10.7%) who received the high-intensity therapy (hazard ratio, 3.1; 95% CI, 0.6 to 15). Thus, high-intensity warfarin therapy (INR, 3.1 to 4.0) did not provide improved antithrombotic protection. The high-intensity regimen has been previously shown to be associated with a high risk (20%) of clinically important bleeding in a series of three randomized trials[47,52,72] in patients with DVT. The evidence outlined above provides the basis for the recommendation of an INR of 2.0 to 3.0 as the preferred intensity of anticoagulant treatment with VKA.

Duration of long-term treatment

The appropriate duration of anticoagulant treatment using a VKA for patients with DVT has been evaluated in multiple randomized trials.[49–51,58–61] Of these randomized trials, three studies[49–51] have sought to determine if the duration of treatment could be shortened, three studies[59–61] have evaluated the risk-benefit of an extended course of anticoagulant therapy for patients with idiopathic DVT, and one trial[58] has evaluated the risk-benefit of indefinite anticoagulant treatment for patients with a second episode of VTE.

The three randomized trials[49–51] evaluating a shortened course of anticoagulant therapy compared treatment for 4 to 6 weeks with the conventional longer duration of 3 to 6 months. The results of these three studies are consistent, and indicate that reducing the duration of treatment to 4 to 6 weeks is associated with an increased incidence of recurrent VTE during the

subsequent 6 months to 1 year (absolute risk increase of approximately 8%). In contrast, the patients who received treatment for 3 to 6 months had a low rate of recurrent VTE during the following 1 to 2 years (an annual incidence of 3 to 4%/yr).[49–51] Further, the episodes of recurrent VTE occurred in patients who either had continuing risk factors (eg, cancer), idiopathic DVT at entry, or a history of previous VTE. Recurrent VTE was uncommon among patients with a first episode of VTE associated with a transient risk factor. The results of these randomized trials are consistent with the results on long-term follow-up in earlier randomized trials[47,52,72] in which patients were treated with warfarin for 3 months. This evidence provides the basis for the recommended duration of treatment for patients with a first episode of DVT secondary to a transient risk factor (see recommendation 2.1.4).

Important information on the long-term clinical course of patients with DVT was provided by a prospective cohort study of Prandoni and colleagues.[57] This study evaluated a total of 355 consecutive patients with a first episode of VTE who received anticoagulant treatment for 3 months and were then followed up for up to 8 years. The cumulative incidences of recurrent VTE at 2 years, 5 years, and 8 years were 17.5%, 25%, and 30%, respectively. The presence of cancer or thrombophilia (eg, deficiency of antithrombin, protein C, or protein S, or the presence of lupus-like anticoagulants) was associated with an increased risk of recurrent VTE (hazard ratios, 1.7 and 1.4, respectively). The presence of transient risk factors, such as surgery or recent trauma, was associated with a decreased risk of recurrent thromboembolism (hazard ratios, 0.4 and 0.5, respectively). The cumulative incidences of PTS at 2 years, 5 years, and 8 years were 23%, 28%, and 29%, respectively. The development of ipsilateral recurrent DVT was strongly associated with an increased risk for PTS (hazard ratio, 6.4). These results provide further support for the inference that treatment for 3 months is sufficient in patients with a first episode of DVT secondary to a transient risk factor, but that a longer course of treatment is required for patients with continuing risk factors for VTE.

The risk-benefit of an extended course of anticoagulant treatment using a VKA for patients with idiopathic DVT has been evaluated by three randomized trials,[59–61] which evaluated extended treatment for 1 to 2 years compared to the control groups who received the conventional duration of treatment of 3 to 6 months. The results indicate that extended treatment with warfarin is highly effective in reducing the incidence of recurrent VTE, producing absolute risk reductions during treatment of 7%/yr and 26%/yr, respectively, in the two studies[59,60] that evaluated standard-intensity (INR, 2.0 to 3.0) warfarin therapy, and an absolute risk reduction of 4.6% during treatment in the study that evaluated low-intensity (INR, 1.5 to 2.0) warfarin therapy.[61] The corresponding relative risk reductions (RRRs) for extended therapy are > 90% for conventional-intensity warfarin, and 64% for low-intensity warfarin treatment. However, results of follow-up studies after

VKA have been discontinued indicate that the benefit for reducing recurrent VTE is not maintained after treatment is withdrawn.[60]

The benefit of extended treatment with VKA is partially offset by the risk of major bleeding. In the two initial studies[59,60] of extended treatment, the incidence of major bleeding was approximately 3% during 1 year of extended treatment with conventional-intensity warfarin. However, the more recent and larger trial by Kearon and colleagues,[62] in which patients received an average of 2.2 years of extended treatment, reported a major bleeding rate of 0.9%/yr for conventional-intensity warfarin, and 1.1%/yr for low-intensity warfarin. The external validity of these results is supported by the observations of Ridker et al,[61] who reported an incidence of major bleeding of 0.9%/yr for low-intensity warfarin treatment, and of Schulman et al,[74] who reported an incidence of major bleeding of 0.9%/yr during treatment with the oral direct thrombin inhibitor ximelagatran.

Thus, for patients with idiopathic DVT, the benefit of extended treatment is partially offset during therapy by the risk of bleeding, particularly major bleeding, and the benefit is lost when treatment is withdrawn. For these reasons, values and preferences associated with decisions about the risk-benefits of treatments bear on the recommendation for extended anticoagulant treatment for idiopathic DVT.

A variety of prothrombotic conditions or markers have been reported to be associated with an increased risk of recurrent VTE.[63–71] These include deficiencies of the naturally occurring inhibitors of coagulation such as antithrombin, protein C and protein S, specific gene mutations including factor V Leiden and prothrombin 20210A, elevated levels of coagulation factor VIII, elevated levels of homocysteine, and the presence of antiphospholipid antibodies. More recently, the presence of residual DVT assessed by compression ultrasonography,[69] and the presence of elevated plasma D-dimer levels after discontinuing anticoagulant therapy,[70] have been associated with an increased incidence of recurrent VTE. However, there have been no randomized trials performed, a priori, in these subgroups of patients with thrombophilic conditions to evaluate different durations of treatment. The available data are limited to subgroup analyses of randomized trials, and to data from nonexperimental studies. Thus, the quality of the evidence for recommendations in this area is low.

Subgroup analysis from the Prevention of Recurrent Venous Thromboembolism (PREVENT) study provides the strongest evidence to date that extended warfarin treatment is of benefit in the subgroup of patients who have the factor V Leiden or prothrombin 20210A gene mutations.[61] Extended treatment with low-intensity warfarin for 2 years resulted in an absolute risk reduction of 6.4% in the annual incidence of recurrent VTE in this subgroup of patients (from 8.6 to 2.2%/yr),[61] whereas in those without factor V Leiden mutation the annual incidence decreased from 6.6 to 2.7%.

The presence of antiphospholipid antibodies have been

shown to be associated with an increased risk of recurrent VTE and increased mortality among patients with VTE.[67,68] In subgroup analyses of the Duration of Anticoagulation (DURAC) studies, Schulman et al[50,58] documented a high incidence of recurrent VTE during follow-up for 4 years in patients who received 6 months of anticoagulant treatment. The incidence of recurrence among those with a first episode of VTE and the presence of anticardiolipin antibodies was 29%, compared to 14% among patients without these antibodies (p < 0.01). The 4-year mortality from all causes was 15% among those patients with anticardiolipin antibodies, and 6% among those without the antibodies (p = 0.01); many of these deaths were the result of thromboembolic causes. These results support the use of a longer course of anticoagulant therapy in patients with VTE and antiphospholipid antibodies.

The risk-benefit of indefinite treatment with a VKA for a second episode of VTE has been evaluated in a randomized trial in which Schulman et al[58] compared 6 months of treatment with indefinite treatment (average, 4 years) in 227 patients with a second episode of VTE. Conventional-intensity anticoagulant treatment (INR, 2.0 to 3.0) was used in both groups. After 4 years of follow-up, the cumulative incidence of recurrent VTE was 20.7% in patients who received 6 months of therapy, compared to 2.6% in patients who continued anticoagulant treatment (p < 0.001; absolute risk reduction, 18.1%; RRR, 87%). This benefit was offset partially by major bleeding. The cumulative incidence of major bleeding was 8.6% for the indefinite treatment group, compared with 2.7% in the 6-months group (p = 0.084; absolute risk increase, 5.9%). Thus, during extended treatment for an average of 4 years, the number needed to treat (NNT) to prevent one episode of recurrent VTE was 6, and the number needed to harm (NNH) for major bleeding was 17.

Recommendations

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

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

Remark: This applies to patients with proximal vein thrombosis, and to patients with symptomatic DVT confined to the calf veins.

2.1.2.1. For patients with a first episode of idiopathic DVT, we recommend treatment with a VKA for at least 6 to 12 months (**Grade 1A**).

2.1.2.2. We suggest that patients with first-episode idiopathic DVT be considered for indefinite anticoagulant therapy (**Grade 2A**).

Underlying values and preferences. This recommenda-

tion ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

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

2.1.4. For patients with a first episode of DVT who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (*eg*, combined factor V Leiden and prothrombin 20210 gene mutations), we recommend treatment for 12 months (**Grade 1C+**). We suggest indefinite anticoagulant therapy in these patients (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

2.1.5. For patients with a first episode of DVT who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal), we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy as for patients with idiopathic thrombosis (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

2.1.6. For patients with two or more episodes of objectively documented DVT, we suggest indefinite treatment (**Grade 2A**).

2.1.7. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). We recommend **against** high-intensity VKA therapy (INR range, 3.1 to 4.0) [**Grade 1A**]. We recommend **against** low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).

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

2.1.9. We suggest repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma D-dimer (**Grade 2C**).

2.2 SC UFH for the long-term treatment of DVT

Adjusted-dose SC UFH is an effective approach for the long-term treatment of DVT.[52] However, the use of UFH has been replaced by LMWH for most patients because LMWH can be administered once daily with-

out the need for anticoagulant monitoring.[53–56] The use of adjusted-dose UFH may continue to have a role in the long-term treatment of patients with DVT during pregnancy (see chapter by Bates et al in this Supplement).

2.3 LMWH for the long-term treatment of DVT

The use of LMWH for the long-term treatment of acute DVT has been evaluated in three randomized clinical trials.[53–55] Taken together, these studies indicate that long-term treatment with SC LMWH for 3 to 6 months is at least as effective, and in cancer patients, more effective, than adjusted doses of oral VKA therapy (INR, 2.0 to 3.0) for preventing recurrent VTE. LMWH was also associated with less bleeding complications than VKA treatment, due to a reduction in minor bleeding.

Lee et al[53] compared SC LMWH (dalteparin) with oral coumarin therapy for the long-term treatment of patients with cancer who had acute proximal DVT or PE. The patients were randomly assigned to receive treatment with dalteparin, 200 IU/k body weight SC qd for 5 to 7 days, followed by oral treatment with a coumarin VKA for 6 months (target INR, range 2.0 to 3.0), or to SC dalteparin alone for 6 months (200 IU/kg qd for 1 month, followed by approximately 150 IU/kg qd for 5 months). During the 6-month study period, recurrent VTE occurred in 53 of 336 patients (15.7%) who received the VKA treatment, compared with 27 of 336 patients (8.0%) who received LMWH (dalteparin) alone (p = 0.002; absolute risk reduction, 7.7%; RRR, 49%). Major bleeding occurred in 6% of patients in the LMWH group and 4% in the VKA group (p = 0.027). Any bleeding occurred in 14% of patients receiving LMWH and in 19% receiving VKA treatment (p = 0.09). Mortality was similar in the two groups (39% and 41% for LMWH and VKA treatment, respectively).

Hull et al[54,55] performed two randomized trials evaluating long-term treatment with LMWH. The regimen of LMWH was tinzaparin 175 IU/kg body weight SC qd for 3 months; in one study,[54] this regimen was compared with IV UFH followed by VKA therapy, and in the second study,[55] with the same tinzaparin regimen for the initial 5 days followed by warfarin for 3 months. In both of these randomized trials, the LMWH regimen was as effective for preventing recurrent VTE as the regimens that used warfarin for long-term treatment. The LMWH (tinzaparin) regimen was safer, however, than the regimen of IV UFH followed by oral warfarin; bleeding complications occurred in 73 of 368 patients (19.8%) who received UFH followed by warfarin, compared with 48 of 369 patients (13.0%) who received LMWH (p = 0.01); this difference was due to a reduction in minor bleeding. In an analysis of the patients with cancer at entry, based on an *a priori* stratification of these patients before randomization, the LMWH regimen was more effective for preventing recurrent VTE than the regimen of UFH followed by warfarin.[56]

Recommendation

2.3.1. For most patients with DVT and cancer, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade1A**).

Remark: The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin 200 IU/kg body weight qd for 1 month, followed by 150 IU/kg qd thereafter or tinzaparin, 175 IU/kg body weight SC qd.

3.0 PTS

PTS (or postphlebitic syndrome) is defined by a cluster of symptoms and signs in patients with previous venous thrombosis. PTS occurs in 20 to 50% of patients after a documented episode of DVT.[75] These symptoms can also occur in the absence of a documented diagnosis of DVT; this is frequently referred to as *chronic venous insufficiency*.[75] Several scoring systems have been developed to assess the severity of these signs and symptoms; of these the Clinical, Etiological, Anatomical, Pathophysiological Classification is most widely used, and the Prandoni scoring system the best validated.[76] These scores differentiate between moderate and severe PTS. The most prominent symptoms are chronic postural dependent swelling and pain or local discomfort. The severity of symptoms may vary over time and the most extreme manifestation is a venous ulcer of the ankle. Usually the symptoms are nonacute and the decision on the need for treatment is based on the patient's perception. First the studies on the prevention of the PTS are discussed, followed by the trials on the treatment of this syndrome.

3.1 Elastic stockings for the prevention of PTS

Three randomized trials[77–79] have addressed the efficacy of compression stockings for the prevention of PTS after an episode of DVT. The trials of Brandjes et al[77] and Prandoni[78] consisted of 194 patients and 180 patients, respectively, who were included immediately after their first episode of thrombosis. Both compared graduated elastic compression stockings with an ankle pressure of 30 to 40 mm Hg during 2 years vs no intervention. The trial of Ginsberg and colleagues[79] included 47 patients 1 year after their thrombosis, and compared the effectiveness of below-knee elastic compression stockings (20 to 30 mm Hg pressure at the ankle) with placebo stockings (one to two sizes too large). These patients had at the time of inclusion no pain or swelling of the leg but all had venous valvular insufficiency measured by plethysmography or Doppler ultrasound. In this study,[79] both patients with symptomatic (n = 33) and asymptomatic (n = 12) deep venous thrombosis were included, while in two patients the clinical presentation was unknown.

In the study by Brandjes et al,[77] PTS occurred in 19 of 96 patients (20%) treated with stockings, and was severe in 11 patients; in the control group PTS occurred in 46 of 98 patients (47%), and was severe in 23

patients. Prandoni[78] obtained similar results in his study: PTS occurred in 22 of 90 patients (24%) treated with stockings, and was severe in 3 patients; in the control group, PTS occurred in 44 of 90 patients (49%), and was severe in 9 patients. The risk reductions in the incidences of all and severe PTS in these studies were highly statistically significant, with $p < 0.001$ for both. In the study of Ginsberg and colleagues,[79] none of the 24 patients (0%) in the active stocking group were considered treatment failures, compared with 1 of the 23 patients (4.3%) treated with placebo stockings. Overall, the use of elastic compression stockings was associated with a highly statistically significant reduction in the incidence of all PTS (odds ratio, 0.31; 95% CI, 0.20 to 0.48). Also, the incidence of severe PTS was reduced (odds ratio, 0.39; 95% CI, 0.20 to 0.76).

Recommendation

3.1.1. We recommend the use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle during 2 years after an episode of DVT (**Grade 1A**).

3.2 Physical treatment of PTS

The treatment of PTS has only been evaluated in small or methodologically flawed trials. Treatment is usually based on physical methods designed to counteract the raised venous pressure. Of these approaches, elastic stocking have been evaluated in patients with relatively mild PTS in a small underpowered trial.[7] The results failed to show a benefit, but a large beneficial effect could not be excluded due to the small sample size.[79] In a cross-over study[80] of 15 patients with a severe PTS, intermittent pneumatic compression at a pressure of 40 mm Hg was more effective than a lower (placebo) pressure. Twelve of 15 patients preferred the therapeutic pressure.[80]

Recommendations

3.2.1. We suggest a course of intermittent pneumatic compression for patients with severe edema of the leg due to the PTS (**Grade 2B**).

3.2.2. We suggest the use of elastic compression stockings for patients with mild edema of the leg due to PTS (**Grade 2C**).

3.3 Drug treatment of PTS

In patients with mild-to-moderate PTS, there is limited evidence that rutosides had beneficial effects. These rutosides were tested in one blinded trial[81] that included only 84 of the 101 patients in the efficacy analysis. There was a reduction in circumference of the calf and ankle, which was more prominent at week 4 than at week 8.[81] Similar effects were seen in a meta-analysis[82] on the effect of rutosides in patients with chronic venous insufficiency. It should be stressed that these findings do not apply to patients with a venous

ulcer. Other drugs, such as LMWHs, UFH, and dermatan sulfate, were only evaluated in small (dose-finding) studies, without a nonactive control group,[83–87] precluding any conclusion.

Recommendation

3.3.1. In patients with mild edema due to PTS, we suggest administration of rutosides (**Grade 2B**).

4.0 Initial Treatment of Acute PE

Treatment regimens for DVT and PE are similar because the two conditions are manifestations of the same disease process. When patients with VTE are carefully studied, the majority of those with proximal DVT also have PE (symptomatic or asymptomatic) and *vice versa*. Furthermore, clinical trials in patients with DVT alone have validated treatment regimens that are similar to those used in patients with both DVT and PE and in patients known to have only PE. The vast majority of patients with VTE who receive adequate anticoagulation survive. However, patients who are treated for PE are almost four times more likely (1.5% vs 0.4%) to die of recurrent VTE in the next year than are patients who are treated for DVT.[88]

4.1 IV UFH or LMWH for the initial treatment of PE

UFH has been shown to be effective in the treatment of PE in comparison to no treatment.[1] Meta-analyses of studies in patients with DVT (with likely asymptomatic PE in a substantial proportion of these patients) have shown that LMWH treatment administered SC in doses adjusted to body weight only is at least as effective and safe for initial treatment as IV, dose-titrated UFH.[26] Five studies[29,89–92] in patients presenting with symptomatic nonmassive PE or VTE confirmed these findings of a comparable safety and efficacy of LMWH administered SC.

Recommendations about the initiation of UFH or LMWH as well as the overlap with VKA and monitoring of the anticoagulant effects are largely based on the findings in patients with DVT. This is assumed to be appropriate since DVT and PE are considered to be manifestation of a single clinical entity. As a result, the following recommendations are the same as for DVT apart from massive PE and thromboembolic pulmonary hypertension.

Recommendations

4.1.1. For patients with objectively confirmed nonmassive PE, we recommend short-term treatment with SC LMWH, or IV UFH (both **Grade 1A**).

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

4.1.3. In patients with acute nonmassive PE, we recommend LMWH over UFH (**Grade 1A**).

4.1.4. In acute nonmassive PE, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).

4.1.5. In patients with acute nonmassive PE treated with LMWH, we recommend **against** routine monitoring with anti-factor Xa levels (**Grade 1A**).

4.1.6. In patients with severe renal failure, we suggest IV UFH over LMWH (**Grade 2C**).

4.1.7. If IV UFH is chosen, we recommend administration by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).

4.1.8. In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, we recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).

4.1.9. We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (**Grade 1A**).

4.2 Systemically and locally administered thrombolytic drugs for the initial treatment of PE

The use of thrombolytic agents in the treatment of PE continues to be highly individualized, and clinicians should have latitude in using these agents. In general, patients with hemodynamically unstable PE, who are at low risk to bleed, are the most appropriate candidates.

In a systematic review[93] of nine trials in patients with acute PE, thrombolytic therapy led to a more rapid resolution of the radiographic and hemodynamic abnormalities associated with acute PE than did anticoagulant therapy alone, although these benefits were short-lived. No difference was detected in clinically relevant outcomes such as the death rate or the resolution of symptoms between patients receiving thrombolytic therapy and those receiving anticoagulant therapy alone.[93]

Both streptokinase and urokinase have similar thrombolytic effects as judged by large clinical trials[94,95] in PE. Using paired angiographic comparisons in each patient, resolution of PE, seen with 12 h or 24 h of urokinase therapy or 24 h of streptokinase therapy, was comparable at 24 h and was approximately three times that seen with heparin alone. Pulmonary vascular resistance was also reduced at 24 h by 35% compared with 4% in the heparin group. Whereas initial lung scan improvement was greater in the thrombolytic group at day 1 and day 3, a subsequent scan improvement was similar in the two groups. Twelve hours of urokinase therapy had equivalent thrombolytic efficacy to 24 h of streptokinase therapy, and these are the recommended infusion times for PE.[96] tPA has comparable thrombolytic capacity to urokinase and streptokinase, and can be administered for shorter duration (2 h).[97–103]

Patients with VTE who receive thrombolytic therapy have a 1 to 2% risk of intracranial bleeding. Furthermore, there is as yet no clearly established short-term mortality effect with a thrombolytic agent in PE.[104] This finding is not surprising, since previous trials were designed primarily to establish the thrombolytic effects of these agents. The low all-cause mortality at 3 months ($< 10\%$) of patients treated with heparin and VKA has precluded the identification of a mortality effect of thrombolytic therapy because a relatively small number of patients were studied. Studies[29,88–90,105] have shown that when PE is promptly diagnosed and properly treated with anticoagulants, subsequent mortality directly due to PE is approximately 2%. Because of the favorable results with anticoagulants, thrombolytic therapy should usually be reserved for treatment of patients with acute massive embolism, who are in hemodynamically unstable condition and do not seem prone to bleeding. Confirmatory evidence is needed before one can state that thrombolytic therapy decreases the incidence of long-term disability after massive PE.

Another unsettled issue is the use of thrombolytic agents in hemodynamically stable patients with echocardiographic evidence of right ventricular dysfunction. Further studies are required to document a clinically relevant improvement in the benefit-risk ratio of thrombolytic treatment over conventional anticoagulant therapy in these patients.

All thrombolytic agents are administered IV in dosing regimens that are designed to activate fibrinolysis systemically in $> 90\%$ of patients. The regimens will achieve thrombolysis throughout the vasculature. Although tPA and its variants are more fibrin specific than streptokinase and urokinase, all of these agents have the potential to lyse a fresh platelet-fibrin plug anywhere in the vasculature and cause bleeding at that site. Therefore catheter administration of thrombolytic therapy locally to the pulmonary vasculature should be avoided since there is an increased risk of bleeding at the insertion site. For PE, streptokinase is recommended in a 250,000-IU loading dose followed by 100,000 IU/h for 24 h. Urokinase is recommended in a 4,400 IU/kg body weight loading dose followed by 2,200 IU/kg for 12 h. For PE, tPA is recommended in a 100-mg infusion over 2 h. Reteplase is not currently approved in the United States for treatment of VTE, but this agent shows promise for rapid thrombolysis.[106] The drug is administered in two separate IV boluses of 10 U approximately 30 min apart. Heparin should not be infused concurrently with streptokinase or urokinase. For tPA or reteplase, concurrent use of heparin is optional.

Recommendations

4.2.1. For most patients with PE, we recommend clinicians **not** use systemic thrombolytic therapy (**Grade 1A**). In selected patients, we suggest systemic administration of thrombolytic therapy (**Grade 2B**). For patients who are hemodynamically unstable, we suggest use of thrombolytic therapy (**Grade 2B**).

4.2.2. We suggest clinicians **not** use local administration of thrombolytic therapy via a catheter (**Grade 1C**).

4.2.3. For patients with PE who receive thrombolytic regimens, we suggest use of thrombolytic regimens with a short infusion time over those with prolonged infusion times (**Grade 2C**).

4.3 Catheter extraction or fragmentation for the initial treatment of PE

A cap device has been developed that fits over an 8.5F, double-lumen, balloon-tipped steerable catheter to permit suction extraction of PE under fluoroscopy with ECG monitoring.[107] In a series[108] of 26 patients undergoing catheter embolectomy, extraction was successful in 23 patients, with a mortality rate of 27%. Two patients subsequently underwent open embolectomy. Over the same time in the same institution, six patients had open embolectomy for acute PE with a mortality of 33%.[108] A report[109] of catheter embolectomy in 18 patients with a 28% mortality rate has also been published.

More recently, a catheter system has been devised that fragments thromboemboli by generating a Venturi effect at the catheter tip using jets of high-speed saline solution. The fragmented thrombus is then evacuated through the catheter lumen. This device looks promising, but there has been insufficient experience with it to make firm recommendations for its use.[110] Another approach is to use a combination of pharmacologic and mechanical thrombolysis.[111] A fragmentation catheter device that fragments pulmonary emboli by mechanical action of the recoiled rotating pigtail has also shown some promise in three case studies.[112–114] In severely ill patients who may be candidates for catheter extraction or dissolution or for surgical embolectomy, echocardiography may provide rapid bedside diagnosis and hasten therapeutic interventions.[115]

Recommendation

4.3.1. For most patients with PE, we recommend **against** use of mechanical approaches (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, we suggest use of mechanical approaches (**Grade 2C**).

4.4 Pulmonary embolectomy for the initial treatment of PE

Pulmonary embolectomy continues to be performed in emergency situations when more conservative measures have failed. If it is attempted, the candidate should meet the following criteria: (1) massive PE (angiographically documented if possible); (2) hemodynamic instability (shock) despite heparin and resuscitative efforts; and (3) failure of thrombolytic therapy or a contraindication to its use. Operative mortality in the

era of immediately available cardiopulmonary bypass has ranged from 10 to 75% in uncontrolled retrospective case series.[116–118] In patients who have had cardiopulmonary arrest, mortality has been reported between 50% and 94%. In a series[119] of 96 patients (55% of whom did not meet the criteria of hemodynamic instability), univariate analysis identified cardiac arrest and shock as predictors of mortality, and multivariate analysis confirmed the significance of cardiac arrest and underlying cardiopulmonary disease as predictors of mortality. Reported postoperative complications include ARDS, mediastinitis, acute renal failure and, of particular concern, severe neurologic sequelae. Pulmonary embolectomy should be considered when a patient meets the above criteria and an experienced cardiac surgical team is immediately available.[116–119]

Recommendation

4.4.1. For most patients with PE, we recommend **against** pulmonary embolectomy (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, we suggest pulmonary embolectomy (**Grade 2C**).

4.5 Vena caval interruption for the initial treatment of PE

The major rationale for inferior vena caval filters is the presence of a contraindication or complication of anticoagulation in an individual at high risk for recurrent PE. The most popular method of inferior vena caval interruption is placement of a filter developed by Greenfield and Rutherford.[120] This six-legged device can be inserted through the internal jugular vein or femoral vein, and advance into place in the inferior vena cava using fluoroscopic or ultrasonic guidance. In several large series,[120–124] the long-term patency rate of the filter has been 98%. Anticoagulation should be resumed as soon as possible after insertion of a filter because the filter alone is not an effective treatment of VTE. Results and complications with various filters have been summarized.[125] The Bird's Nest filter (Cook Incorporated; Bloomington, IL) also appears to be effective.[126,127] However, results with two other filters (Vena Tech LGM; LG Medical; Chasseneuil, France; and Gunther Tulip filter; Cook) appear to be less satisfactory.[128–130] Venous anatomic abnormalities, pregnancy, and thrombus proximal to the intended point of placement are considered to be contraindications to filter insertion. Filters have been placed with ultrasound guidance at the bedside of critically ill patients.[131] Temporary filters are currently undergoing testing.[132–135] Superior vena caval filters have been placed in patients with upper-extremity DVT.[136]

In a randomized trial of 400 patients with symptomatic DVT (all of whom received either heparin or LMWH), there was a lower incidence of PE at day 12 in patients assigned to receive filters compared with those without filters; however, the incidence of recurrent DVT at 1 year

was higher in the patients with filters compared with those without filters.[39] The devices did not prolong early or late survival in patients after a first episode of VTE. Thus, this benefit was offset by a tendency for more recurrent DVT in those patients who received a filter.[39] Other reports on the use of vena caval filters are of nonrandomized studies.[120,137–153]

Recommendation

4.5.1. In PE patients with a contraindication for, or a complication of anticoagulant treatment as well as in those with recurrent thromboembolism despite adequate anticoagulation, we suggest placement of an inferior vena caval filter (both **Grade 2C**).

4.6 New antithrombotic agents for the initial treatment of PE

Several new antithrombotic agents have been developed in recent years. In patients with PE, the synthetic pentasaccharide fondaparinux administered SC once daily was compared to IV UFH for initial treatment.[154] The study findings indicate that these two regimens have comparable efficacy and safety. Since this new compound has not been registered, no recommendations are made (see chapter by Weitz et all in this Supplement).

5.0 Long-term Treatment of Acute PE

Patients with acute PE require long-term anticoagulant treatment to prevent a high frequency (20 to 50%) of symptomatic extension of thrombosis and/or recurrent VTE. The need for long-term anticoagulant treatment of PE is supported by studies described in section 2 of this chapter. These studies were performed in patients with VTE, the majority of whom had DVT. Given the dearth of studies of patients with PE alone, many of the recommendations about long-term treatment of patients with PE are derived from clinical trials of patients who largely had DVT. PE and DVT are considered manifestations of the same disease, and therefore findings in studies of patients with DVT can be extrapolated to the universe of patients who present with PE, whether or not they have concurrent DVT. As a result, the recommendations about the long-term treatment are the same as for DVT.

5.1 VKAs for the long-term treatment of PE

Very few studies of long-term therapy have focused primarily on patients with PE. The evidence for long-term treatment of patients with PE is supported by studies described in section 2 of this chapter. Patients with PE are at slightly higher risk of dying from recurrent PE than are patients with DVT.[88,155] For this reason, longer treatment of patients with PE has been suggested, although data are lacking to support this hypothesis. Recently, a study[156] examined the risks and benefits of extending VKA beyond 3 months after an initial episode of PE, and concluded that extending VKA to 12 months from 3 months in patients with idiopathic disease only delayed the time to recurrence but did not reduce total recurrences when patients were followed up carefully after discontinuation of anticoagulation.

Treatment with VKA is the preferred approach for long-term treatment in most patients with PE. Treatment with adjusted doses of UFH or therapeutic doses of LMWH is indicated for selected patients in whom VKA are contraindicated (*eg*, pregnancy) or impractical, or in patients with concurrent cancer, for whom LMWH regimens have been shown to be more effective and at least as safe for the first 3 to 6 months of therapy (see section 2).

Recommendations

5.1.1. For patients with a first episode of PE secondary to a transient (reversible) risk factor, we recommend long-term treatment with a VKA for at least 3 months (**Grade 1A**).

5.1.2. For patients with a first episode of idiopathic PE, we recommend treatment with a VKA at least 6 to 12 months (**Grade 1A**).

5.1.3. We suggest that patients with first-episode idiopathic PE be considered for indefinite anticoagulant therapy (**Grade 2A**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

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

5.1.5. For patients with a first episode of PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (*eg*, combined factor V Leiden and prothrombin 20210 gene mutations), we recommend treatment for 12 months (**Grade 1C+**). For these patients, we suggest indefinite anticoagulant therapy (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

5.1.6. For patients with a first episode of PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal), we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy as for patients with idiopathic PE (**Grade 2C**).

Underlying values and preferences. This recommenda-

tion ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

5.1.7. For patients with two or more episodes of objectively documented PE, we suggest indefinite treatment (**Grade 2A**).

5.1.8. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) [**Grade 1A**]. We recommend against low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).

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

5.2 LMWH for the long-term treatment of PE

The use of LMWH for the long-term treatment has been evaluated in three randomized trials[53–55] in patients with DVT. The findings indicate that in patients with cancer, LMWH was more effective than VKA for preventing recurrent VTE. The recommendation about the use of LMWH in patients with cancer and PE is based on these studies.

Recommendation

5.2.1. For most patients with PE and concurrent cancer, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**)

Remark: The LMWH regimens that have been established to be effective for long-term treatment are dalteparin, 200 IU/kg body weight qd for 1 month followed by 150 IU/kg qd thereafter, and tinzaparin at 175 IU/kg body weight SC qd.

6.0 CTPH

CTPH appears to develop in < 1% of individuals who have PE. Many patients with this rare disorder do not give a history of an antecedent episode of PE. The etiology of the syndrome remains unclear. The most common preexisting abnormality in patients with CTPH is a serum antiphospholipid antibody, which is found in 10 to 15% of patients.

6.1 Pulmonary thromboendarterectomy, VKAs, and caval filter for the treatment of CTPH

Pulmonary thromboendarterectomy is currently the only treatment that seems to offer symptomatic relief and prolongation of life in patients with CTPH. There have been no RCTs comparing this surgical procedure to medical therapies such as long-term anticoagulation or treatment with pulmonary vasodilators.

Pulmonary thromboendarterectomy carries an oper-

ative mortality between 5% and 25%, with the most recent case series reporting an operative mortality of approximately 10%.[153,157–167] Only thrombotic material in segmental or more proximal arteries is accessible for removal. Patients selected for operation should show a rough correlation between pulmonary hemodynamic abnormalities and the amount of chronic thrombus present. Best results are obtained when the procedure is performed by an experienced surgeon supported by a team of trained anesthesiologists, cardiologists, pulmonologists, and nurses. The immediate postoperative period is the most problematic, and bleeding, reperfusion pulmonary edema, and persistent pulmonary hypertension are the most common complications. Survivors of the operative procedure seem to be assured of survival for at least 2 years based on follow-up reports. Patients with CTPH are usually in New York Heart Association functional class III or IV before surgery.[168] After surgery, they usually improve to class I or II and are able to assume normal activity. More formal quality-of-life measurements have not been reported in survivors of pulmonary thromboendarterectomy.

Some patients with distal (subsegmental or smaller) vascular involvement or serious comorbidity are not candidates for this surgical procedure. A preliminary report[169] suggests that pulmonary vasodilator therapy may be of benefit to them. At the least, these patients should receive VKA to an INR of 2.0 to 3.0.

Life-long therapy with VKA is nearly always administered after pulmonary thromboendarterectomy, although no RCTs have tested the duration of anticoagulation. An INR of 2.0 to 3.0 is usually sought. In patients with an antiphospholipid antibody, an INR of ≥ 3.0 has usually been recommended, although a recent study[73] demonstrated that anticoagulation to an INR of 2.0 to 3.0 is the preferred intensity in these patients.

Clinicians frequently recommend placement of a vena caval filter before or during pulmonary thromboendarterectomy, although this preventive therapy has never been tested in a controlled trial. Based on a small retrospective analysis,[170] inadequate vena caval filtering and suboptimal long-term anticoagulation both seem to increase risk for recurrent CTPH and the need for reoperative pulmonary thromboendarterectomy.

Recommendations

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

6.1.2. We recommend that life-long treatment with VKA to an INR of 2.0 to 3.0 be administered following pulmonary thromboendarterectomy, and also be administered to patients with CTPH who are ineligible for pulmonary thromboendarterectomy (**Grade 1C**).

6.1.3. We suggest the placement of a vena caval filter before or at the time of pulmonary thromboendarterectomy for CTPH (**Grade 2C**).

7.0 Superficial Thrombophlebitis

Superficial thrombophlebitis frequently occurs as a complication of an IV line, but can also occur spontaneously. Clinical signs and symptoms include a tender, swollen, red, superficial area along the course of a vein. Usually a cord can be palpated. When occurring in the lower extremity, there are often accompanying varices and venous valvular incompetence that can be demonstrated by duplex ultrasound.

7.1 Treatment of superficial thrombophlebitis

In a single, controlled study[171] of 120 patients with infusion-related thrombophlebitis, diclofenac emulsion gel used topically and oral diclofenac (75 mg bid) were superior to placebo in relieving symptoms of thrombophlebitis at 48 h, with positive responses in 60% in both active-treatment groups vs only 20% in the placebo group. Another study that included 68 patients with either spontaneous or infusion-related thrombophlebitis who were randomized to receive a topical cream (Hirudoid Cream, Saukyo Pharma; Buckinghamshire, UK), piroxicam gel, or placebo failed to show a difference.[172]

In superficial thrombophlebitis of the leg, a single, placebo-controlled study[173] is available that evaluated 1 week of enoxaparin in two dosages (40 mg and 1.5 mg/kg SC) and tenoxicam. The study included > 100 patients per group and showed a clear benefit at day 12 for all three active treatment groups as compared to placebo. However, 15 to 17% of patients had symptomatic DVT (4 to 5%) or recurrent superficial thrombophlebitis in the 3 months following cessation of therapy, indicating that 1 week of therapy is too short. In another randomized study[174] in 117 patients, calcium nadroparin SC 6,150 anti-Xa IU or 31.5 anti-Xa IU/kg was superior to naproxen (500 mg once daily) after 6 days in symptomatic relief.

In another study,[175] 60 consecutive patients with acute thrombophlebitis of the great saphenous vein, as assessed by ultrasonography, were randomized to SC injections twice daily of UFH in high unmonitored doses (12,500 IU for 1 week followed by 10,000 IU bid) or prophylactic doses (5,000 IU bid) for 4 weeks. Incidences of (a)symptomatic extension of the thrombus were 20.0% in those randomized to low-dose UFH, compared to 3% in those who received the higher dose. No major bleeding complications were observed in either group. Finally, a nonblinded randomized trial[176] with as many as seven treatment arms, which included only a limited number of patients per arm, showed that compression alone or ligation of the saphenous vein were inferior to other treatment options that included treatment with UFH.

Recommendations

7.1.1. For patients with superficial thrombophlebitis as a complication of an infusion, we suggest topical diclofenac gel (**Grade 1B**) or oral diclofenac (**Grade 2B**).

7.1.2. For patients affected by spontaneous superficial thrombophlebitis, we suggest intermediate dosages of UFH or LMWH for at least 4 weeks (**Grade 2B**).

8.0 Acute Upper-Extremity DVT

Upper-extremity DVT is a multifactorial disease. It can be associated with extrinsic compression or central venous catheterization, be related to effort, or not be associated without any apparent cause. The clinical manifestations are edema, dilated collateral circulation, and pain. The thrombotic obstruction can be located in the subclavian, axillary, or brachial vein. The disease may lead to complications, such as chronic obstructive edema and PE.[177–180] The treatment of patients with an acute DVT of the arm is divided into the initial treatment (with anticoagulants, thrombolytic therapy, or catheter/surgical techniques) and long-term treatment (or secondary prophylaxis) with anticoagulants and/or elastic bandages.

8.1 IV UFH or LMWH for the initial treatment of upper-extremity DVT

It is generally accepted that patients with upper-extremity DVT require treatment to prevent extension and embolization. No RCTs have been performed to evaluate the relative efficacy and safety of initial treatment of upper-extremity DVT with either UFH or LMWH. Several cohort studies[177,180,181] including 50 to 120 patients have used regimens identical to those for patients with DVT of the leg. These regimens are continuous, dose-adjusted IV UFH or SC LMWH, administered in a fixed dose according to body weight.[182,183] These treatments were usually administered for approximately 1 week. One study[182] evaluated out-of-hospital treatment with LMWH. No reliable data are available about the long-term outcome with respect to recurrences, bleeding, and postthrombotic sequelae. No studies are available with the newly developed anticoagulants, such as pentasaccharides and oral thrombin inhibitors.

Recommendation

8.1.1. For patients with acute upper-extremity DVT, we recommend initial treatment with UFH (**Grade 1C+**) or LMWH (**Grade 1C+**).

8.2 Thrombolytic therapy for the initial treatment of upper-extremity DVT

No RCTs have evaluated the efficacy and safety of thrombolytic therapy in the initial treatment of patients with upper-extremity DVT. Several cohort studies[184–191] including 6 to 50 patients evaluated streptokinase, urokinase, or t-PA with a variety of doses, methods, and duration of administration. It is unclear whether initial thrombolytic therapy is superior to anticoagulants, since no formal comparisons have been performed, although some studies[187,190,191] claim excellent success of thrombo-

lytic therapy in terms of patency, particularly in case of effort-related arm vein thrombosis and thrombosis of recent onset. In addition, no reliable data are available about the long-term outcome with respect to recurrences, bleeding, and postthrombotic sequelae.

Recommendation

8.2.1. In selected patients with acute upper-extremity DVT, *eg*, in those with a low risk of bleeding and symptoms of recent onset, we suggest a short course of thrombolytic therapy for initial treatment (**Grade 2C**).

8.3 Catheter extraction, surgical thrombectomy, or superior vena caval filter for the initial treatment of upper-extremity DVT

Only small, noncontrolled case series[192,193] are available about the use of surgical thrombectomy or catheter extraction in the initial treatment of patients with acute upper-extremity DVT. In most reports, these techniques are applied after (failure of) initial anticoagulant or thrombolytic treatment.

Superior vena caval filters have been used in patients with contraindications to anticoagulant treatment.[194] No reliable data are available about the long-term outcome with respect to recurrences and postthrombotic sequelae.

Recommendations

8.3.1. In selected patients with acute upper-extremity DVT, *eg*, those with failure of anticoagulant or thrombolytic treatment and persistent symptoms, we suggest surgical embolectomy (**Grade 2C**) or catheter extraction (**Grade 2C**).

8.3.2. In selected patients with acute upper-extremity DVT, *eg*, those in whom anticoagulant treatment is contraindicated, a superior vena caval filter (**Grade 2C**) could be considered for initial treatment.

8.4 Anticoagulants for the long-term treatment of upper-extremity DVT

Although there appears to be a general agreement that patients with symptomatic acute DVT of the upper extremity require long-term treatment (or secondary prophylaxis) with anticoagulants following their initial treatment, there are no randomized studies to support this view. In the great majority of cohort studies,[177–184,195] patients received VKA (target INR, 2.5; range, 2 to 3) for periods of 3 to 6 months, or longer in case of permanent risk factors, such as the presence of malignant disease. No studies are available with long-term use of LMWH or the newly developed anticoagulants, such as pentasaccharides and oral thrombin inhibitors.

Recommendation

8.4.1. For patients with acute upper-extremity DVT, we recommend long-term treatment with a VKA (**Grade 1C+**).

Remark: As for acute DVT of the leg (section 2.1), a similar process should be considered for determining the duration of VKA treatment.

8.5 Elastic bandages for the long-term treatment of upper-extremity DVT

No controlled studies have evaluated the effectiveness of elastic bandages in patients with upper-extremity DVT. Anecdotal evidence suggests that patients with persistent arm swelling and pain may benefit from elastic bandages.

Recommendation

8.5.1. In patients with upper-extremity DVT who have persistent edema and pain, we suggest elastic bandages for symptomatic relief (**Grade 2C**).

SUMMARY OF RECOMMENDATIONS

1.0 Treatment of Deep Venous Thrombosis

1.1 Initial treatment of acute DVT of the leg

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH or IV UFH or SC UFH (all **Grade 1A**).

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

1.1.3. In acute DVT, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).

1.1.4. We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (**Grade 1A**).

1.2 IV unfractionated heparin for the initial treatment of DVT

1.2.1. If IV UFH is chosen, we recommend that it be administered by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).

1.2.2. In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, we recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).

1.3 Subcutaneous unfractionated heparin for the initial treatment of DVT

1.3.1. In patients with acute DVT, we recommend that SC administered UFH can be used as an adequate alternative to IV UFH (**Grade 1A**).

1.3.2. For patients who receive SC UFH, we recommend an initial dose of 35,000 U/24 h SC, with subsequent dosing to maintain the aPTT in the therapeutic range (**Grade 1C+**).

1.4 Low-molecular-weight heparin for the initial treatment of DVT

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

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

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

1.5 Systematically administered thrombolysis in the initial treatment of DVT

1.5.1. In patients with DVT, we recommend **against** the routine use of IV thrombolytic treatment (**Grade 1A**).

1.5.2. In selected patients, such as those with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, we suggest IV thrombolysis (**Grade 2C**).

1.6 Catheter-directed thrombolysis in the initial treatment of DVT

1.6.1. In patients with DVT, we recommend **against** the routine use of catheter-directed thrombolysis (**Grade 1C**).

1.6.2. We suggest that this treatment should be confined to selected patients such as those requiring limb salvage (**Grade 2C**).

1.7 Catheter extraction or fragmentation and surgical thrombectomy for the initial treatment of DVT

1.7.1. In patients with DVT, we recommend **against** the routine use of venous thrombectomy (**Grade 1C**).

1.7.2. In selected patients such as patients with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, we suggest venous thrombectomy (**Grade 2C**).

1.8 Vena caval interruption for the initial treatment of DVT

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

1.8.2. We suggest the placement of an inferior vena caval filter in patients with a contraindication for, or a complication of anticoagulant treatment (**Grade 2C**), as well as in those with recurrent thromboembolism despite adequate anticoagulation (**Grade 2C**).

1.9 Nonsteroidal antiinflammatory agents for the initial treatment of DVT

1.9.1. For the initial treatment of DVT, we recommend **against** the use of nonsteroidal anti-inflammatory agents (**Grade 2B**).

1.11 Immobilization

1.11.1. For patients with DVT, we recommend ambulation as tolerated (**Grade 1B**).

2.0 Long-term Treatment of Acute DVT of the Leg

2.1 Vitamin K antagonists for the long-term treatment of DVT

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

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

Remark: The latter recommendation applies both to patients with proximal vein thrombosis, and to patients with symptomatic DVT confined to the calf veins.

2.1.2.1. For patients with a first episode of idiopathic DVT, we recommend treatment with a VKA at least 6 to 12 months (**Grade 1A**).

2.1.2.2. We suggest that patients with first-episode idiopathic DVT be considered for indefinite anticoagulant therapy (**Grade 2A**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

2.1.3. For patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (**Grade 1A**). For these patients, we

recommend anticoagulant therapy indefinitely or until the cancer is resolved (**Grade 1C**).

2.1.4. For patients with a first episode of DVT who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (*eg*, combined factor V Leiden and prothrombin 20210 gene mutations), we recommend treatment for 12 months (**Grade 1C+**). We suggest indefinite anticoagulant therapy in these patients (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

2.1.5. For patients with a first episode of DVT who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal), we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy as for patients with idiopathic thrombosis (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

2.1.6. For patients with two or more episodes of objectively documented DVT, we suggest indefinite treatment (**Grade 2A**).

2.1.7. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). We recommend **against** high-intensity VKA therapy (INR range, 3.1 to 4.0) [Grade 1A]. We recommend **against** low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).

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

2.1.9. We suggest repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma D-dimer (**Grade 2C**).

2.3 Low-molecular-weight heparin for the long-term treatment of DVT

2.3.1. For most patients with DVT and cancer, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**).

Remark: The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin, 200 IU/kg body weight qd for 1 month, followed by 150 IU/kg qd thereafter, or tinzaparin at 175 IU/kg body weight SC qd.

3.0 The Post-Thrombotic Syndrome

3.1 Elastic stockings for the prevention of the post-thrombotic syndrome

3.1.1. We recommend the use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle during 2 years after an episode of DVT (**Grade 1A**).

3.2 Physical treatment of the post-thrombotic syndrome

3.2.1. We suggest a course of intermittent pneumatic compression for patients with severe edema of the leg due to PTS (**Grade 2B**).

3.2.2. We suggest the use of elastic compression stockings for patients with mild edema of the leg due to the PTS (**Grade 2C**).

3.3 Drug treatment of the post-thrombotic syndrome

3.3.1. In patients with mild edema due to PTS, we suggest administration of rutosides (**Grade 2B**).

4.0 Initial Treatment of Acute Pulmonary Embolism

4.1 IV unfractionated heparin or low-molecular-weight heparin for the initial treatment of pulmonary embolism

4.1.1. For patients with objectively confirmed nonmassive PE, we recommend short-term treatment with SC LMWH, or IV UFH (both **Grade 1A**).

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

4.1.3. In patients with acute nonmassive PE, we recommend LMWH over UFH (**Grade 1A**).

4.1.4. In acute nonmassive PE, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).

4.1.5. In patients with acute nonmassive PE treated with LMWH, we recommend **against** routine monitoring with anti-factor Xa levels (**Grade 1A**).

4.1.6. In patients with severe renal failure, we suggest IV UFH over LMWH (**Grade 2C**).

4.1.7. If IV UFH is chosen, we recommend administration by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).

4.1.8. In patients requiring large daily doses of UFH

without achieving a therapeutic aPTT, we recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).

4.1.9. We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (**Grade 1A**).

4.2 Systemically and locally administered thrombolytic drugs for the initial treatment of pulmonary embolism

4.2.1. For most patients with PE, we recommend clinicians **not** use systemic thrombolytic therapy (**Grade 1A**). In selected patients, we suggest systemic administration of thrombolytic therapy (**Grade 2B**). For patients who are hemodynamically unstable, we suggest use of thrombolytic therapy (**Grade 2B**).

4.2.2. We suggest clinicians **not** use local administration of thrombolytic therapy via a catheter (**Grade 1C**).

4.2.3. For patients with PE who receive thrombolytic regimens, we suggest use of thrombolytic regimens with a short infusion time over those with prolonged infusion times (**Grade 2C**).

4.3 Catheter extraction or fragmentation for the initial treatment of pulmonary embolism

4.3.1. For most patients with PE, we recommend **against** use of mechanical approaches (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, we suggest use of mechanical approaches (**Grade 2C**).

4.4 Pulmonary embolectemy for the initial treatment of pulmonary embolism

4.4.1. For most patients with PE, we recommend **against** pulmonary embolectomy (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, we suggest pulmonary embolectomy (**Grade 2C**).

4.5 Vena caval interruption for the initial treatment of pulmonary embolism

4.5.1. In PE patients with a contraindication for, or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate anticoagulation, we suggest placement of an inferior vena caval filter (both **Grade 2C**).

5.0 Long-term Treatment of Acute Pulmonary Embolism

5.1 Vitamin K antagonists for the long-term treatment of pulmonary embolism

5.1.1. For patients with a first episode of PE secondary to a transient (reversible) risk factor, we recommend long-term treatment with a VKA for at least 3 months (**Grade 1A**).

5.1.2. For patients with a first episode of idiopathic PE, we recommend treatment with a VKA at least 6 to 12 months (**Grade 1A**).

5.1.3. We suggest that patients with first-episode idiopathic PE be considered for indefinite anticoagulant therapy (**Grade 2A**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

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

5.1.5. For patients with a first episode of PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (*eg*, combined factor V Leiden and prothrombin 20210 gene mutations), we recommend treatment for 12 months (**Grade 1C+**). For these patients, we suggest indefinite anticoagulant therapy (**Grade 2C**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

5.1.6. For patients with a first episode of PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal), we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy for patients with idiopathic PE (**Grade 2C**)

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

5.1.7. For patients with two or more episodes of objectively documented PE, we suggest indefinite treatment (**Grade 2A**).

5.1.8. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). We recommend **against** high-intensity VKA therapy (INR range, 3.1 to 4.0) [**Grade 1A**]. We recommend **against** low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).

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

5.2 LMWH for the long-term treatment of PE

5.2.1. For most patients with PE and concurrent cancer, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**)

Remark: The LMWH regimens that have been established to be effective for long-term treatment are dalteparin, 200 IU/kg body weight qd for 1 month followed by 150 IU/kg qd thereafter, and tinzaparin at 175 IU/kg body weight SC qd.

6.0 Chronic Thromboembolic Pulmonary Hypertension

6.1 Pulmonary thromboendarterectomy, vitamin K antagonists, and caval filter for the treatment of chronic thromboembolic pulmonary hypertension

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

6.1.2. We recommend that life-long treatment with VKA to an INR of 2.0 to 3.0 be administered following pulmonary thromboendarterectomy, and also be administered to patients with CTPH who are ineligible for pulmonary thromboendarterectomy (**Grade 1C**).

6.1.3. We suggest the placement of a vena caval filter before or at the time of pulmonary thromboendarterectomy for CTPH (**Grade 2C**).

7.0 Superficial Thrombophlebitis

7.1 Treatment for superficial thrombophlebitis

7.1.1. For patients with superficial thrombophlebitis as a complication of an infusion, we suggest topical diclofenac gel (**Grade 1B**) or oral diclofenac (**Grade 2B**).

7.1.2. For patients affected by spontaneous superficial thrombophlebitis, we suggest intermediate dosages of UFH or LMWH for at least 4 weeks (**Grade 2B**).

8.0 Acute Upper Extremity DVT

8.1 IV unfractionated heparin or low-molecular-weight heparin for the initial treatment of upper extremity DVT

8.1.1. For patients with acute upper-extremity DVT, we recommend initial treatment with UFH (**Grade 1C+**) or LMWH (**Grade 1C+**).

8.2 Thrombolytic therapy for the initial treatment of upper extremity DVT

8.2.1. In selected patients with acute upper-extremity DVT, *eg*, in those with a low risk of bleeding and symptoms of recent onset, we suggest a short course of thrombolytic therapy for initial treatment (**Grade 2C**).

8.3 Catheter extraction, surgical thrombectomy, or superior vena caval filter for the initial treatment of upper extremity DVT

8.3.1. In selected patients with acute upper-extremity DVT, *eg*, those with failure of anticoagulant or thrombolytic treatment and persistent symptoms, we suggest surgical embolectomy (**Grade 2C**) or catheter extraction (**Grade 2C**).

8.3.2. In selected patients with acute upper-extremity DVT, *eg*, those in whom anticoagulant treatment is contraindicated, a superior vena caval filter (**Grade 2C**) could be considered for initial treatment.

8.4 Anticoagulants for the long-term treatment of upper extremity DVT

8.4.1. For patients with acute upper-extremity DVT, we recommend long-term treatment with a VKA (**Grade 1C+**).

Remark: As for acute DVT of the leg (section 2.1), a similar process should be considered for determining the duration of VKA treatment.

8.5 Elastic bandages for the long-term treatment of upper extremity DVT

8.5.1. In patients with upper-extremity DVT who have persistent edema and pain, we suggest elastic bandages for symptomatic relief (**Grade 2C**).

References

1 Barrit DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1960; 1:1309–1312
2 Kernohan RJ, Todd C. Heparin therapy in thromboembolic disease. Lancet 1966; 1:621–623
3 Alpert JS, Smith R, Carlson J, et al. Mortality in patients treated for pulmonary embolism. JAMA 1976; 236:1477–1480
4 Kanis JA. Heparin in the treatment of pulmonary

thromboembolism. Thromb Diath Haemorrh 1974; 32: 519–527

5 Gallus A, Jackaman J, Tillett J, et al. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. Lancet 1986; 2:1293–1296

6 Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990; 322:1260–1264

7 Harrison L, Johnston M, Massicotte MP, et al. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997; 126:133–136

8 Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Arch Intern Med 1999; 159:46–48

9 Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. Ann Intern Med 2003; 138:714–719

10 Brill-Edwards P, Ginsberg JS, Johnston M, et al. Establishing a therapeutic range for heparin therapy. Ann Intern Med 1993; 119:104–109

11 Levine MN, Hirsh J, Gent M, et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 1994; 154: 49–56

12 Hull RD, Raskob GE, Rosenbloom D, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. Arch Intern Med 1992; 152:1589–1595

13 Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. Ann Intern Med 1993; 119:874–881

14 Cruickshank MK, Levine MN, Hirsh J, et al. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med 1991; 151:333–337

15 Anand SS, Bates S, Ginsberg JS, et al. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin times. Arch Intern Med 1999; 159:2029–2032

16 Brandjes DP, Heijboer H, Büller HR, et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992; 327:1485–1489

17 Levine MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. Chest 2001; 119(suppl):108S–121S

18 Salzman EW, Deykin D, Shapiro RM, et al. Management of heparin therapy: controlled prospective trial. N Engl J Med 1975; 292:1046–1050

19 Glazier RL, Crowell EB. Randomized prospective trial of continuous vs intermittent heparin therapy. JAMA 1976; 236:1365–1367

20 Wilson JR, Lampman J. Heparin therapy: a randomized prospective study. Am Heart J 1979; 97:155–158

21 Mant MJ, O'Brien BD, Thong KL, et al. Haemorrhagic complications of heparin therapy. Lancet 1977; 1:1133–1135

22 Fagher B, Lundh B. Heparin treatment of deep vein thrombosis: effects and complications after continuous or intermittent heparin administration. Acta Med Scand 1981; 210:357–361

23 Wilson JE III, Bynum LJ, Parkey RW. Heparin therapy in venous thromboembolism. Am J Med 1981; 70:808–816

24 Hommes DW, Bura A, Mazzolai L, et al. Subcutaneous heparin compared with continuous intravenous heparin administration in the initial treatment of deep vein thrombosis: a meta-analysis. Ann Intern Med 1992; 116: 279–284

25 Lensing AW, Prins MH, Davidson BL, et al. Treatment of deep venous thrombosis with low-molecular-weight heparins: a meta-analysis. Arch Intern Med 1995; 155: 601–607

26 Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160:181–188

27 Levine M, Gent M, Hirsh J, et al. A Comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334:677–681

28 Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home: the Tasman Study Group. N Engl J Med 1996; 334:682–687

29 The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337:657–662

30 Wells PS. Outpatient treatment of patients with deep-vein thrombosis or pulmonary embolism. Curr Opin Pulm Med 2001; 7:360–364

31 Harrison L, McGinnis J, Crowther M, et al. Assessment of outpatient treatment of deep-vein thrombosis with low-molecular-weight heparin. Arch Intern Med 1998; 158: 2001–2003

32 Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001; 134:191–202

33 Charbonnier BA, Fiessinger JN, Banga JD, et al. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. Thromb Haemost 1998; 79:897–901

34 Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. Am J Med 1990; 88:235–240

35 Lensing AW, Hirsh J. Rationale and results of thrombolytic therapy for deep vein thrombosis. In: Bernstein EF, ed. Vascular diagnosis. 4th ed. St. Louis, MO: Mosby, 1994; 875–879

36 Ouriel K, Gray B, Clair DG, et al. Complications associated with the use of urokinase and recombinant tissue plasminogen activator for catheter-directed peripheral arterial and venous thrombolysis. J Vasc Interv Radiol 2000; 11:295–298

37 Winter C, Weber H, Loeprecht H. Surgical treatment of

iliofemoral vein thrombosis technical aspects: possible secondary interventions. Int Angiol 1989; 8:188–193

38 Lansing AM, Davis WM. Five-year follow-up study of iliofemoral venous thrombectomy. Ann Surg 1968; 168:620–628

39 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998; 338:409–416

40 Nielsen HK, Husted SE, Krusell LR, et al. Anticoagulant therapy in deep venous thrombosis: a randomized controlled study. Thromb Res 1994; 73:215–226

41 The Rembrandt Investigators. Treatment of proximal deep vein thrombosis with a novel synthetic compound (SR90107A/ORG31540) with pure anti-factor Xa activity: a phase II evaluation. Circulation 2000; 102:2726–2731

42 Schellong SM, Schwarz T, Kropp J, et al. Bed rest in deep vein thrombosis and the incidence of scintigraphic pulmonary embolism. Thromb Haemost 1999; 82(suppl): 127–129

43 Aschwanden M, Labs KH, Engel H, et al. Acute deep vein thrombosis: early mobilization does not increase the frequency of pulmonary embolism. Thromb Haemost 2001; 85:42–46

44 Partsch H, Blattler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg 2000; 32:861–869

45 Partsch H. Therapy of deep vein thrombosis with low molecular weight heparin, leg compression and immediate ambulation. Vasa 2001; 30:195–204

46 Lagerstedt CI, Olsson CG, Fagher BO, et al. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985; 2:515–518

47 Hull R, Delmore T, Genton E, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979; 301:855–858

48 Lohr JM, Kerr TM, Lutter KS, et al. Lower extremity calf thrombosis: to treat or not to treat? J Vasc Surg 1991; 14:618–623

49 Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Lancet 1992; 340: 873–876

50 Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. N Engl J Med 1995; 332:1661–1665

51 Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost 1995; 74:606–611

52 Hull R, Delmore T, Carter C, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med 1982; 306:189–194

53 Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–153

54 Hull R, Pineo GF, Mah A, et al. A randomized trial evaluating long-term low-molecular-weight heparin therapy for three months versus intravenous heparin followed by warfarin sodium [abstract]. Blood 2002; 100:148a

55 Hull R, Pineo GF, Mah A, et al. Safety and efficacy results for a study investigating the long-term out-of-hospital treatment of patients with proximal-vein thrombosis using subcutaneous low-molecular-weight heparin versus warfarin [abstract]. Thromb Haemost 2001; (suppl): abstract OC1647

56 Hull R, Pineo GF, Mah A, et al. A randomised trial evaluating long-term low-molecular-weight heparin therapy for three months vs. intravenous heparin followed by warfarin sodium in patients with current cancer [abstract]. Thromb Haemost 2003; (suppl): P137a

57 Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125:1–7

58 Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism: The Duration of Anticoagulation Trial Study Group. N Engl J Med 1997; 336:393–398

59 Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340:901–907

60 Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. N Engl J Med 2001; 345:165–169

61 Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003; 348: 1425–1434

62 Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631–639

63 van Den Belt AG, Sanson BJ, Simioni P, et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. Arch Intern Med 1997; 157:2227–2232

64 Crowther MA, Kelton JG. Congenital thrombophilic states associated with venous thrombosis: a qualitative overview and proposed classification system. Ann Intern Med 2003; 138:128–134

65 Simioni P, Prandoni P, Lensing AW, et al. The risk of recurrent venous thromboembolism in patients with an Arg506–> Gln mutation in the gene for factor V (factor V Leiden). N Engl J Med 1997; 336:399–403

66 Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med 2000; 343:457–462

67 Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy: Duration of Anticoagulation Study Group. Am J Med 1998; 104:332–338

68 Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993–997

69 Prandoni P, Lensing AW, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002; 137:955–960

70 Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. JAMA 2003; 290:1071–1074

71 De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 1999; 341:801–806

72 Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982; 307:1676–1681

73 Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349:1133–1138

74 Schulman S, Wahlander K, Lundstrom T, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349:1713–1721

75 Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev 2002; 16:155–165

76 Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 2002; 162:1144–1148

77 Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759–762

78 Prandoni P. Below-knee compression stockings for prevention of the post-thrombotic syndrome: a randomized study [abstract]. Pathophysiol Haemost Thromb 2002; 32(suppl 2):72

79 Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001; 161:2105–2109

80 Ginsberg JS, Magier D, MacKinnon B, et al. Intermittent compression units for severe post-phlebitic syndrome: a randomized crossover study. Can Med Assoc J 1999; 160: 1303–1306

81 de Jongste AB, Jonker JJ, Huisman MV, et al. A double blind three center clinical trial on the short-term efficacy of 0-(beta-hydroxyethyl)-rutosides in patients with post-thrombotic syndrome. Thromb Haemost 1989; 62:826–829

82 Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency: a criteria-based systematic review. Arch Dermatol 1998; 134:1356–1360

83 Catania G, Tesauro B, Megha A, et al. Preliminary comparison of the clinical efficacy and tolerability of low-molecular-weight dermatan sulfate and calcium heparin in postthrombotic syndrome. Curr Ther Res 1996; 57:969–979

84 Andreozzi GM, Signorelli S, Di Pino L, et al. Postphlebitic syndrome: clinical activity and tolerability of desmin, new LMW dermatan sulfate. Angiology 1996; 47:1001–1010

85 Monreal MCJ, Callejas JM, Martorell A, et al. A prospective study of the long-term efficacy of two different venoactive drugs in patients with post-thrombotic syndrome. Phlebology 1994; 9:37–40

86 Verardi S, Ippoliti A, Pistolese GR. Antithrombotic treatment during acute inflammatory complications of patients affected by postphlebitic syndrome: LMW-heparin versus standard heparin. Int Angiol 1988; 7(3 Suppl):33–40

87 Morl H. Treatment of postthrombotic syndrome with a mixture of enzymes [in German]. Therapiewoche 1986; 36:2443–2446

88 Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458–462

89 Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism: American-Canadian Thrombosis Study Group. Arch Intern Med 2000; 160:229–236

90 Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997; 337:663–669

91 de Valk HW, Banga JD, Wester JW, et al. Comparing subcutaneous danaparoid with intravenous unfractionated heparin for the treatment of venous thromboembolism: a randomized controlled trial. Ann Intern Med 1995; 123: 1–9

92 Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995; 74:1432–1435

93 Anderson DR, Levine MN. Thrombolytic therapy for the treatment of acute pulmonary embolism. Can Med Assoc J 1992; 146:1317–1324

94 Urokinase pulmonary embolism trial: phase 1 results; a cooperative study. JAMA 1970; 214:2163–2172

95 Urokinase-streptokinase embolism trial: phase 2 results; a cooperative study. JAMA 1974; 229:1606–1613

96 Marder VJ. The use of thrombolytic agents: choice of patient, drug administration, laboratory monitoring. Ann Intern Med 1979; 90:802–808

97 Goldhaber SZ, Kessler CM, Heit J, et al. Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. Lancet 1988; 2:293–298

98 Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507–511

99 Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis: an international multicenter randomized trial: The Bolus Alteplase Pulmonary Embolism Group. Chest 1994; 106:718–724

100 Meneveau N, Schiele F, Vuillemenot A, et al. Streptokinase vs alteplase in massive pulmonary embolism: a randomized trial assessing right heart haemodynamics and pulmonary vascular obstruction. Eur Heart J 1997; 18:1141–1148

101 Cella G, Palla A, Sasahara AA. Controversies of different regimens of thrombolytic therapy in acute pulmonary embolism. Semin Thromb Haemost 1987; 13:163–170

102 Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988; 77:353–360

103 Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 1990; 98:1473–1479

104 Sharma GV, Burleson VA, Sasahara AA. Effect of thrombo-

lytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 1980; 303:842–845

105 Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med 1992; 326:1240–1245

106 Tebbe U, Graf A, Kamke W, et al. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. Am Heart J 1999; 138:39–44

107 Stewart JR, Greenfield LJ. Transvenous vena caval filtration and pulmonary embolectomy. Surg Clin North Am 1982; 62:411–430

108 Greenfield LJ, Langham MR. Surgical approaches to thromboembolism. Br J Surg 1984; 71:968–970

109 Timsit JF, Reynaud P, Meyer G, et al. Pulmonary embolectomy by catheter device in massive pulmonary embolism. Chest 1991; 100:655–658

110 Koning R, Cribier A, Gerber L, et al. A new treatment for severe pulmonary embolism: percutaneous rheolytic thrombectomy. Circulation 1997; 96:2498–2500

111 Fava M, Loyola S, Flores P, et al. Mechanical fragmentation and pharmacologic thrombolysis in massive pulmonary embolism. J Vasc Interv Radiol 1997; 8:261–266

112 Schmitz-Rode T, Janssens U, Duda SH, et al. Massive pulmonary embolism: percutaneous emergency treatment by pigtail rotation catheter. J Am Coll Cardiol 2000; 36:375–380

113 Schmitz-Rode T, Janssens U, Schild HH, et al. Fragmentation of massive pulmonary embolism using a pigtail rotation catheter. Chest 1998; 114:1427–1436

114 de Gregorio M, Gimeno M, Alfonso R, et al. Mechanical fragmentation and intrapulmonary fibrinolysis in the treatment of massive pulmonary embolism hemodynamic repercussions. Arch Bronconeumol 2001; 37:58–64

115 Tapson VF, Davidson CJ, Kisslo KB, et al. Rapid visualization of massive pulmonary emboli utilizing intravascular ultrasound. Chest 1994; 105:888–890

116 Meyer G, Tamisier D, Sors H, et al. Pulmonary embolectomy: a 20-year experience at one center. Ann Thorac Surg 1991; 51:232–236

117 Gray HH, Morgan JM, Paneth M, et al. Pulmonary embolectomy for acute massive pulmonary embolism: an analysis of 71 cases. Br Heart J 1988; 60:196–200

118 Clarke DB, Abrams LD. Pulmonary embolectomy: a 25 year experience. J Thorac Cardiovasc Surg 1986; 92:442–445

119 Ullmann M, Hemmer W, Hannekum A. The urgent pulmonary embolectomy: mechanical resuscitation in the operating theatre determines the outcome. Thorac Cardiovasc Surg 1999; 47:5–8

120 Greenfield LJ, Rutherford RB. Recommended reporting standards for vena caval filter placement and patient follow-up: Vena Caval Filter Consensus Conference. J Vasc Interv Radiol 1999; 10:1013–1019

121 Greenfield LJ, Proctor MC, Williams DM, et al. Long-term experience with transvenous catheter pulmonary embolectomy. J Vasc Surg 1993; 18:450–457

122 Greenfield LJ, Proctor MC. The percutaneous Greenfield filter: outcomes and practice patterns. J Vasc Surg 2000; 32:888–893

123 Fink JA, Jones BT. The Greenfield filter as the primary means of therapy in venous thromboembolic disease. Surg Gynecol Obstet 1991; 172:253–256

124 Leach TA, Pastena JA, Swan KG, et al. Surgical prophylaxis

for pulmonary embolism. Am Surg 1994; 60:292–295

125 Dorfman GS. Percutaneous inferior vena caval filters. Radiology 1990; 174:987–992

126 Hubbard KP, Roehm JO Jr, Abbruzzese JL. The Bird's Nest filter: an alternative to long-term oral anticoagulation in patients with advanced malignancies. Am J Clin Oncol 1994; 17:115–117

127 Lord RS, Benn I. Early and late results after Bird's Nest filter placement in the inferior vena cava: clinical and duplex ultrasound follow up. Aust N Z J Surg 1994; 64:106–114

128 Murphy TP, Dorfman GS, Yedlicka JW, et al. LGM vena cava filter: objective evaluation of early results. J Vasc Interv Radiol 1991; 2:107–115

129 Millward SF, Peterson RA, Moher D, et al. LGM (Vena Tech) vena caval filter: experience at a single institution. J Vasc Interv Radiol 1994; 5:351–356

130 Bull PG, Mendel H, Schlegl A. Gunther vena caval filter: clinical appraisal. J Vasc Interv Radiol 1992; 3:395–399

131 Tola JC, Holtzman R, Lottenberg L. Bedside placement of inferior vena cava filters in the intensive care unit. Am Surg 1999; 65:833–837

132 Linsenmaier U, Rieger J, Schenk F, et al. Indications, management, and complications of temporary inferior vena cava filters. Cardiovasc Interv Radiol 1998; 21:464–469

133 Bovyn G, Gory P, Reynaud P, et al. The Tempofilter: a multicenter study of a new temporary caval filter implantable for up to six weeks. Ann Vasc Surg 1997; 11:520–528

134 Zwaan M, Lorch H, Kulke C, et al. Clinical experience with temporary vena caval filters. J Vasc Interv Radiol 1998; 9:594–601

135 Millward SF, Oliva VL, Bell SD, et al. Gunther Tulip retrievable vena cava filter: results from the Registry of the Canadian Interventional Radiology Association. J Vasc Interv Radiol 2001; 12:1053–1058

136 Spence LD, Gironta MG, Malde HM, et al. Acute upper extremity deep venous thrombosis: safety and effectiveness of superior vena caval filters. Radiology 1999; 210:53–58

137 Greenfield LJ, Proctor MC. Suprarenal filter placement. J Vasc Surg 1998; 28:432–438

138 Greenfield LJ, Cho KJ, Proctor M, et al. Results of a multicenter study of the modified hook-titanium Greenfield filter. J Vasc Surg 1991; 14:253–257

139 Rohrer MJ, Scheidler MG, Wheeler HB, et al. Extended indications for placement of an inferior vena cava filter. J Vasc Surg 1989; 10:44–49

140 Golueke PJ, Garrett WV, Thompson JE, et al. Interruption of the vena cava by means of the Greenfield filter: expanding the indications. Surgery 1988; 103:111–117

141 Cohen JR, Tenenbaum N, Citron M. Greenfield filter as primary therapy for deep venous thrombosis and/or pulmonary embolism in patients with cancer. Surgery 1991; 109:12–15

142 Calligaro KD, Bergen WS, Haut MJ, et al. Thromboembolic complications in patients with advanced cancer: anticoagulation versus Greenfield filter placement. Ann Vasc Surg 1991; 5:186–189

143 Emerson RH Jr, Cross R, Head WC. Prophylactic and early therapeutic use of the Greenfield filter in hip and knee joint arthroplasty. J Arthroplasty 1991; 6:129–135

144 Sarasin FP, Eckman MH. Management and prevention of

thromboembolic events in patients with cancer-related hypercoagulable states: a risky business. J Gen Intern Med 1993; 8:476–486

145 Rogers FB, Shackford SR, Wilson J, et al. Prophylactic vena cava filter insertion in severely injured trauma patients: indications and preliminary results. J Trauma 1993; 35:637–641

146 Rosenthal D, McKinsey JF, Levy AM, et al. Use of the Greenfield filter in patients with major trauma. Cardiovasc Surg 1994; 2:52–55

147 Webb LX, Rush PT, Fuller SB, et al. Greenfield filter prophylaxis of pulmonary embolism in patients undergoing surgery for acetabular fracture. J Orthop Trauma 1992; 6:139–145

148 Collins DN, Barnes CL, McCowan TC, et al. Vena caval filter use in orthopaedic trauma patients with recognized preoperative venous thromboembolic disease. J Orthop Trauma 1992; 6:135–138

149 Cotroneo AR, Di Stasi C, Cina A, et al. Venous interruption as prophylaxis of pulmonary embolism: vena cava filters. Rays 1996; 21:461–480

150 Ascher E, Hingorani A, Tsemekhin B, et al. Lessons learned from a 6-year clinical experience with superior vena cava Greenfield filters. J Vasc Surg 2000; 32:881–887

151 Rousseau H, Perreault P, Otal P, et al. The 6-F nitinol TrapEase inferior vena cava filter: results of a prospective multicenter trial. J Vasc Interv Radiol 2001; 12:299–304

152 Athanasoulis CA, Kaufman JA, Halpern EF, et al. Inferior vena caval filters: review of a 26-year single-center clinical experience. Radiology 2000; 216:54–66

153 Mertens R, Valdes F, Kramer A, et al. Inferior vena cava filters: indications and results in 111 patients. Rev Med Chile 1998; 126:655–660

154 The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695–1702

155 Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999; 159:445–453

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

157 Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. Curr Probl Surg 2000; 37:165–252

158 Masuda M, Nakajima N. Our experience of surgical treatment for chronic pulmonary thromboembolism. Ann Thorac Cardiovasc Surg 2001; 7:261–265

159 Mayer E, Kramm T, Dahm M, et al. Early results of pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension. Z Kardiol 1997; 86:920–927

160 Gilbert TB, Gaine SP, Rubin LJ, et al. Short-term outcome and predictors of adverse events following pulmonary thromboendarterectomy. World J Surg 1998; 22:1029–1032

161 Miller WT Jr, Osiason AW, Langlotz CP, et al. Reperfusion edema after thromboendarterectomy: radiographic patterns of disease. J Thorac Imaging 1998; 13:178–183

162 Dartevelle P, Fadel E, Chapelier A, et al. Angioscopic video-assisted pulmonary endarterectomy for post-embolic

pulmonary hypertension. Eur J Cardiothorac Surg 1999; 16:38–43

163 Ando M, Okita Y, Tagusari O, et al. Surgical treatment for chronic thromboembolic pulmonary hypertension under profound hypothermia and circulatory arrest in 24 patients. J Card Surg 1999; 14:377–385

164 Mares P, Gilbert TB, Tschernko EM, et al. Pulmonary artery thromboendarterectomy: a comparison of two different postoperative treatment strategies. Anesth Analg 2000; 90:267–273

165 Rubens F, Wells P, Bencze S, et al. Surgical treatment of chronic thromboembolic pulmonary hypertension. Can Respir J 2000; 7:49–57

166 D'Armini AM, Cattadori B, Monterosso C, et al. Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: hemodynamic characteristics and changes. Eur J Cardiothorac Surg 2000; 18:696–701

167 Tscholl D, Langer F, Wendler O, et al. Pulmonary thromboendarterectomy: risk factors for early survival and hemodynamic improvement. Eur J Cardiothorac Surg 2001; 19:771–776

168 Fedullo PF, Auger WR, Kerr KM, et al. Chronic thromboembolic pulmonary hypertension. N Engl J Med 2001; 345:1465–1472

169 McLaughlin VV, Genthner DE, Panella MM, et al. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. Ann Intern Med 1999; 130:740–743

170 Mo M, Kapelanski DP, Mitruka SN, et al. Reoperative pulmonary thromboendarterectomy. Ann Thorac Surg 1999; 68:1770–1776

171 Becherucci A, Bagilet D, Marenghini J, et al. Effect of topical and oral diclofenac on superficial thrombophlebitis caused by intravenous infusion. Med Clin (Barc) 2000; 114:371–373

172 Bergqvist D, Brunkwall J, Jensen N, et al. Treatment of superficial thrombophlebitis: a comparative trial between placebo, Hirudoid cream and piroxicam gel. Ann Chir Gynaecol 1990; 79:92–96

173 Superficial Thrombophlebitis Treated by Enoxaparin Study Group. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a nonsteroidal anti-inflammatory agent, and placebo in the treatment of superficial vein thrombosis. Arch Intern Med 2003; 163:1657–1663

174 Titon JP, Auger D, Grange P, et al. Therapeutic management of superficial venous thrombosis with calcium nadroparin: dosage testing and comparison with a non-steroidal anti-inflammatory agent. Ann Cardiol Angeiol (Paris) 1994; 43:160–166

175 Marchiori A, Verlato F, Sabbion P, et al. High versus low doses of unfractionated heparin for the treatment of superficial thrombophlebitis of the leg: a prospective, controlled, randomized study. Haematologica 2002; 87:523–527

176 Belcaro G, Nicolaides AN, Errichi BM, et al. Superficial thrombophlebitis of the legs: a randomized, controlled, follow-up study. Angiology 1999; 50:523–529

177 Burihan E, de Figueiredo LF, Francisco JJ, et al. Upper-extremity deep venous thrombosis: analysis of 52 cases. Cardiovasc Surg 1993; 1:19–22

178 Goldstein M, Dereume JP, van der SJ. Les thromboses

veineuses du membre supérieur. Schweiz Rundsch Med Prax 1976; 65:1450–1452

179 Hingorani A, Ascher E, Ward M, et al. Combined upper and lower extremity deep venous thrombosis. Cardiovasc Surg 2001; 9:472–477

180 Lindblad B, Tengborn L, Bergqvist D. Deep vein thrombosis of the axillary-subclavian veins: epidemiologic data, effects of different types of treatment and late sequelae. Eur J Vasc Surg 1988; 2:161–165

181 Marinella MA, Kathula SK, Markert RJ. Spectrum of upper-extremity deep venous thrombosis in a community teaching hospital. Heart Lung 2000; 29:113–117

182 Savage KJ, Wells PS, Schulz V, et al. Outpatient use of low molecular weight heparin (Dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost 1999; 82:1008–1010

183 Marie I, Levesque H, Cailleux N, et al. Upper-extremity deep venous thrombosis: a report of 49 cases. Rev Med Intern 1998; 19:399–408

184 Feugier P, Aleksic I, Salari R, et al. Long-term results of venous revascularization for Paget-Schroetter syndrome in athletes. Ann Vasc Surg 2001; 15:212–218

185 Horne MK III, Mayo DJ, Cannon RO III, et al. Intraclot recombinant tissue plasminogen activator in the treatment of deep venous thrombosis of the lower and upper extremities. Am J Med 2000; 108:251–255

186 Lokanathan R, Salvian AJ, Chen JC, et al. Outcome after thrombolysis and selective thoracic outlet decompression for primary axillary vein thrombosis. J Vasc Surg 2001; 33:783–788

187 Machleder HI. Evaluation of a new treatment strategy for Paget-Schroetter syndrome: spontaneous thrombosis of the axillary-subclavian vein. J Vasc Surg 1993; 17:305–315

188 Massoure PL, Constans J, Caudry M, et al. Thromboses veineuses profondes des members supérieurs. J Mal Vasc 2000; 25:250–255

189 Pegis JD, Papon X, Pasco A, et al. Thrombolyse in situ dans le traitement des thromboses veineuses d'effort du membre supérieur. J Mal Vasc 1997; 22:187–192

190 Petrakis IE, Katsamouris A, Kafassis E, et al. Two different therapeutic modalities in the treatment of the upper extremity deep vein thrombosis: preliminary investigation with 20 case reports. Int J Angiol 2000; 9:46–50

191 Yilmaz EN, Vahl AC, Heek van NT, et al. Long-term results of local thrombolysis followed by first rib resection: an encouraging clinical experience in treatment of subclavian vein thrombosis. Vasc Surg 2000; 34:17–23

192 Lee MC, Grassi CJ, Belkin M, et al. Early operative intervention after thrombolytic therapy for primary subclavian vein thrombosis: an effective treatment approach. J Vasc Surg 1998; 27:1101–1107

193 Sanders RJ, Cooper MA. Surgical management of subclavian vein obstruction, including six cases of subclavian vein bypass. Surgery 1995; 118:856–863

194 Ascer E, Gennaro M, Lorensen E, et al. Superior vena caval Greenfield filters: indications, techniques, and results. J Vasc Surg 1996; 23:498–503

195 Prandoni P, Bernardi E. Upper extremity deep vein thrombosis. Curr Opin Pulm Med 1999; 5:222–226

196 Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. 2004; 140:867–873