Treatment of deep vein thrombosis

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INTRODUCTION — Deep vein thrombosis (DVT) and acute pulmonary embolism (PE) are two manifestations of the same disorder, venous thromboembolism (VTE). DVT of the lower extremity is subdivided into either distal (calf vein) or proximal (popliteal, femoral, or iliac vein) thrombosis. Proximal vein thrombosis is of greater importance clinically, since it is more commonly associated with serious disease. As an example, over 90 percent of cases of acute PE are due to emboli emanating from the proximal, rather than the distal, veins of the lower extremities.

VTE is an important cause of morbidity and mortality, particularly in hospitalized patients. PE is the cause of death or a major contributing factor in up to 16 percent of patients who die in the hospital. However, in some series, the diagnosis of PE is suspected before death in less than one-third of patients. It is therefore important to have a high index of suspicion for the presence of VTE and to initiate appropriate diagnostic tests and therapy. Primary prophylaxis with pharmacologic agents and/or mechanical methods should be used in patients with moderate to high risk of venous thromboembolism [1]. This subject is discussed separately. (See "Prevention of venous thromboembolic disease in surgical patients".)

Because of the complexity of the issues surrounding diagnosis, screening, prevention, and treatment of VTE, we have provided the reader with an overview which can serve as a general introduction to all of the issues surrounding this subject. (See "Approach to the diagnosis and therapy of deep vein thrombosis".) More specific information on each of the aspects of this disorder is presented separately, as follows:

- Initial evaluation — The initial approach to the patient with suspected or established venous thrombosis, with emphasis upon clinical features surrounding the event and the indications for testing (screening) for an inherited or acquired cause of thrombophilia, are discussed separately. (See "Evaluation of the patient with established venous thrombosis" and "Overview of the causes of venous thrombosis".)

- Establishing the diagnosis — Establishing the diagnosis of DVT and PE is discussed separately. (See "Diagnosis of suspected deep vein thrombosis of the lower extremity" and "Diagnosis of acute pulmonary embolism".)

- Upper extremity DVT — DVT occurs less frequently in the upper extremity than in the lower extremity, but the incidence is increasing because of greater use of indwelling central venous catheters, especially in patients with malignancy, who are prone to thrombotic complications. Prevention, complications, and treatment of upper extremity DVT, which generally differ from those employed for lower extremity DVT, are discussed separately. (See "Catheter-induced upper extremity venous thrombosis".)

- DVT in children — The pathogenesis, clinical manifestations, diagnosis, and treatment of DVT in infants and children are presented separately. (See "Pathogenesis and clinical manifestations of venous thromboembolism in infants and children" and "Diagnosis and treatment of venous thromboembolism in infants and children".)

- Prevention of VTE — A discussion of the various means for preventing VTE in subjects at risk is presented separately. (See "Prevention of venous thromboembolic disease in surgical patients".)

- Treatment of VTE in patients with malignancy including those with primary or secondary brain tumors — This subject is discussed separately. (See "Treatment of venous thromboembolism in patients with malignancy" and "Anticoagulant and antiplatelet therapy in patients with brain tumors".)

The treatment of acute DVT in adults will be reviewed here [2,3], The treatment of pulmonary embolism and patient information on DVT are discussed separately. (See "Treatment of acute pulmonary embolism" and "Patient information: Deep vein thrombosis (DVT)".)

GENERAL OBJECTIVES — The primary objectives of treatment of DVT are to prevent further clot extension, acute PE, recurrence of thrombosis, as well as the development of late complications, such as the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

Prevention of further thrombosis — Anticoagulant therapy is indicated for patients with symptomatic proximal lower extremity DVT, since pulmonary embolism will occur in approximately 50 percent of untreated individuals, most often within days or weeks of the event [4,5]. The benefit of anticoagulation was first demonstrated in 1960 [6] and confirmed by randomized clinical trials [3,7]. A mortality rate of less than 5 percent should be achieved with the use of intravenous heparin and oral anticoagulants; this may be further reduced with the use of low molecular weight heparin (see 'Low molecular weight heparin' below [8].

Anticoagulation is usually achieved initially with unfractionated or low molecular weight heparin, followed by oral anticoagulation with warfarin for a minimum of three months [9]. As will be described below, the duration of warfarin therapy is determined in part by the presence or absence of persistent risk factors (table 1) and whether the DVT represents a first or a recurrent episode. (See "Overview of the causes of venous thrombosis".)

Prevention of post-thrombotic syndrome — Post-thrombotic syndrome is the development of symptoms of venous insufficiency after DVT and eventually occurs in about 28 percent of patients who have had a symptomatic DVT. Prevention of this complication is discussed separately. (See "Post-thrombotic (postphlebitic) syndrome", section on 'Prevention'.)

Testing for thrombophilia — Testing for thrombophilia in patients with established DVT, including interference with such testing caused by treatment with heparin or warfarin (table 2), is discussed separately. (See "Evaluation of the patient with established venous thrombosis".)

UNFRACTIONATED HEPARIN — The anticoagulant response to a standard dose of unfractionated heparin varies widely among patients. Further, there is insufficient information in the literature to modify the initial dose according to estimates of the patient's "wet" versus "dry" weight or rapidly changing weight. This makes it necessary to monitor the response in each patient, using either the activated partial thromboplastin time (aPTT) or heparin levels, and to titrate the dose to the individual patient [10,11]. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Heparin monitoring'.)

Goals — Experimental studies and clinical trials have established that the efficacy of heparin therapy depends upon achieving a critical therapeutic level of heparin within the first 24 hours of treatment,

usually via a continuous intravenous of unfractionated heparin [12-17]. The critical therapeutic level of heparin, as measured by the aPTT, is 1.5 times the mean of the control value or the upper limit of the normal aPTT range, with a target range (aPTT ratio) of 1.5 to 2.5.

- In one prospective study, there was a threefold increase in the risk of recurrent venous thromboembolism in patients who were initially treated with a heparin infusion of 1000 international units/hr and who had an aPTT ratio of <1.5 times control for three days or more [12].

- In another report evaluating patient groups entered into a series of three consecutive double-blind randomized trials, failure to achieve a therapeutic aPTT by 24 hours was associated with a 23.3 percent frequency of recurrent VTE compared with 4 to 6 percent for those whose aPTT exceeded the therapeutic threshold by 24 hours [17].

- Additional evidence for the importance of rapid adequate heparinization was reported in a randomized study conducted by the Galilei Investigators. Among patients allocated to receive UFH, recurrent thromboembolism occurred one-third as often (7 of 263 patients, 2.7 percent) in those who reached the aPTT therapeutic threshold within 24 hours, as compared with those who did not reach this threshold (8 of 97, 8.2 percent) [18].

Although there is a strong correlation between subtherapeutic aPTT values and recurrent thromboembolism, the relationship between supratherapeutic aPTT (ie, an aPTT ratio 2.5 or more) and bleeding is less definite (see 'Complications' below [19].

The level of anticoagulation described above (aPTT ratio 1.5 to 2.5) corresponds to a heparin blood level of 0.3 to 0.7 U/mL by the amidolytic anti-factor Xa assay [3,20]. There is a wide variability in relationship between the aPTT and heparin blood levels with different reagents and even with different batches of the same reagent [20,21].

Heparin is usually given simultaneously with warfarin and is overlapped with warfarin for a minimum of four to five days until the International Normalized Ratio (INR) has been within the therapeutic range (2.0 to 3.0) for two consecutive days [22]. This overlap is required because, during the first few days of warfarin therapy, prolongation of the INR mainly reflects depression of factor VII, which has a half-life of only five to seven hours. Thus, although the extrinsic coagulation pathway is suppressed, the intrinsic coagulation pathway that does not require factor VII remains intact during this early period (see 'Warfarin' below.

When combined with early administration of warfarin, four to five days of heparin therapy is as effective as 10 to 14 days of treatment [23,24]. In one trial of patients with proximal DVT, as an example, five and 10 days of heparin were associated with an equivalent incidence of recurrent venous thromboembolism (7.1 versus 7.0 percent, respectively) [24].

Administration and adequacy — Audits have shown that administration of intravenous heparin is fraught with difficulty and that the clinical practice of using an ad hoc approach to heparin dose-titration frequently results in inadequate therapy [25-28]. As an example, an audit at three university-affiliated hospitals documented that 60 percent of treated patients failed to achieve an adequate aPTT response during the initial 24 hours of therapy and that 30 to 40 percent of patients remained subtherapeutic over the next three to four days [26].

The increased incidence of recurrent venous thromboembolism after inadequate initial heparinization has been described above [12,17]. Several practices were identified that led to inadequate therapy. The common theme was fear of bleeding complications on the part of clinicians. These observations led to the initiation of protocols designed to avoid inadequate dosing. The value of these prescriptive or protocol approaches for administering intravenous heparin therapy has been evaluated in two studies in patients with venous thromboembolism:

- The first trial evaluated patients with proximal venous thrombosis who were given either intravenous heparin alone followed by warfarin, or intravenous heparin and simultaneous warfarin [19]. The heparin nomogram used in this study is summarized in the tables (table 3 and table 4). Only 1 and 2 percent of the patients were subtherapeutic for more than 24 hours in the heparin group and in the heparin and warfarin group, respectively. Objectively documented recurrent venous thromboembolism occurred infrequently in both groups (7 percent), rates similar to those previously reported.

- The second trial compared a weight-based heparin dosing nomogram with a standard-care nomogram (table 5) [14]. Patients treated with the weight-adjusted regimen received a starting bolus dose of 80 units/kg followed by an 18 units/kg per hour infusion. Patients in the standard-care group received a bolus of 5000 units followed by a 1000 units/h infusion. The heparin dose was adjusted to maintain an aPTT of 1.5 to 2.3 times control. A higher percentage of patients in the weight-adjusted group achieved a therapeutic aPTT within 24 hours (97 versus 77 percent). The incidence of recurrent thromboembolism was much higher (relative risk: 5.0, 95% CI 1.1-21.9) in the standard-care group.

We routinely use the approach outlined in the first trial described above (table 3 and table 4) [19]. However, the two approaches yield comparable results (based on the cited studies), and either is acceptable.

Heparin resistance — This subject is discussed separately. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Heparin resistance'.)

Complications — The major side effects of heparin therapy are bleeding and thrombocytopenia; the latter is often associated with thrombosis (ie, heparin-induced thrombocytopenia with thrombosis, HIT, HITT). These issues are discussed in detail elsewhere. (See "Therapeutic use of heparin and low molecular weight heparin" and "Heparin-induced thrombocytopenia".)

LOW MOLECULAR WEIGHT HEPARIN — The main type of unfractionated heparin in current clinical use is polydispersed unmodified heparin (mean molecular weight ranging from 10,000 to 16,000 daltons). Low molecular weight (LMW) derivatives of commercial heparin are available that have a mean molecular weight of 4000 to 6000 daltons [29]. Such LMW heparins have a number of advantages over unfractionated heparin [29]. (See "Therapeutic use of heparin and low molecular weight heparin".)

- Greater bioavailability when given by subcutaneous injection
- Duration of the anticoagulant effect is greater, permitting once or twice daily administration
- Anticoagulant response (anti-Xa activity) is highly correlated with body weight, permitting administration of a fixed dose
- Laboratory monitoring is not necessary; in fact, there is little correlation between anti-Xa activity and either bleeding or recurrent thrombosis
- Lower risk of heparin-induced thrombocytopenia

There have been few studies comparing different LMW heparins with respect to clinical outcomes, and the doses of the different LMW heparins have been established empirically and are not necessarily interchangeable.

Subcutaneous, unmonitored LMW heparin has been compared with continuous intravenous heparin for the treatment of proximal venous thrombosis in a number of clinical trials. LMW heparin, given once or twice daily, is at least as effective and safe as, and may be superior to [30], unfractionated heparin in patients with proximal venous thrombosis and may be associated with greater inhibition of in vivo thrombin generation [31], higher rates of thrombus regression, and lower rates of recurrent venous

thromboembolism, major bleeding, and mortality (table 6) [32-36].

- In one meta-analysis, LMW heparin was associated with a lower rate of both recurrent DVT (2.7 versus 7.0 percent) and major bleeding (0.9 versus 3.2 percent) than unfractionated heparin [33].
- A second meta-analysis of 11 trials found a significantly lower mortality rate at three to six months among patients treated with LMW heparin compared with those receiving unfractionated heparin (odds ratio: 0.71, 95% CI 0.53-0.94); differences in recurrent thromboembolism and bleeding complications were statistically and/or clinically insignificant between the two treatments [37].
- A meta-analysis of five trials directly comparing LMW heparin given once versus twice daily found no differences in symptomatic or asymptomatic recurrence of VTE between the two treatment schedules [38]. There were insufficient data in head-to-head studies to exclude the possibility of a higher frequency of fatal bleeding with once-daily treatment.

As noted above, the doses of the different LMW heparins have been established empirically and are not necessarily interchangeable. Accordingly, treatment regimens recommended specifically for each agent should be adhered to, pending further data (table 6).

Outpatient use — A literature search of studies on the outpatient treatment of DVT has suggested that the following four criteria can help to identify patients with DVT for whom outpatient treatment might not be appropriate [39]:

- Presence of massive DVT (eg, iliofemoral DVT)
- Presence of symptomatic pulmonary embolism
- High risk of bleeding with anticoagulant therapy
- Presence of comorbid conditions or other factors that warrant in-hospital care

However, when feasible, patients with proximal DVT can be safely treated with LMW heparin in an outpatient setting without loss of efficacy (table 6) [30,40-44], thus avoiding hospitalization associated with use of unfractionated heparin [45]. The minimal elements that should be in place to insure safety of such outpatient treatment have been outlined (table 7). (See "Low molecular weight heparin for venous thromboembolic disease".)

As an example of this approach, 89 patients with acute DVT entered into an outpatient treatment protocol were treated with LMW heparin for a median time of one day in a hospital setting [46]. Following this, they received outpatient LMW heparin for a mean of 4.7 days, three months of warfarin, and daily home nursing visits to monitor treatment and complications. Recurrent thromboembolism, major bleeding, and minor bleeding were noted in 1, 2, and 2 percent, respectively, with no deaths, and with an estimated cost saving of $1645 per patient.

A meta-analysis of eight trials comparing outpatient use of LMW heparin to inpatient unfractionated heparin found that the two treatments resulted in similar rates of recurrent DVT (4 versus 6 percent) and major bleeding (0.5 versus 1.0 percent), although use of LMW heparin was associated with shorter hospital stays (2.7 versus 6.5 days) and lower costs (median difference $1600) [47]. Comparisons of outpatient versus inpatient use of LMW heparin revealed no differences in outcomes, but outpatient use was more cost-effective, with a median difference in cost of 57 percent.

A 2007 Cochrane analysis of six randomized controlled trials involving 1708 participants concluded that patients treated at home with LMW heparin were significantly less likely to have VTE recurrence (RR 0.61; 95% CI 0.42-0.90) than those treated in the hospital with unfractionated or LMW heparin [48]. Rates of mortality, major, and minor bleeding were not significantly different.

Long-term use — In patients unable or unwilling to use vitamin K antagonists after initial

anticoagulation with unfractionated heparin or LMW heparin, anticoagulation can be continued with LMW heparin without sacrificing effectiveness or causing increases in bleeding or overall mortality [49], and may result in a lowered frequency of post-thrombotic syndrome [50,51]. However, the use and acceptability of long-term LMW heparin will depend upon such variables as the clinical setting, patient comorbidity, ability of the patient or a family member to inject the medication, availability of health care resources, and reimbursement policies.

Treatment with LMW heparin may actually result in better outcomes than treatment with vitamin K antagonists in patients with acute VTE and malignancy. This subject is discussed separately. (See "Hypercoagulable disorders associated with malignancy", section on 'Treatment of VTE'.)

A 2000 Cochrane review of randomized trials of three months of treatment with vitamin K antagonists versus three months of LMW heparin concluded that the latter agents are "possibly" as effective and safe as vitamin K antagonists, but have the disadvantage of much higher costs [52].

Cost-effectiveness — Randomized trials and meta-analyses of nonrandomized trials have indicated that the cost of treatment of acute DVT with LMW heparin is similar to, or lower than, strategies utilizing unfractionated heparin, generally regardless of treatment setting (eg, inpatient versus outpatient) [30,53-57]. As examples:

- A randomized trial analyzed the cost-effectiveness of standard intravenous heparin compared with LMW heparin in the treatment of acute proximal DVT [53]. There was a cost savings of $15,252 (Canadian dollars) or $40,149 (US dollars) per 100 patients in favor of LMW heparin. It was further estimated that 37 percent of the patients in the study would have been eligible for outpatient therapy with LMW heparin, thereby increasing the cost savings to $95,736 (Canadian dollars) or $91,332 (US dollars) per 100 patients with proximal deep vein thrombosis.

- One decision analysis found similar costs for the inpatient use of unfractionated or LMW heparin for six days while warfarin was initiated [55]. A decreased risk of early complications and a small increase in quality-adjusted life expectancy in the LMW heparin group translated into an incremental advantage of $7820 per quality-adjusted life year gained among these patients.

In Canada, three preparations are approved for the treatment of venous thromboembolism; tinzaparin and enoxaparin are approved for this indication in the United States, while dalteparin is approved for prophylaxis. Where these agents are approved for use, the simultaneous initiation of LMW heparin (weight adjusted, once or twice daily subcutaneous injection) and warfarin therapy is effective.

As with unfractionated heparin, LMW heparin therapy should be overlapped with warfarin for a minimum of four to five days and until the INR has been within the therapeutic range (2.0 to 3.0) for two consecutive days. (See "Low molecular weight heparin for venous thromboembolic disease".)

Bleeding — For patients who experience bleeding while receiving LMW heparin, protamine sulfate (1 mg/100 anti-Xa units of LMW heparin) can reduce clinical bleeding, although the anti-factor Xa activity of LMW heparin is only partially reversed with protamine [58]. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Bleeding and protamine reversal'.)

Use in special population groups — The use of LMW heparins in the elderly, the obese, and in those with varying degrees of renal insufficiency is discussed separately. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Special patient groups'.)

THROMBOLYTIC THERAPY AND THROMBECTOMY — The use of thrombolytic therapy in the treatment of DVT is controversial, since most patients have an uncomplicated course when treated with unfractionated or low molecular weight heparin [59]. This issue is discussed in detail elsewhere and will

be only briefly reviewed here. (See "Fibrinolytic (thrombolytic) therapy in pulmonary embolism and deep vein thrombosis", section on 'Deep vein thrombosis'.)

Randomized trials with streptokinase and intravenous tissue-type plasminogen activator (tPA) suggest that the rate of lysis and likelihood of normal follow-up venography are greater with these agents than with heparin [60-63]. These changes may be associated with a reduction in incidence of post-thrombotic syndrome, but this has not been proven definitively. Bleeding may be more frequent among patients treated with thrombolytic therapy compared with heparin [60].

In addition to increased bleeding, it is not clear how many patients with DVT are actually candidates for thrombolytic therapy. One study, as an example, found that 194 of 209 patients (93 percent) had a contraindication to thrombolysis, most often recent surgery [64]. In addition, involvement of the patient in the decision is essential. In a decision analysis of 36 patients, all were unwilling to accept the small increase in death or disability due to bleeding just to prevent the post-thrombotic syndrome [65].

Assuming there are no absolute or relative contraindications, thrombolytic therapy, surgical thrombectomy, or percutaneous mechanical thrombectomy could be considered in patients with proximal occlusive DVT associated with significant swelling and symptoms. If thrombolytic therapy is to be used, it should be started at the earliest opportunity. As in the treatment of acute myocardial infarction and stroke, the angiographic response to thrombolytic therapy is greatest when there is a shorter interval between the onset of symptoms and the initiation of therapy [66]. (See "Fibrinolytic (thrombolytic) therapy in pulmonary embolism and deep vein thrombosis", section on 'Indications'.)

Phlegmasia cerulea dolens — Phlegmasia cerulea dolens is an uncommon form of massive proximal (eg, iliofemoral) venous thrombosis of the lower extremities associated with a high degree of morbidity, including sudden severe pain with swelling, cyanosis, edema, venous gangrene, compartment syndrome, and arterial compromise, often followed by followed by circulatory collapse and shock. Delay in treatment may result in death or loss of the patient's limb. Accordingly, catheter-directed thrombolysis or rapid removal of the occluding thrombus using manual techniques (eg, surgical thrombectomy) should be seriously considered for such patients [3,67-69].

INFERIOR VENA CAVA FILTER — Insertion of an inferior vena cava (IVC) filter is generally employed in patients with acute venous thromboembolism who have an absolute contraindication to anticoagulant therapy (eg, recent surgery, hemorrhagic stroke, active bleeding), or who have recurrent VTE despite adequate anticoagulation. Other indications for an IVC filter are less well established. This subject is discussed in depth separately. (See "Inferior vena cava filters".)

WARFARIN — Treatment with heparin is usually followed by at least a three to six month period of anticoagulation to prevent recurrent disease [70,71]. Warfarin therapy is highly effective for this purpose and is preferred in most patients. In patients with a proximal DVT, long-term therapy with warfarin reduces the frequency of objectively documented recurrent venous thromboembolism from 47 to 2 percent [70,71]. Prolonged high dose subcutaneous unfractionated heparin or LMW heparin may be an equally effective alternative, especially in patients who are unable to take warfarin therapy.

The anticoagulant effect of warfarin, which is mediated by inhibition of the vitamin K-dependent gamma-carboxylation of coagulation factors II, VII, IX, and X, is delayed until the normal clotting factors are cleared from the circulation; the peak effect does not occur until 36 to 72 hours after drug administration [72]. During the first few days of warfarin therapy, prolongation of the prothrombin time (INR) mainly reflects the depression of factor VII, which has a half-life of five to seven hours (graph 1). This does not represent adequate anticoagulation because the intrinsic clotting pathway remains intact until factors II, IX and X are sufficiently reduced, which takes about five days with adequate dosing. For this reason, heparin and warfarin treatment should overlap by four to five days when warfarin is initiated in patients with thrombotic disease [22]. (See "Therapeutic use of warfarin" and "Overview of hemostasis",).

Monitoring — The laboratory test most commonly used to measure the effects of warfarin is the one-stage prothrombin time (PT). Confusion about the appropriate therapeutic range had occurred in the past because different tissue thromboplastins used in the measurement of the PT vary considerably in sensitivity to the vitamin K-dependent clotting factors and in response to warfarin [70]. In order to promote standardization of the PT for monitoring oral anticoagulant therapy, the World Health Organization (WHO) developed an international reference thromboplastin from human brain tissue and recommended that the PT ratio be expressed as the International Normalized Ratio or INR. (See "Therapeutic use of warfarin" and "Clinical use of coagulation tests", section on 'Measurement of INR'.)

Dose and therapeutic range — Warfarin is generally administered in an initial oral dose of 5 mg/day for the first two days, with the daily dose then adjusted according to the INR. Heparin is discontinued on the fourth or fifth day following initiation of warfarin therapy, provided the INR has been in the recommended therapeutic range for VTE (INR 2.0 to 3.0) for two consecutive days [22].

Because some individuals are either fast or slow metabolizers of the drug, and because increased age and other factors may alter the response to warfarin, the selection of INITIAL and SUBSEQUENT doses of warfarin must be individualized. There are also many interactions between warfarin and other drugs, which may either increase or decrease warfarin's overall effect. Thus, frequent INR determinations are required initially to establish therapeutic anticoagulation. (See "Therapeutic use of warfarin", section on 'Initial dose' and "Therapeutic use of warfarin", section on 'Maintenance therapy'.)

In a patient known to have protein C deficiency, it is important to initiate oral anticoagulation GRADUALLY under the cover of full heparinization because of the risk of warfarin-induced skin necrosis (graph 1). (See "Protein C deficiency", section on 'Warfarin-induced skin necrosis'.)

Attainment of an INR of 2.0 to 3.0 or its equivalent in patients with DVT markedly reduces the risk of bleeding (from 22 to 4 percent) compared with more intense regimens, without loss of effectiveness [73]; similar observations have been made in patients with atrial fibrillation (graph 2).

Once the anticoagulant effect and patient's warfarin dose requirements are stable, the INR should be monitored every three to four weeks throughout the course of warfarin therapy for venous thromboembolism. More frequent monitoring is indicated if factors are present that may produce an unpredictable response to warfarin (eg, concomitant therapy with drugs that interact with warfarin). (See "Therapeutic use of warfarin", section on 'Excessive anticoagulation'.)

OTHER AGENTS — Other anticoagulants, some of which may be orally active, are in various stages of drug development and testing for the treatment of patients with VTE. These are discussed separately. (See "Anticoagulants other than heparin and warfarin" and "Therapeutic use of fondaparinux".)

LENGTH OF TREATMENT — Most patients with a first episode of VTE should receive warfarin therapy for at least three months. Attempts to decrease the treatment to four weeks [74] or six weeks [75] have resulted in higher rates of recurrent VTE in comparison with either 12 or 26 weeks of therapy. In a randomized trial of almost 900 patients with a first VTE, which included patients with both idiopathic VTE and VTE due to a reversible or time-limited risk factor, the rate of recurrent thromboembolism at two years was almost twice as high with six weeks compared with six months of warfarin (18.1 versus 9.5 percent; relative risk 2.1, 95% CI 1.4-3.1) [75].

Idiopathic VTE — Patients without an identifiable risk factor (ie, spontaneous or idiopathic VTE) are at increased risk for a recurrent event once anticoagulation is discontinued. This was shown in a multicenter Austrian study of 826 patients with a first episode of idiopathic VTE, who were followed for an average of 36 months following cessation of treatment with oral anticoagulation [76]. The diagnosis of DVT was made via venography or duplex ultrasonography, while PE was diagnosed via ventilation-perfusion lung scanning. Despite the protocol's exclusion of patients with deficiencies of antithrombin, protein C, protein S, or a lupus anticoagulant, the incidence of recurrent VTE after the cessation of anticoagulant therapy

was 12.3 percent at a median follow-up of 26 months.

Two randomized trials showed significantly worse outcomes among patients treated for three months compared with those treated for 12 or more months [77,78], while two trials showed that short-term outcomes among patients treated for three months were similar to those of patients treated for six months [79,80]. In one of these trials, involving 267 patients with a first idiopathic DVT, recurrent VTE was significantly more likely during months 3 through 12 in patients treated with warfarin for three months compared with those receiving treatment for the entire 12-month period (8.3 versus 0.7 percent) [78]. However, the initial clinical benefit of longer term treatment was not maintained after warfarin was discontinued, with a recurrence rate of 5 percent per patient-year in both groups. This observation provides a rationale for continued anticoagulation therapy beyond one year.

Thus, although there are published guidelines for the MINIMUM length of time the patient with a first episode of idiopathic VTE should be treated with warfarin at an INR of 2.0 to 3.0 [3,9,81], the OPTIMAL length of time is not known [82,83]. A number of large randomized cooperative trials have addressed this issue, employing various combinations of placebo, warfarin at varying intensities (eg, INR 2.0 to 3.0 versus INR 1.5 to 1.9), low molecular weight heparin, or other anticoagulants (eg, ximelagatran) following three to six months of treatment with warfarin at standard doses (ie, target INR 2.0 to 3.0).

PREVENT trial — The PREVENT trial in patients with idiopathic VTE was designed to test whether, after at least three months of warfarin treatment (goal INR 2.0 to 3.0), long-term lower dose warfarin (goal INR 1.5 to 2.0) was better than placebo in reducing the rate of recurrent VTE [84]. Patients with anticardiolipin antibodies or a lupus anticoagulant were excluded from this trial. The diagnosis of DVT was made via venography, compression ultrasonography or MRI, while PE was diagnosed via ventilation-perfusion lung scanning, angiography, or chest CT. The study was stopped prematurely after 508 of the planned 750 patients had undergone randomization and had been followed for up to 4.3 years (mean 2.1 years), due to a significantly lower rate of recurrent VTE in the warfarin treatment arm compared with placebo on an intention to treat analysis (2.6 versus 7.2 per 100 patient-years, hazard ratio [HR] 0.36, 95% CI 0.19-0.67) as well as on a "treatment per protocol" analysis (HR 0.24, 95% CI 0.10-0.54). The increase in risk for recurrent VTE occurred throughout the follow-up period.

The baseline risk for recurrence and the risk reductions following use of warfarin were similar for all subgroups studied, including the 24 percent of study subjects with factor V Leiden, and the 5 percent with prothrombin G20210A. The incidence of major bleeding was similar in the two treatment arms (0.9 and 0.4 per 100 patient-years, respectively), while minor bleeding was more common in the warfarin-treated group (12.8 versus 6.7 per 100 patient-years, respectively, HR 1.9, 95% CI 1.3-2.9).

ELATE trial — The ELATE trial compared two different dose intensity levels of warfarin (target INR 1.5 to 1.9 versus target INR 2.0 to 3.0) in 738 patients who had received three or more months of warfarin at a target INR of 2.0 to 3.0 following an episode of idiopathic VTE [85]. Patients were followed for an average of 2.4 years. The diagnosis of DVT was made via compression ultrasonography or venography, while PE was diagnosed via ventilation-perfusion lung scanning or angiography.

The incidence of recurrent VTE was significantly greater in those subjects treated with the lower intensity of warfarin (1.9 versus 0.7 per 100 patient-years, HR 2.8, 95% CI 1.1-7.0). The incidence of major bleeding was similar in the two arms, being 1.1 and 0.9 per 100 patient-years in the lower and higher warfarin intensity groups, respectively.

A retrospective review indicated that one or more thrombophilic defects were present in 42 percent of the participants [86]. The overall rate of recurrent VTE WHILE TAKING WARFARIN was 0.9 percent, and was not increased in the presence of one, or more than one, thrombophilic defects.

THRIVE III trial — The preceding trials demonstrated the efficacy of prolonged warfarin therapy. The THRIVE III trial of 1233 patients with idiopathic VTE was designed to test whether, after 6 months of

warfarin treatment with a goal INR of 2.0 to 3.0, 18 months of treatment with the oral direct thrombin inhibitor ximelagatran was better than placebo in reducing the rate of recurrent VTE [87]. The diagnosis of DVT was made via bilateral compression ultrasonography or venography, while PE was diagnosed via ventilation-perfusion lung scanning. The estimated cumulative risk over 18 months for recurrent VTE was significantly greater in those subjects randomly assigned to receive placebo (12.6 versus 2.8 percent, HR 6.2, 95% CI 3.3-11.1). The estimated 18-month cumulative risk for major bleeding was similar in the two arms, being 1.3 and 1.1 percent in the placebo and ximelagatran-treated groups, respectively.

While ximelagatran has since been removed from the market because of hepatic toxicity issues, the THRIVE III trial indicated that continuation of anticoagulation was better than placebo in reducing the incidence of recurrence in patients with idiopathic VTE treated with warfarin for six months.

Issues to consider — The following issues should be considered when a patient with a first idiopathic VTE has received at least three months of anticoagulation with warfarin at an INR of 2.0 to 3.0:

- The patient should be informed of the estimated incidence of VTE recurrence should all anticoagulation be stopped (7.2 to 8.4 episodes per 100 patient-years in the PREVENT and THRIVE III trials) [84,87] compared with continued therapy with either lower dose warfarin (goal INR 1.5 to 2.0, 1.9 to 2.6 episodes per 100 patient-years in the ELATE and PREVENT trials) [84,85], or compared with usual dose warfarin (goal INR 2.0 to 3.0, 0.7 episodes per 100 patient-years in the ELATE trial) [85].

Lower dose warfarin compared with no warfarin will prevent an estimated 4.6 to 5.8 recurrences per 100 patient-years, while usual dose warfarin compared with lower dose warfarin will prevent an additional 1.3 to 2.0 recurrences per 100 patient-years with little or no increase in bleeding risk as long as the patient's INR is well controlled (graph 2) [88].

- The patient should also be informed of the estimated incidence of major bleeding should warfarin be continued. In a large meta-analysis, the rate of major bleeding if anticoagulation was continued beyond three months was 2.7 per 100 patient-years, with a case fatality rate of 9.1 percent (95% CI 2.5-22) [89]. (See "Therapeutic use of warfarin", section on 'Bleeding'.)

- The patient's age and comorbidities, comfort with the difficulties of continuing anticoagulation (eg, costs, frequency of testing of the patient's INR, need for closer follow-up, and other quality of life issues should be reviewed at this time [90-93]. (See 'Estimation of individual risk' below.)

RECURRENT VTE

Relationship to length of treatment — Warfarin treatment for an indefinite period is indicated for patients with recurrent venous thromboembolism or those in whom there is a continuing risk factor for venous thromboembolism (eg, active malignancy, antiphospholipid syndrome). The optimum duration of therapy in such patients, as well as in those with an initial episode of unprovoked (idiopathic) VTE is still unclear, and has been the subject of both completed and ongoing clinical trials.

- A multicenter clinical trial evaluated the outcome of patients who received six months of oral anticoagulation compared with indefinite therapy after a second episode of VTE (19 percent with a temporary risk factor and about 20 percent with a family history of VTE) [94]. Indefinite therapy (target INR 2.0 to 2.85) was associated with a significantly lower incidence of recurrent disease at four years (2.6 versus 20.7 percent in those treated for six months, relative risk 0.13, 95% CI 0.04-0.40) and a trend to a higher risk for major hemorrhage (8.6 versus 2.7 percent; relative risk 3.3 95% CI 0.9-10).

- In the PREVENT trial, patients with one or more recurrences of VTE received at least three months of treatment with warfarin (target INR 2.0 to 3.0) and were then randomly assigned to receive either

continuous treatment with a lower intensity of warfarin (target INR 1.5 to 2.0) or placebo [84]. The incidence rate for a further episode of VTE was significantly reduced in the warfarin-treated group (4.8 versus 11.4 per 100 patient-years with placebo; HR 0.43, 95% CI 0.20-0.90).

The site of the initial episode of DVT may influence the rate of recurrence. In a study of 1149 consecutive patients with symptomatic proximal DVT treated with conventional anticoagulation, the rate of recurrence during the initial three months of treatment was 5.1, 5.3, and 11.8 percent for those with popliteal, femoral, or iliofemoral vein thrombosis, respectively [95]. Multivariate regression analysis indicated a trend to higher rates of recurrence in patients with iliofemoral vein thrombosis versus the two other sites (odds ratio 2.4, 95% CI 0.95-5.9).

Estimation of individual risk — There is substantial interpatient variability in the risk of recurrent DVT following cessation of warfarin therapy after an initial episode of idiopathic VTE. Measurement of D-dimer levels, serial imaging, and measurement of thrombin generation [96,97] may be helpful in determining this risk in an individual patient.

D-Dimer levels — A number of reports suggest that D-dimer levels can be used to predict the risk of VTE recurrence during treatment [98,99] or after withdrawal of oral anticoagulants used to treat a first episode of VTE [100-106].

In one of these studies, there were only five idiopathic recurrences in the 186 patients with consistently normal D-dimer levels (negative predictive value >96 percent) [101]. In a second report, the odds ratio for VTE recurrence was 3.1 for elevated D-dimer, 2.4 for an elevated level of prothrombin activation fragment F1+2, and 4.3 when both abnormalities were present [105].

- In one meta-analysis of seven studies, the annualized risk of VTE recurrence was significantly higher in subjects with abnormal (8.9 percent; 95% CI 5.8-12) versus normal (3.5 percent; 95% CI 2.7-4.3) D-dimer following at least three months of anticoagulation therapy [107].
- A second meta-analysis was confined to studies of patients with idiopathic VTE who had levels of D-dimer measured one month after discontinuation of oral anticoagulants. Elevated D-dimer levels obtained at this time were significantly associated with recurrent VTE (odds ratio 2.36; 95% CI 1.65-3.36) [106].

The PROLONG II prospective cohort study will address the natural history of D-dimer levels after withdrawal of anticoagulation therapy in order to gather information on the predictive value of D-dimer results that change from normal to abnormal during follow-up [108].

Serial imaging — A number of studies have examined the predictive value of serial invasive (eg, venography) [109] or noninvasive (eg, impedance plethysmography or ultrasound) [110-114] studies for predicting VTE recurrence after the cessation of oral anticoagulation (OAT). Initial results indicate that the presence of residual vein thrombosis (RVT) at the time of cessation of OAT may be a risk factor for VTE recurrence.

In one prospective study in which patients were treated with OAT for a minimum of three months, the hazard ratio for recurrent VTE in patients with RVT on ultrasound (versus those with early recanalization) was 2.4 (95% CI 1.3-4.4) [111].

In a second study, patients with a first episode of DVT, and not at high risk for DVT recurrence (eg, no active cancer, no antiphospholipid syndrome or other high-risk hypercoagulable state), were treated with OAT for three months, and underwent further management according to the presence or absence of RVT, as assessed by compression ultrasonography at three months. OAT was stopped in those without RVT (78 subjects, 30 percent), while those with RVT (180 subjects, 70 percent) were randomly assigned to receive either OAT for an additional nine months or no further treatment. The following findings were

noted [113]:

- VTE recurrences were seen in 23 versus 1.3 percent of those with or without RVT, respectively (HR 25; 95% CI 3.4-180), suggesting that three months of OAT was sufficient for SELECTED patients without evidence for RVT at three months.

- For those with RVT at three months, recurrent events were not significantly different for those who were or were not treated with an additional nine months of OAT (19 versus 27 percent, respectively, HR 1.6; 95% CI 0.85-2.9), indicating that patients with RVT at three months were still at a high risk of recurrence after an additional nine months of OAT.

A third study randomly assigned patients with unprovoked or secondary DVT who had completed three months of anticoagulation to receive one of two regimens:

Fixed-duration anticoagulation (268 patients): no further anticoagulation for secondary (provoked) DVT and an additional 3 months for unprovoked (idiopathic) DVT.

Flexible-duration, ultrasonography-guided anticoagulation (270 patients): no further anticoagulation for those with recanalized veins and continued anticoagulation in all other patients for up to 9 additional months for secondary (provoked) DVT and up to 21 months for unprovoked (idiopathic) DVT.

Results included the following [114]:

- Overall, the rates of recurrent VTE were significantly lower in those receiving flexible- versus fixed-duration treatment (11.9 versus 17.2 percent, respectively; HR 0.64; 95% CI 0.39-0.99).

- The sample size was insufficient to detect effectiveness of these interventions in DVT subgroups. The adjusted HR for the benefit of flexible-duration treatment was 0.61 (95% CI 0.36-1.02) for those with unprovoked DVT and 0.81 (95% CI 0.32-2.06) for those with provoked DVT.

- The study was underpowered to detect significant differences between the two treatment arms in the rates of significant bleeding.

Thrombin generation — In a study of 254 patients with a first episode of unprovoked, objectively documented VTE who were followed for 2.7 years after discontinuation of vitamin K antagonists, those with higher values for thrombin generation measured one month after discontinuation of treatment had hazard ratios for VTE recurrence that were 3.0 to 6.3-fold higher than those with lesser values of thrombin generation [115,116].

A larger study involving 914 selected patients with a first episode of spontaneous idiopathic VTE, who were treated with oral anticoagulants for a minimum of three months, also investigated the association between VTE recurrence and in vitro thrombin generation [117]. After four years, the cumulative probability of objectively documented VTE recurrence was 20 and 6.5 percent for those whose thrombin generation, determined at a median of 13 months following cessation of anticoagulation, was greater than versus less than 400 nM, respectively (relative risk 2.50 (95% CI 1.7-3.7) for those with the higher values of thrombin generation).

Increased risk in men — In the Austrian, THRIVE III trials, Cambridge and Leiden studies, and a meta-analysis of 15 studies, the risk of recurrent VTE after cessation of oral anticoagulant therapy was significantly increased among men, with relative risks varying from 1.3 to 3.6 [76,87,118-121]. A trend toward increased risk of recurrence in men was noted in the PREVENT trial (8.6 versus 5.9 percent per year) [84], but no sex difference was noted in two Italian studies [122].

The reasons for this apparent difference in the rate of recurrence in some studies are not clear [123,124]. However, in one study, the rates of recurrent thrombosis in men and women were similar when women with hormone-related thrombosis (eg, treatment with exogenous hormones, pregnancy, post-partum status) were removed from the analysis [125]. Hormone-related factors also appear to be related to a reduced risk of recurrent venous thrombosis in women from thrombophilic families [126].

Risk in women — A multicenter prospective cohort study of 646 participants with a first, unprovoked episode of major VTE collected data on 69 potential predictors for recurrent VTE while patients were still taking oral anticoagulants for 5 to 7 months [99].

The overall annual risk of recurrence was 9.3 percent, and was 5.5 versus 13.7 percent for women and men, respectively.

There was no combination of clinical predictors that satisfied criteria for identifying a low-risk subgroup in men. However, the following characteristics helped to define a low-risk group in women:

- Hyperpigmentation, edema, or redness of either leg
- D-dimer ≥250 microg/L while still taking warfarin
- Body mass index ≥30 kg/m2
- Age ≥65 years

Women with zero or one of these adverse risk factors had an annual risk of VTE recurrence of 1.6 percent (95% CI 0.3-4.6), while those with two or more had an annual risk of 14.1 percent (95% CI 10.9-17.3).

Conclusions — The above-noted approaches for preventing recurrent VTE (ie, fixed length of treatment versus individualized treatment) need to be confirmed in larger studies before they can be routinely employed in the decision concerning the risk of recurrence for an individual patient and whether (as well as when) treatment with anticoagulation can be safely discontinued [127,128].

PREGNANCY — The risk of VTE is increased in association with pregnancy, primarily during the postpartum period [129]. Pregnant women with inherited thrombophilias are at even higher risk and prophylactic anticoagulation maybe recommended. (See "Deep vein thrombosis and pulmonary embolism in pregnancy: Epidemiology, pathogenesis, and diagnosis" and "Management of inherited thrombophilia".)

Acute DVT should be managed initially with heparin in an identical fashion as when DVT occurs in the nonpregnant patient. Warfarin freely crosses the placental barrier and can produce an embryopathy when given between the sixth and ninth weeks of pregnancy. For this reason, either subcutaneous unfractionated or LMW heparin (which should be switched to unfractionated heparin two weeks prior to the expected delivery) at full doses should be continued until delivery; a four to six week course of warfarin should be completed after delivery [129,130]. (See "Anticoagulation during pregnancy".)

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Deep vein thrombosis (DVT)" and "Patient information: Warfarin (Coumadin®)".) We encourage you to print or e-mail this topic review, or to refer patients to our public website, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS — The following recommendations for the treatment of acute venous thromboembolic disease are in general accord with recommendations from the following sources: the 2008 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [131], the British Committee for Standards in Haematology [132], the joint guidelines of the American College of

Physicians and the American Academy of Family Physicians [133,134], and the American Heart Association/American College of Cardiology [135].

Initial anticoagulation regimen — We recommend that patients with DVT be treated acutely with LMW heparin, unfractionated intravenous heparin, adjusted-dose or fixed dose subcutaneous heparin, or subcutaneous fondaparinux (**Grade 1A**). In comparison to unfractionated heparin, LMW heparin and fondaparinux offer the major benefits of convenient dosing, facilitation of outpatient treatment, and a lower incidence of heparin-induced thrombocytopenia. If direct cost to the patient is not an issue, we recommend that clinicians use LMW heparin over unfractionated heparin (**Grade 1A**) [133]. (See 'Low molecular weight heparin' above.)

- Dosing requirements for LMW heparin are individualized for each product. Enoxaparin and tinzaparin are approved for this use in the United States and Canada, while dalteparin and nadroparin are approved in Canada. Minimal elements for early discharge or outpatient therapy are shown in the table (table 7).

- The dosing of LMW heparin in special patient groups (eg, the elderly, obesity, renal failure) is discussed separately. In patients with severe renal failure (eg, creatinine clearance <30 mL/min), we suggest intravenous unfractionated heparin over LMW heparin (**Grade 2C**) [131]. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Special patient groups'.)

- When unfractionated heparin is used, we recommend that the dose should be sufficient to prolong the aPTT to a range that corresponds to a plasma heparin level of 0.3 to 0.7 U/mL by an anti-Xa assay (**Grade 1B**). (See 'Unfractionated heparin' above.)

- We recommend that treatment with LMW heparin, heparin, or fondaparinux should be continued for at least five days and that oral anticoagulation be initiated simultaneously and both agents overlapped for at least five days (**Grade 1A**). The heparin or fondaparinux can be discontinued on day 5 or 6 if the INR has been in the therapeutic range for at least 24 hours or two consecutive days.

- To monitor for heparin-induced thrombocytopenia, platelet counts should be regularly obtained. The timing and frequency of such testing differs with the clinical setting, and is discussed separately. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Platelet count monitoring'.)

All heparin products should be stopped if any one of the following occurs: a precipitous or sustained fall in the platelet count, or a platelet count <100,000/microL. (See "Heparin-induced thrombocytopenia".)

- The use of thrombolytic agents in the treatment of venous thromboembolism must be individualized and requires further investigation. Patients with hemodynamically unstable PE or massive iliofemoral thrombosis, and who are also at low risk to bleed, are the most appropriate candidates. (See "Fibrinolytic (thrombolytic) therapy in pulmonary embolism and deep vein thrombosis".)

- The placement of an inferior vena cava filter is recommended when there is a contraindication to, or a failure of, anticoagulant therapy in an individual with acute proximal vein DVT (**Grade 1C**). (See 'Inferior vena cava filter' above.)

- As an integral part of the initial treatment of VTE, we recommend that oral anticoagulation with warfarin should prolong the INR to a target of 2.5 (INR range: 2.0 to 3.0) (**Grade 1A**). We recommend against high-intensity therapy (INR range: 3.1 to 4.0) as well as against low-intensity therapy (INR range: 1.5 to 1.9), compared with an INR range of 2.0 to 3.0 (**Grade 1A**) [131].

If oral anticoagulants are contraindicated or inconvenient, long-term therapy can be undertaken with either low molecular weight heparin or adjusted-dose unfractionated heparin. (See 'Warfarin' above.)

General medical management and ambulation — A number of small randomized studies have shown that early ambulation with or without the use of leg compression does not increase the incidence of silent, recurrent, or fatal pulmonary emboli and, in one study, resulted in a significantly faster rate of resolution of pain and swelling when compared with bed rest alone [40,41,131,136-140].

The general medical management of the acute attack of DVT is individualized. Once warfarin/heparin have been started and symptoms (eg, pain, swelling) are under control, we recommend early ambulation in preference to bed rest (**Grade 1A**).

During initial ambulation, and for the first two years following an episode of VTE, we recommend use of an elastic graduated compression stocking with a pressure of 30 to 40 mmHg at the ankle (**Grade 1A**) [30,131,133]. This recommendation places a higher priority on prevention of post-thrombotic syndrome than on the discomfort attendant to their use. (See "Post-thrombotic (postphlebitic) syndrome", section on 'Prevention'.)

There are no studies which address the timing of aggressive exercise or physical therapy rehabilitation for patients recovering from VTE [140]. In this setting, the clinical status of the patient (eg, cardiopulmonary reserve, presence or absence of vascular compromise of the lower extremity) as well as the clinical judgment of the treating clinician are both critical.

VTE and a reversible or time-limited risk factor — We recommend that patients with a first thromboembolic event in the context of a reversible or time-limited risk factor (eg, surgery, trauma, pregnancy, use of oral contraceptives) should be treated for a minimum of three months, rather than for a shorter period of time (**Grade 1A**). Longer-term therapy (ie, longer than 6 months) is not necessary, since the risk of recurrence in such patients is low, being ≤3 percent in the first year [133,141]. (See 'Length of treatment' above.)

In those patients with a continuing risk factor that is potentially reversible (eg, prolonged immobilization), long-term therapy should be continued until the risk factor is reversed.

First episode of idiopathic VTE

- For a patient with a first episode of idiopathic VTE, we recommend anticoagulation for a minimum of three months (**Grade 1A**). Following this time, and periodically thereafter, all patients should be evaluated for the risk/benefit ratio of long-term anticoagulation.

- For patients with a first unprovoked proximal VTE, we suggest indefinite treatment (eg, >12 months) over treatment for a lesser period of time (**Grade 2A**).

Patient values and preferences, bleeding risks, and the ability to achieve good anticoagulation monitoring factor heavily into this decision. Thus, for patients with a first unprovoked proximal VTE, no risk factors for bleeding, for whom good anticoagulant monitoring is achievable, and who place a higher value on prevention of recurrent VTE and a lower value on the burdens and risks of long-term anticoagulation, the 2008 ACCP Guidelines have given a strong recommendation for indefinite treatment (**Grade 1A**) [131].

However, many patients will not fit this pattern, and the appropriate length of treatment for them is unclear. (See 'Length of treatment' above and "Therapeutic use of warfarin", section on 'Bleeding'.)

Recurrent VTE and antiphospholipid syndrome — For patients with a second episode of unprovoked VTE and for those with the antiphospholipid syndrome and VTE, we recommend indefinite anticoagulation

(**Grade 1A**). (See "Treatment of the antiphospholipid syndrome", section on 'Duration of warfarin use'.)

The presence of hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation in the 2008 ACCP Guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of VTE recurrence [131].

Isolated calf vein (distal) thrombosis — For patients with unprovoked symptomatic isolated calf vein (ie, distal) thrombosis, we suggest that anticoagulation for 3 months is sufficient, rather than indefinite therapy (**Grade 2B**). If anticoagulation is not administered (eg, isolated asymptomatic distal venous thrombosis), serial noninvasive studies of the lower extremity should be performed over the next 10 to 14 days to assess for proximal extension of the thrombus.

The natural history of isolated symptomatic thrombosis involving the veins draining the gastrocnemius and soleus muscles in the calf is not known, and guidelines for the treatment of this condition do not exist [142].

Malignancy — Treatment of patients with malignancy and VTE is discussed separately. (See "Treatment of venous thromboembolism in patients with malignancy".)

Anticoagulation for VTE in patients with primary or secondary brain tumors is discussed separately. (See "Anticoagulant and antiplatelet therapy in patients with brain tumors".)

Anticoagulation failure — On occasion, patients may have recurrent VTE despite adequate anticoagulation. The recourses for such patients include insertion of an inferior vena cava filter or one or more vascular interventions such as thrombolytic therapy or thrombectomy. A vascular surgery consultation should be obtained under such circumstances; the selected intervention(s) will depend upon available expertise [131]. (See 'Thrombolytic therapy and thrombectomy' above and 'Inferior vena cava filter' above.)

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GRAPHICS

Causes of venous thrombosis

Inherited thrombophilia
Factor V Leiden mutation
Prothrombin gene mutation
Protein S deficiency
Protein C deficiency
Antithrombin (AT) deficiency
Rare disorders
Dysfibrinogenemia
Acquired disorders
Malignancy
Presence of a central venous catheter
Surgery, especially orthopedic
Trauma
Pregnancy
Oral contraceptives
Hormone replacement therapy
Tamoxifen, Bevacizumab, Thalidomide, Lenalidomide
Immobilization
Congestive failure
Antiphospholipid antibody syndrome
Myeloproliferative disorders
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome
Hyperviscosity
Waldenstrom's macroglobulinemia
Multiple myeloma
Marked leukocytosis in acute leukemia
Sickle cell anemia
HIV/AIDS

Thrombophilia workup: Effects of anticoagulant therapy and acute thrombosis

Hypercoagulable disorder for testing	Confounding Factors		
	Acute thrombosis	Heparin therapy	Coumadin therapy
Antithrombin (deficiency)	Can be lowered*	Lowered	NC; Rarely increased
Antiphospholipid antibodies	NC	NC	NC
Factor V Leiden	NC	NC	NC
Factor VIII level	Acute phase reactant. Do not test while inflammation is still present.		
Lupus anticoagulant	NC	Cannot measure	False positives possible
Protein C (deficiency)	Can be lowered*	NC	Cannot measure•
Protein S (deficiency)	Can be lowered*	NC	Cannot measure•
Prothrombin gene mutation	NC	NC	NC
Acquired AT deficiency:			
neonatal period, pregnancy, liver disease, DIC, nephrotic syndrome, major surgery, acute thrombosis, treatment with L-asparaginase, heparin, or estrogens			
Acquired Protein C deficiency:			
neonatal period, liver disease, DIC, chemotherapy (CMF), inflammation, acute thrombosis, treatment with warfarin or L-asparaginase			
Acquired Protein S deficiency:			

neonatal period, pregnancy, liver disease, DIC, acute thrombosis, treatment with warfarin, L-asparaginase, or estrogens

NC: not changed; LMW heparin: low molecular weight heparin; AT: antithrombin; DIC: disseminated intravascular coagulation; CMF: cyclophosphamide, methotrexate, 5-fluorouracil.

* Results can be affected by acute thrombosis; it is most cost effective to avoid testing for these deficiencies during the initial presentation. However, if plasma levels are well within the normal range at presentation, deficiency of these proteins is essentially excluded. Common causes for an acquired deficiency of Antithrombin (AT), Protein C, or Protein S are listed below:

- If it is important to measure for these deficiencies while the patient is still anticoagulated, switch the treatment to full dose heparin or LMW heparin and discontinue coumadin for at least two weeks before measurement. Comparing protein S or C levels with prothrombin antigen in stably anticoagulated patients is not reliable, as accurate measurement of prothrombin antigen levels is a research assay which is not generally available.

Heparin protocol-I

Initial intravenous heparin bolus: 5,000 units.
Continuous intravenous heparin infusion: commence at 42 mL/hour of 20,000 units (1,680 units/hour) in 500 mL of two-thirds dextrose and one-third saline (a 24-hour heparin dose of 40,320 units), except in the following patients, in whom heparin infusion will be commenced at a rate of 31 mL/hour (1240 units/hour) (ie, a 24 hour dose of 29,760 units).
Patients who have undergone surgery within the previous two weeks.
Patients with a previous history of peptic ulcer disease, gastrointestinal or genitourinary bleeding.
Patients with (thrombotic) stroke within the previous two weeks.
Patients with a platelet count <150,000/µL.
Patients with miscellaneous reasons for a high risk of bleeding (eg, hepatic failure, renal failure, or vitamin K deficiency).
Heparin dose adjusted using the aPTT. The aPTT is performed in all patients as outlined below:
4 to 6 hours after commencing heparin; the heparin dose is then adjusted according to the nomogram shown in Heparin Protocol-II until the aPTT is within the therapeutic range.
Thereafter, the aPTT will be performed once daily. If the value is outside the therapeutic range, the heparin dose is then adjusted according to the nomogram shown in Heparin Protocol-II until the aPTT is within the therapeutic range.

Adapted from Hull, RD, Raskob, GE, Rosenbloom, D, et al, Arch Intern Med 1992; 152:1589.

Intravenous heparin dose-titration nomogram for aPTT

IV infusion			
aPTT	**Rate change, mL/h**	**Dose change, Units/24 h***	**Additional action**
≤45	+6	+5760	Repeated aPTT● in 4 to 6 hours
46-54	+3	+2880	Repeated aPTT in 4 to 6 hours
55-85	0	0	None▲
86-110	-3	-2880	Stop heparin sodium treatment for 1 hour; repeated aPTT 4 to 6 hours after restarting heparin treatment
>110	-6	-5760	Stop heparin treatment for 1 hour; repeated aPTT 4 to 6 hours after restarting heparin treatment

aPTT: activated partial thromboplastin time; IV: intravenous.
* Heparin sodium concentration, 20,000 units in 500 mL = 40 units/mL.
● With the use of Actin-FS thromboplastin reagent (Dade, Mississauga, Ontario).
▲ During the first 24 hours, repeated aPTT in 4 to 6 hours. Thereafter, the aPTT will be determined once daily, unless subtherapeutic.
NOTE: This table reflects the original aPTT ranges, bolus sizes, and suggested changes in infusion rate which were present at the time this study was performed. The therapeutic ranges (ie, relationship between the aPTT and anti-factor Xa activity), initial and subsequent bolus sizes, and sizes of the infusion rate changes, as well as dosing differences depending on the disorder under treatment (eg, venous thromboembolism, stroke, acute coronary syndrome) should be established separately for each institution.
Redrawn from Hull, RD, Raskob, GE, Rosenbloom, D, et al Arch Intern Med 1992; 152:1589.

Weight-based nomogram for intravenous heparin infusion

Initial dose	80 units/kg bolus, then 18 units/kg per hour
aPTT <35 sec (<1.2 x control)	80 units/kg bolus, then increase infusion rate by 4 units/kg per hour
aPTT 35-45 sec (1.2-1.5 x control)	40 units/kg bolus, then increase infusion rate by 2 units/kg per hour
aPTT 46-70 sec (1.5-2.3 x control)	No change
aPTT 71-90 sec (2.3-3.0 x control)	Decrease infusion rate by 2 units/kg per hour
aPTT >90 sec (>3.0 x control)	Hold infusion 1 hour, then decrease infusion rate by 3 units/kg per hour

aPTT: activated partial thromboplastin time. Should be drawn every 6 hours after initial dose or after each dose change.
NOTE: This table reflects the original aPTT ranges, bolus sizes, and suggested changes in infusion rate which were present at the time this study was performed. The therapeutic ranges (ie, relationship between the aPTT and anti-factor Xa activity), initial and subsequent bolus sizes, and sizes of the infusion rate changes, as well as dosing differences depending on the disorder under treatment (eg, venous thromboembolism, stroke, acute coronary syndrome) should be established separately for each institution.
Modified from Raschke, RA, Reilly, BM, Guidry, JR, et al, Ann Intern Med 1993; 119:874.

Clinical outcome of trials of low molecular weight heparin for the treatment of venous thrombosis

Study	Design	Regimens	Recurrence of VTE, n/n (%)	Occurrence of major bleeding, n/n (%)	Death, n/n (%)
N Engl J Med 1992; 326:975	Randomized, double blind	Tinzaparin 175 Xa U/kg sc once daily **vs**	6/213 (3)	1/213 (0.5)*	10/213 (5)*
		IV heparin aPTT 1.5-2.5	15/219 (7)	11/219 (5.0)	21/219 (10)
Thromb Haemost 1994; 72:186	Randomized, open, home treatment	Dalteparin 200 Xa U/kg sc once daily **vs**	5/101 (5)	0	2 (2)
		IV heparin aPTT 1.5-3.0	3/103 (3)	0	2 (2)
N Engl J Med 1996: 334:677	Randomized, open, home treatment	Enoxaparin 1 mg/kg sc bid **vs**	13/247 (5)	5/247 (2)	11/247 (4)
		IV heparin aPTT 60-85 s	17/253 (7)	3/253 (1)	17/253 (7)
N Engl J Med 1996; 334:682	Randomized open, home treatment	Nadroparin sc bid● **vs**	14/202 (7)	1/202 (0.5)	14/202 (7)
		IV heparin aPTT 1.5-2.0	17/198 (9)	4/198 (2)	16/198 (8)
Ann Int Med 2001; 134:191	Randomized single blind	Revaparin sc bid● **vs**	9/312 (3)	4/312 (1)	7/312 (2)
		Reviparin sc once/day **vs**	13/298 (4)	5/298 (2)	11/298 (4)
		IV heparin aPTT 1.5-2.5	12/290 (4)	6/290 (2)	9/290 (3)
N Engl J Med 2001; 344:626	Randomized single blind	Reviparin sc bid△ **vs**	24/375 (6)	27/388 (7)	9/388 (2)
		Reviparin sc once/day **vs**	13/374 (4)	26/374 (7)	15/374 (4)
		IV heparin aPTT 1.5-2.5	24/375 (6)	28/375 (8)	11/375 (3)
N Engl J Med 2003;349:146	Randomized single blind	Dalteparin 200 IU/kg once daily for 5-7 days and coumarin for 6 months (INR 2.5) **vs**	27/336 (8)◊	19/338 (6)	130/336 (39)
		Dalteparin 200 IU/kg once daily for 1 month followed by dalteparin 150 IU/kg for 5 months	53/336 (16)	12/335 (4)	136/336 (41)

aPTT: activated partial thromboplastin time; bid: twice daily; sc: subcutaneously; VTE: venous thromboembolism
* P<0.05 by comparison to intravenous (IV) heparin group.
● Total daily doses were: 8,200 I Xa U for patients weighing less than 50 kg, 12,300 I Xa U for patients between 50 and 70 kg, and 18,400 I Xa U for patients weighing more than 70 kg; patients were treated at home if they did not require hospital for management of other conditions; about 40 to 50 percent of patients were treated without ever being admitted to the hospital, and in the remaining patients, the hospital stay was significantly reduced.
△ Total daily doses were 7,000 anti-Xa U for patients weighing 35-45 kg, 8,400 anti-Xa U for patients between 46 and 60 kg, and 12,600 U for patients weighing over 60 kg.
◊ p=0.002

Minimal requirements for early hospital discharge or outpatient therapy of VTE

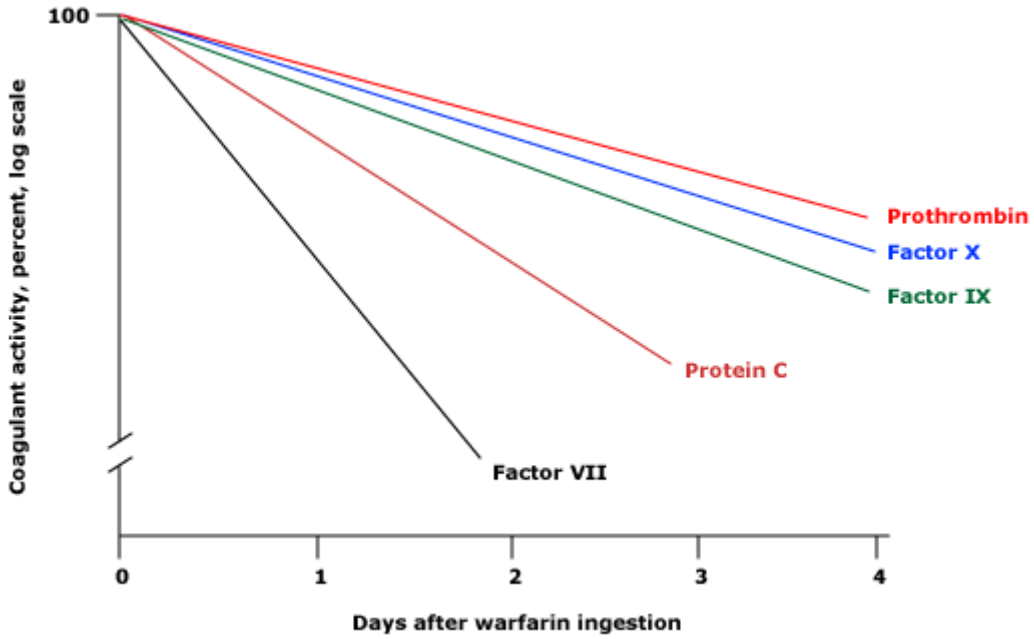
The responsible physician must ensure that all of the following conditions apply:
The patient is ambulatory and in stable condition, with normal vital signs
There is a low a priori risk of bleeding in the patient
Severe renal insufficiency is not present
There is a practical system in place for the following:
Administration of LMW heparin and/or warfarin with appropriate monitoring, **and**
Surveillance and treatment of recurrent VTE and bleeding complications

VTE: venous thromboembolism; LMW heparin: low molecular weight heparin.

Adapted from Hyers, TM, Agnelli, G, Hull, RD, et al. Antithrombotic therapy for venous thromboembolic disease. Chest

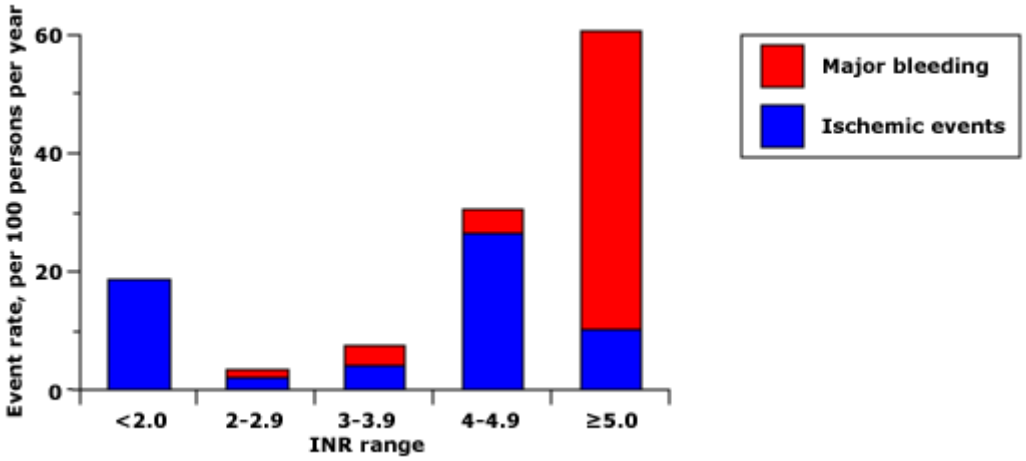
2001; 119:176S. (Sixth ACCP Consensus Conference on Antithrombotic Therapy).

Effect of warfarin on blood clotting proteins



The activity of various clotting proteins (logarithmic scale) is shown here as a function of time after ingestion of warfarin (10 mg/day PO for four consecutive days) by a normal subject. Factor VII activity, to which the prothrombin time is most sensitive, is the first to decrease. Full anticoagulation, however, does not occur until factors IX, X, and prothrombin are sufficiently reduced. Protein C activity falls quickly, and, in some patients, a transient hypercoagulable state may ensue (eg, coumarin necrosis).
Redrawn from Furie, B. Oral anticoagulant therapy. In: Hematology: Basic Principles and Practice, 3rd edition, Hoffman, R, Benz, EJ, Shattil, SJ, Furie, B, et al [Eds], Churchill Livingstone, New York, 2000, p. 2040.

Optimal INR in atrial fibrillation



Incidence of ischemic events and major bleeding episodes according to the INR in 214 patients with atrial fibrillation and a recent episode of minor cerebral ischemia. The total incidence of events was highest at INR values below 2.0 (where all events were ischemic) and above 5.0 (where most events were hemorrhagic). The optimal INR range was between 2.0 and 3.9.
Data from The European Atrial Fibrillation Trial Study Group, N Engl J Med 1995; 333:5.