Anticoagulation in acute pulmonary embolism

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INTRODUCTION — Anticoagulation is the main therapy for acute pulmonary embolism (PE). Its goal is to decrease mortality by preventing recurrent PE. In the only trial ever performed in patients with PE comparing treatment with anticoagulants to no treatment, anticoagulation decreased mortality [1]. Subsequent uncontrolled trials have confirmed that anticoagulation decreases mortality [2-4].

Common questions asked by clinicians caring for patients with acute PE include:

- Should I initiate anticoagulant therapy?
- Which anticoagulant should I initiate?
- What is the appropriate dose?
- How should I monitor the treatment?
- What is the clinical evidence supporting its use?
- What are the common complications?
- For how long should I treat?

Each of these issues are reviewed here. Other aspects of the treatment of acute PE, including thrombolysis, inferior vena caval filters, and embolectomy are discussed separately. (See "Treatment of acute pulmonary embolism" and see "Fibrinolytic (thrombolytic) therapy in pulmonary embolism and deep vein thrombosis" and see "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and see "Deep vein thrombosis and pulmonary embolism in pregnancy: Prevention").

INITIATION OF THERAPY — We recommend that anticoagulation be initiated in all patients for whom there is a high clinical suspicion of PE or in whom PE has been confirmed. This recommendation is based upon the high incidence of mortality in untreated patients due to recurrent PE (approximately 30 percent), which outweighs the risk of major bleeding (less than 3 percent) [5-9]. In contrast, anticoagulant therapy should be considered on a case-by-case basis when PE has not been confirmed and the clinical suspicion of PE is low to moderate.

The efficacy of anticoagulant therapy depends upon achieving a therapeutic level of anticoagulation within the first 24 hours of treatment [10-12]. Therapeutic options include

subcutaneous low molecular weight heparin (SC LMWH), intravenous unfractionated heparin (IV UFH), subcutaneous unfractionated heparin (SC UFH), and SC fondaparinux [13]:

- SC LMWH is the preferred anticoagulant for most hemodynamically stable patients with PE. (See "Low molecular weight heparin" below).
- We use IV UFH when there is persistent hypotension due to PE (ie, massive PE), an increased risk of bleeding, concern about subcutaneous absorption (eg, morbid obesity), or thrombolysis is being considered. (See "Unfractionated heparin" below).
- We use UFH (either IV or SC) when the creatinine clearance is ≤30 mL/min [14]. The rationale for this approach is two-fold. First, the efficacy of LMWH and fondaparinux in patients with PE and severe renal failure has not been well studied because most randomized trials excluded such patients. Second, severe renal insufficiency alters the pharmacokinetics of the anticoagulants, requiring that activity be monitored. It is more convenient to monitor UFH than SC LMWH because activated partial thromboplastin time (aPTT) testing is more readily available than anti-Xa assays. (See "Unfractionated heparin" below).

In the rare patient in whom there is a high clinical suspicion of PE but a strong contraindication to anticoagulation (eg, active bleeding), diagnostic evaluation should be expedited. Anticoagulation-independent therapies (eg, inferior vena caval filter) should be pursued if PE is confirmed (show figure 1). (See "Treatment of acute pulmonary embolism").

LOW MOLECULAR WEIGHT HEPARIN — We recommend subcutaneous low molecular weight (SC LMWH) for most hemodynamically stable patients with PE. Compared to intravenous unfractionated heparin (IV UFH), SC LMWH results in lower mortality, fewer recurrent thrombotic events, and less major bleeding [15-27]. The magnitude of these benefits was illustrated by a meta-analysis of randomized trials comparing these two approaches in patients with PE or deep vein thrombosis (DVT) [15]:

- In 18 trials (8054 patients), SC LMWH decreased mortality (odds ratio 0.76, 95% CI 0.62-0.92).
- In 22 trials (8867 patients), SC LMWH decreased recurrent thrombosis (odds ratio 0.68, 95% CI 0.55-0.84).
- In 12 trials, thrombus size reduction was more common with LMWH (odds ratio 0.69, 95% CI 0.59-0.81).

Additional advantages of SC LMWH over IV UFH include greater bioavailability, more predictable pharmacokinetics, once or twice daily administration, fixed dosing that does not require adjustment, and a decreased likelihood of thrombocytopenia [13,28].

We also prefer SC LMWH to fondaparinux or SC UFH for the treatment of hemodynamically stable PE, mainly because there is greater clinical experience using SC LMWH. SC LMWH has not been directly compared to fondaparinux, but has been compared to SC UFH. Randomized trials indicate that SC LMWH and SC UFH have similar outcomes and risks, regardless of whether or not such therapy was titrated to goal aPTT:

- A trial randomly assigned 720 patients with PE or DVT to receive SC LMWH, or SC UFH titrated to a goal aPTT [29]. The groups had similar rates of recurrent events (3.9 versus 4.2 percent for SC UFH) and major bleeding (0.8 versus 1.1 percent for SC UFH).
- In a similar trial, 708 patients with PE or DVT were randomly assigned to receive SC LMWH, or an initial weight-based dose of SC UFH followed by a fixed dose [30]. The groups had similar rates of recurrent events (3.4 versus 3.8 percent for SC UFH) and major bleeding (1.4 versus 1.1 percent for SC UFH).

Different formulations of SC LMWH have been infrequently compared. In one trial, 505 patients with PE or DVT were randomly assigned to receive tinzaparin or dalteparin for at least five days [31]. There was no difference in the frequency of major bleeding, recurrent PE, or recurrent DVT, suggesting that tinzaparin and dalteparin are equally safe and effective in the management of acute PE. Similar trials comparing other types of LMWH are lacking. (See "Low molecular weight heparin for venous thromboembolic disease" and see "Therapeutic use of heparin and low molecular weight heparin").

Dosing — Formulations of SC LMWH include enoxaparin, tinzaparin, dalteparin, nadroparin, ardeparin, and reviparin.

- Enoxaparin — Enoxaparin can be administered subcutaneously at a dose of 1 mg/kg of actual body weight every 12 hours. Alternatively, it can be administered subcutaneously at a dose of 1.5 mg/kg of actual body weight once daily. The 1 mg/kg every 12 hours regimen is preferred for patients with cancer, extensive clot burden, an actual body weight between 101 and 150 kg, or a body mass index (BMI) between 30 and 40 [22,32,33].
- Tinzaparin — Tinzaparin is administered subcutaneously at a dose of 175 international units/kg of actual body weight once daily [14]. It is contraindicated in patients who are older than 70 years and have renal insufficiency because administration of tinzaparin has been associated with increased mortality in such patients [34].
- Dalteparin — Dalteparin is administered subcutaneously at a dose of 200 international units/kg of actual body weight once daily (up to a maximum dose of 18,000 international units) for 30 days. It is then administered subcutaneously at a dose of 150 international units/kg of actual body weight once daily (up to a maximum dose of 18,000 international units). Patients who are >90 kg may receive less than the optimal weight-based dose of dalteparin since the maximum dose of dalteparin is 18,000 international units. This increases their risk for subtherapeutic anti-Xa activity. As a result, patients who require LMWH and who are >90 kg should receive enoxaparin or tinzaparin, rather than dalteparin.

Monitoring — Monitoring anti-Xa levels is not necessary for most patients receiving LMWH. However, it may be warranted in special circumstances, such as morbid obesity, low body weight, renal insufficiency, and pregnancy.

- Morbid obesity — The adequacy of subcutaneous absorption of LMWH is a concern in

morbidly obese individuals (BMI >40). Thus, titration of the dose to a therapeutic anti-Xa level may be desirable in this situation.

- Low body weight — Patients with low body weight (<45 kg women, <57 kg men) appear to have increased exposure to the anticoagulant effects of LMWH, even at prophylactic doses [35]. This might increase their risk of bleeding, although this belief is based on a paucity of data. In patients with low body weight, LMWH should be dosed according to the actual body weight and periodic monitoring of anti-Xa activity is warranted [32].

- Renal insufficiency — There is no specific dose adjustment for LMWH in patients with mild or moderate renal insufficiency (CrCl of 30 to 80 mL/minute). In contrast, patients with severe renal insufficiency (CrCl <30 mL/minute) are generally NOT treated with LMWH because anti-Xa activity will accumulate significantly. The 2008 American College of Chest Physicians (ACCP) Antithrombotic and Thrombolytic Therapy guidelines suggest that UFH be used instead of LMWH in such patients [14]. If LMWH is used in a patient with severe renal insufficiency, there should be an approximately 50 percent daily dose reduction [14]. Monitoring of the anti-Xa activity is also warranted [32,36]. (See "Unfractionated heparin" below).

- Pregnancy — The dosing and monitoring of LMWH during pregnancy are discussed separately. (See "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and see "Deep vein thrombosis and pulmonary embolism in pregnancy: Prevention").

UNFRACTIONATED HEPARIN — Intravenous unfractionated heparin (IV UFH) was once the preferred initial treatment for acute PE because it was the only anticoagulant that had been compared to no treatment in a controlled trial and shown to reduce mortality due to PE [1]. However, data suggesting that subcutaneous low molecular weight heparin (SC LMWH) decreases mortality, recurrent PE, and major bleeding compared to IV UFH have made SC LMWH the preferred anticoagulant for initial therapy in most cases of acute PE [15]. The better outcomes with SC LMHH were described above. (See "Low molecular weight heparin" above).

IV UFH is our preferred agent when any of the following circumstances exist:

- Persistent hypotension due to PE — There is extensive clinical experience using IV UFH in this setting. In contrast, the effect of LMWH in patients with persistent hypotension due to PE (ie, massive PE) is uncertain because the clinical trials that evaluated LMWH in acute PE excluded this patient subgroup [37].

- Increased risk of bleeding — IV UFH is the shortest-acting anticoagulant and its activity can be reversed if major bleeding occurs. (See "Therapeutic use of heparin and low molecular weight heparin", section on Heparin reversal and use of protamine sulfate).

- Thrombolysis is being considered — Most patients are already receiving anticoagulation when it is determined that thrombolysis is necessary. In such patients, the anticoagulant is generally discontinued and the thrombolytic agent is then infused. The patient is subjected to concomitant anticoagulant and thrombolytic activity for the shortest duration when IV UFH is the anticoagulant used prior to thrombolysis.

- Concern about subcutaneous absorption (eg, morbid obesity, severe anasarca) — IV UFH bypasses the unpredictability of subcutaneous absorption.

Subcutaneous unfractionated heparin (SC UFH) is also an acceptable agent for the initial management of acute PE. However, its use has not surpassed SC LMWH. While randomized trials suggest that SC UFH and SC LMWH have similar efficacy and risks, most clinicians have more experience using SC LMWH to treat acute PE [29,30]. (See "Low molecular weight heparin" above).

UFH (either IV or SC) is also preferred in patients with severe renal failure, which alters the pharmacokinetics of the anticoagulants, requiring that activity be monitored. UFH is more convenient than SC LMWH to monitor because activated partial thromboplastin time (aPTT) testing is more readily available in most institutions than anti-Xa assays.

Dosing

Intravenous — Several protocols for the administration of IV UFH can rapidly achieve and sustain a therapeutic level of heparin. All of the protocols administer the IV UFH by continuous infusion because intermittent IV bolus dosing is associated with an increased incidence of major bleeding [9].

We use a weight-based dosing protocol, which is shown in the table (show table 1). We administer a starting bolus of 80 units/kg, followed by an infusion at 18 units/kg per hour. We titrate the infusion rate every four to six hours to a goal activated partial thromboplastin time (aPTT). This regimen is among those suggested by the 2008 ACCP Antithrombotic and Thrombolytic Therapy guidelines [13]. The goal aPTT and titration of the continuous IV UFH infusion are discussed below. (See "Monitoring" belowSee "Monitoring" belowSee "Monitoring" belowSee "Monitoring" below).

Our preference for weight-based IV UFH dosing is based upon a study that evaluated weight-based dosing (bolus of 80 units/kg, followed by an infusion at 18 units/kg per hour) versus fixed dosing (bolus of 5000 units, followed by an infusion at 1000 units/hour) [11]. Significantly more patients in the weight-based group achieved a therapeutic aPTT value within 24 hours (97 versus 77 percent).

For clinicians who prefer fixed dosing, several regimens are effective. The fixed dosing protocol that is suggested in the 2008 ACCP guidelines is a bolus of 5000 units, followed by a continuous infusion of 1300 units/hour [13]. Alternatively, the protocol shown in the tables (show table 2A-2B) was used in a clinical trial in which fewer than 2 percent of patients had a subtherapeutic aPTT for more than 24 hours [38]. With either protocol, the continuous IV UFH infusion is titrated every four to six hours to a goal aPTT.

Subcutaneous — Several protocols for the administration of SC UFH are reasonable, according to the 2008 ACCP guidelines [13]:

- SC UFH can be initiated at a dose of 17,500 units or 250 units/kg every 12 hours. The dose should then be titrated to achieve a therapeutic aPTT. The first aPTT is generally

measured six hours after the second dose. The magnitude of most dose adjustments should be an increase or decrease of 10 to 30 percent. The aPTT should be measured six hours after the second injection that follows each dose adjustment. Once a stable dose is achieved, the aPTT may be measured after three to four days of treatment and then every few weeks if SC UFH rather than warfarin is used for long-term therapy. (See "Monitoring" belowSee "Monitoring" belowSee "Monitoring" belowSee "Monitoring" below).

- SC UFH may also be administered by giving an initial dose of 333 units/kg, followed by a standing dose of 250 units/kg every 12 hours. The aPTT is not monitored with this protocol.

Monitoring — UFH therapy is most commonly monitored using the aPTT, which measures the antithrombotic activity of heparin. Individual hospital laboratories determine the range of aPTT values that correspond to 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (or 0.2 to 0.4 IU/mL anti-Xa activity by the protamine sulfate titration assay) [13]. In most patients, the therapeutic aPTT is 1.5 to 2.5 times the control aPTT.

The therapeutic aPTT range varies from institution to institution because the relationship between the aPTT and anti-factor Xa activity is variable. As a result, each institution must establish its own protocol for dose adjustment on the basis of the measured aPTT.

The efficacy of IV UFH depends upon achieving a therapeutic level of heparin (ie, aPTT) within the first 24 hours of treatment [10-12,39]. Observational data extracted from three double-blind, randomized trials (746 patients) showed that failure to achieve a therapeutic aPTT within 24 hours was associated with a significantly higher rate of recurrent DVT or PE (23 versus 3 percent) [39]. The importance of achieving a therapeutic aPTT within 24 hours was confirmed in a study that evaluated SC UFH [29].

Inadequate initial heparin therapy may increase the probability of recurrent thromboembolism for at least three months, despite ongoing therapeutic anticoagulation. This was illustrated in a study in which 32 patients had recurrent PE or DVT within 3 months after the initial event [40]. Among these patients, 63 percent had a therapeutic prothrombin time (PT) or international normalized ratio (INR) at the time of the recurrence, but most had not achieved a therapeutic aPTT within 24 hours of the initial DVT or PE.

Unfortunately, the aPTT does not always correlate with heparin levels. Patients requiring unusually high doses of UFH without achieving a therapeutic aPTT (ie, heparin-resistant patients) should have their UFH dose adjusted by anti-Xa assay instead of aPTT.

FONDAPARINUX — Fondaparinux is a synthetic highly sulfated pentasaccharide, which has a sequence derived from the minimal antithrombin binding region of heparin [41]. It catalyzes factor Xa inactivation by antithrombin without inhibiting thrombin. (See "Therapeutic use of fondaparinux").

An open-label trial randomly assigned 2213 patients with symptomatic PE to receive either subcutaneous fondaparinux once daily without monitoring, or continuous intravenous unfractionated heparin (IV UFH) [42]. Both medications were transitioned to an oral vitamin K

antagonist for long-term therapy. The two regimens were associated with similar rates of recurrent PE (3.8 versus 5.0 percent), major bleeding (2.0 versus 2.4 percent), nonmajor bleeding (5.7 versus 8.4 percent), thrombocytopenia (0.9 versus 1.2 percent), and death (5.2 versus 4.4 percent). Fondaparinux has not been directly compared to SC UFH or SC LMWH.

Idraparinux, a similar synthetic heparin pentasaccharide, appears to be less effective and is not recommended for the management of acute PE [13,43].

Dosing — Fondaparinux is administered subcutaneously once per day. The dose is weight-based: 5 mg for patients <50 kg, 7.5 mg for patients 50 to 100 kg, and 10 mg for patients >100 kg.

Fondaparinux is contraindicated in patients with severe renal insufficiency (CrCl <30 mL/minute) because it will accumulate and increase the risk of hemorrhage. Accumulation also occurs in patients with mild to moderate renal insufficiency (CrCl 30 to 80 mL/minute) and no dosage adjustment recommendations are available.

Monitoring — Monitoring anti-Xa levels is not necessary for most patients receiving fondaparinux. However, it is suggested that renal function, hemoglobin or hematocrit, and platelets be measured periodically.

WARFARIN — In most cases of PE, either heparin (low molecular weight or unfractionated) or fondaparinux is administered short-term and then transitioned to a long-term oral anticoagulant. The majority of anticoagulants are vitamin K antagonists, which suppress production of the vitamin K-dependent clotting factors (II, VII, IX, and X). Warfarin is the most common and best studied vitamin K antagonist.

Long-term treatment with warfarin is highly effective for preventing recurrent PE [13,44-47]. This is best illustrated by a meta-analysis of eight randomized, controlled trials (2994 patients) that demonstrated that patients with symptomatic PE had a decreased likelihood of recurrent PE or DVT when treated with long-term warfarin compared to cessation of warfarin after one to four months (odds ratio 0.18, 95% CI 0.13-0.26) [47].

Initiation — Warfarin can be initiated on the same day or after heparin or fondaparinux is begun. It should NOT be initiated prior to heparin or fondaparinux because warfarin alone is associated with a three-fold increase in the incidence of recurrent PE or DVT [12,48].

Warfarin should be overlapped with heparin or fondaparinux for a minimum of five days and until the International Normalized Ratio (INR) has been within the therapeutic range (2.0 to 3.0) for at least 24 hours [13]. The rationale is as follows. Warfarin impairs production of the vitamin K-dependent clotting factors; thus, its anticoagulant effect is not realized until the preexisting clotting factors are cleared from the circulation, a process that requires approximately 36 to 72 hours. During the first few days of warfarin therapy, the prolonged PT reflects only the loss of factor VII (which has a half-life of five to seven hours) and does not represent adequate anticoagulation because the intrinsic clotting pathway remains intact. It takes about five days for the activity of the intrinsic clotting pathway to be sufficiently suppressed. (See "Therapeutic use of warfarin", section on Mechanism of action).

Dosing — We administer warfarin using an initial dose of not more than 5 mg per day for the first two days (we use smaller doses in elderly patients), then adjust the daily dose according to the INR. Selection of a maintenance dose must be individualized because the rate at which individuals metabolize warfarin varies greatly. In addition, the required dose can be impacted by multiple variables, including age, concomitant medications, and diet. (See "Therapeutic use of warfarin").

Patients with known protein C deficiency have an increased risk of warfarin-induced skin necrosis. In such patients, it is important to initiate oral anticoagulation gradually, while heparin or fondaparinux therapy is ongoing. (See "Protein C deficiency").

Monitoring — The laboratory test most commonly used to measure the effects of warfarin is the INR. Warfarin therapy for PE should target an INR of 2.5 (range 2.0 to 3.0) [13]. Randomized trials indicate that less intense anticoagulation (INR <2.0) is associated with an increased likelihood of recurrent PE or DVT and more intense anticoagulation is associated with bleeding [9,49-52].

Initially, INR measurements are required every one to two days. Once the patient's warfarin dose has stabilized for at least one to two weeks, subsequent INR monitoring can be performed at two to four week intervals[53]. More frequent monitoring is indicated if there are factors that may produce an unpredictable response to warfarin (eg, concomitant drug therapy, other medical conditions) [53,54]. (See "Therapeutic use of warfarin").

COMPLICATIONS

Bleeding — In the following discussion, we define major bleeding as intracranial hemorrhage, retroperitoneal hemorrhage, or bleeding that led directly to death, hospitalization, or transfusion [9].

Heparin — The frequency of major bleeding during intravenous unfractionated heparin (IV UFH) therapy for PE or DVT is less than 3 percent [9]. Major bleeding has been associated with too much heparin (ie, a supratherapeutic activated partial thromboplastin time [aPTT]), recent surgery, recent trauma, advanced patient age (>70 years), concurrent aspirin, and renal failure [9,55-62].

Compared to IV UFH, the risk of major bleeding appears to be similar with fondaparinux and subcutaneous UFH [29,30,42], and less with subcutaneous low molecular weight heparin (SC LMWH). In a meta-analysis of 22 randomized, controlled trials (8867 patients with PE or DVT) that compared SC LMWH to IV UFH, there was a significantly lower rate of major bleeding in the group that received SC LMWH (odds ratio 0.57, 95% CI 0.39-0.83) [15].

Warfarin — It is estimated that major bleeding occurs in fewer than 3 percent of patients receiving warfarin to treat PE or DVT [9,63]. The mortality rate associated with these major bleeding episodes can be as high as 13 percent [63]. The association of warfarin therapy with bleeding risk is discussed in detail separately. (See "Therapeutic use of warfarin", section on Bleeding).

Management — Protamine sulfate reduces clinical bleeding by neutralizing antithrombin

activity, although anti-factor Xa activity is only partially reversed. It can be administered to patients who experience bleeding while receiving SC LMWH, IV UFH, or SC UFH. (See "Therapeutic use of heparin and low molecular weight heparin", section on Heparin reversal and use of protamine).

Vitamin K and fresh frozen plasma can be administered to patients who experience bleeding while taking an oral vitamin K antagonist. (See "Correcting excess anticoagulation after warfarin").

Thrombocytopenia — Heparin-induced thrombocytopenia (HIT) is another complication of heparin therapy. Aside from having a previous episode of HIT, there are no known risk factors for developing HIT. HIT is distinctly less common after the use of LMWH compared to UFH. HIT is discussed in detail separately. (See "Heparin-induced thrombocytopenia").

DURATION OF THERAPY — The appropriate duration of therapy varies depending upon whether the PE is the patient's first and the type of risk factor(s) that exist. Decisions about long-term anticoagulation invariably involve individual patient preferences. Longer term therapy reduces the risk of recurrent events, but increases the risk of bleeding. Additionally, many patients will find warfarin therapy burdensome because it necessitates monitoring, a consistent diet, and restrictions on activity.

First episode of PE — Treatment duration among patients with a first episode of PE or DVT is determined by whether a risk factor can be identified and, if so, whether the risk factor is reversible.

Reversible risk factor — Patients with a first episode of PE or DVT who have a reversible or temporary risk factor that has resolved should receive warfarin therapy for at least three months [13]. Examples of temporary risk factors include immobilization, surgery, and trauma.

Attempts to decrease treatment duration may result in a higher rate of recurrent thromboembolism [64,65]. This is illustrated by a trial that randomly assigned 712 patients to receive one month or three months of anticoagulant therapy [65]. Patients who received anticoagulant therapy for one month had more recurrent PE or DVT than patients who received anticoagulants for three months (11 versus 4 percent).

It appears that anticoagulation for longer than three months does not confer additional benefit. Two randomized trials compared anticoagulant therapy for three versus six months in patients with DVT or PE [66,67]. In both trials, the incidence of recurrent DVT or PE was the same in both groups.

Unprovoked — There is conflicting evidence about whether patients with a first episode of unprovoked PE (ie, PE that is NOT due to a temporary or reversible risk factor) benefit from receiving more than three months of warfarin therapy:

- Supporting the notion that greater than three months of anticoagulant therapy is beneficial, a trial randomly assigned 508 patients with idiopathic PE or DVT who had completed three months of anticoagulant therapy to receive long-term low dose warfarin or placebo [46]. Patients who received warfarin had a significantly lower rate

of recurrent DVT or PE than patients who received placebo (hazard ratio 0.36, 95% CI 0.19-0.67). These findings are supported by another randomized trial that found that patients with idiopathic PE or DVT who were treated for two years had significantly fewer recurrent PE or DVT than those treated for three months (1.3 versus 27 percent per patient-year) [68].

- Arguing against the need for greater than three months of anticoagulant therapy, a trial randomly assigned 181 patients with idiopathic PE (not DVT) who had completed three months of anticoagulant therapy to either continue or discontinue therapy [69]. There was no difference in the rate of recurrent DVT or PE, or mortality.

The major difference in these trials is that those supporting more than three months of anticoagulant therapy enrolled patients with DVT or PE, whereas the trial that does not support more than three months of anticoagulant therapy included patients with PE only. On the basis of this and other evidence, the 2008 ACCP Antithrombotic and Thrombolytic Therapy guidelines recommend three months of warfarin therapy and then reassessment for unprovoked PE [13]. Indefinite anticoagulation is recommended for patients who do NOT have risk factors for bleeding and are willing to continue anticoagulant monitoring.

Recurrent PE — Indefinite warfarin therapy should be administered to patients with two or more episodes of PE or DVT. In one trial, 227 patients with recurrent PE or DVT were randomly assigned to receive warfarin for six months or indefinitely [70]. After four years of follow-up, recurrent DVT or PE was reduced in the group receiving indefinite anticoagulant therapy (3 versus 21 percent), but major bleeding was increased (9 versus 3 percent).

SPECIAL CONSIDERATIONS

Cancer — The risk of PE is increased among patients who have a malignancy. Treatment of PE or DVT in this clinical setting is discussed in detail separately, including the management of anticoagulation. (See "Treatment of venous thromboembolism in patients with malignancy").

Pregnancy — The risk of PE is increased during pregnancy, especially during the early postpartum period. Treatment of PE or DVT in this clinical setting is discussed in detail separately, including the management of anticoagulation. (See "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and see "Anticoagulation during pregnancy").

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Pulmonary embolism"). We encourage you to print or e-mail this topic, or to refer patients to our public web site www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS

Initial therapy

- We recommend that anticoagulation be initiated immediately when there is a high clinical suspicion of pulmonary embolism (PE) and continued during the diagnostic evaluation (show figure 1) (**Grade 1B**). (See "Initiation of therapy" above and see

"Treatment of acute pulmonary embolism", section on General approach).

- For hemodynamically stable patients with PE, we recommend initial treatment with subcutaneous low molecular weight heparin (SC LMWH), rather than intravenous unfractionated heparin (IV UFH) (**Grade 1A**). For the same patient population, we suggest SC LMWH, rather than subcutaneous unfractionated heparin (SC UFH) or fondaparinux (**Grade 2B**). The evidence is inadequate to suggest use of one SC LMWH preparation over another. (See "Low molecular weight heparin" above).
- For patients with PE who have persistent hypotension due to the PE, an increased risk of bleeding, potential abnormal subcutaneous absorption (eg, morbid obesity), or in whom thrombolysis may be performed, we suggest IV UFH rather than an alternative anticoagulant (**Grade 2B**). (See "Unfractionated heparin" above).
- For patients with PE and severe renal failure (creatinine clearance ≤30 mL/min), we suggest UFH rather than SC LMWH (**Grade 2B**). The UFH may be administered subcutaneously or intravenously. (See "Initiation of therapy" above).

Long-term therapy — After initial therapy with heparin (LMWH or UFH) or fondaparinux, long-term therapy is generally completed with a vitamin K antagonist, such as warfarin.

- Warfarin therapy can be initiated at the same time or after heparin or fondaparinux. It should NOT be started prior to heparin or fondaparinux. (See "Initiation" above).
- We recommend that the warfarin dose be adjusted to achieve an international normalized ration (INR) of 2.5 (range 2.0 to 3.0) (**Grade 1A**). Warfarin should be overlapped with heparin for a minimum of five days and until the INR has been within the therapeutic range for at least 24 hours. (See "Warfarin" aboveSee "Warfarin" above).

Duration — We advocate the following treatment durations for warfarin therapy. Recommendations for indefinite therapy ascribe a higher value to preventing recurrent PE and a lower value to bleeding, cost, and inconvenience.

- For patients with a first episode of PE due to a temporary risk factor (eg, surgery, immobilization, trauma), we recommend warfarin therapy for three months, rather than a shorter duration (**Grade 1A**). (See "Reversible risk factor" above).
- For patients with a first episode of unprovoked PE, we recommend warfarin therapy for at least three months, rather than a shorter duration (**Grade 1A**). The potential benefits and risks of indefinite anticoagulant therapy should be assessed after the three months of anticoagulant therapy. For patients who do NOT have an increased risk of bleeding, we suggest indefinite warfarin therapy (**Grade 2B**). (See "Unprovoked" above).
- For patients with two or more episodes of PE, we recommend indefinite warfarin therapy (**Grade 1A**). (See "Recurrent PE" above).
- Anticoagulant therapy for patients with a PE who are pregnant or have a malignancy is discussed separately. (See "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and see "Treatment of venous thromboembolism in patients

with malignancy").

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