15 Deep Venous Thrombosis and Pulmonary Embolism

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Natural History

At least 300–600,000 patients per year in the USA suffer a first deep venous thrombosis, with 5–10 per 10,000 population suffering a thrombotic event each year. More than 90% of pulmonary emboli occur as a complication of thrombosis in the deep venous system of the legs. Therefore, treatment and prevention of deep venous thrombosis will reduce the occurrence of pulmonary embolism. Another key point is that more than 90% of the deaths attributable to pulmonary embolism occur in the first hour. Thus, management is aimed toward prevention of a repeat embolism and not treatment of the initial embolus. It is estimated that the mortality rate of untreated pulmonary embolism is 30–40%, and the risk of pulmonary embolism from untreated proximal deep venous thrombosis is 50–80%.

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Diagnostic Tests for Pulmonary Embolism and Deep Venous Thrombosis

Clinical Signs and Symptoms Patients first notice dyspnea and cough following a pulmonary embolism. Chest pain occurs hours to days after the event with development of lung infarction. One-third of patients will have hemoptysis, and 10–20% will have syncope. Most patients on exam will have tachypnea (70–92%), but less than half have tachycardia (30% of patients in the classic PIOPED study). Chest x-rays are normal in only 30%. A nonspecific infiltrate is seen in 50–70%, and an effusion is seen in 35%. In the PIOPED study, *15%* of patients had PO_2 greater than 90 mmHg, and *20%* had alveolar-arterial gradients less than 20 mmHg. These results demonstrate that patients with pulmonary embolism need not be hypoxic or have an abnormal a-A gradient.

Prediction Rules Recently there has been great interest in clinical prediction rules for deep venous thrombosis and pulmonary embolism. Using these rules, clinicians can better predict which patients are at higher risk of thrombosis, and this will guide testing. Several examples exist (Tables 15.1, 15.2a, and 15.2b). The best validated for DVT are the Wells criteria, and two prediction rules – Wells and Geneva – have also been validated for PE in multiple studies. Use of these prediction rules along with the D-dimer

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Table 15.1 Clinical probability score for deep venous thrombosis

Variable	Points
Active cancer	+1
Paralysis or recent plaster immobilization of the lower extremity	+1
Recently bedridden for >3 days or major surgery within 4 weeks	+1
Local tenderness	+1
Calf swelling greater than 3 cm than asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema in symptomatic leg	+1
Dilated superficial veins (non-varicose) in symptomatic leg only	+1
Alternative diagnoses as or more likely than DVT	−2

Low probability <0, moderate probability 1–2, and high probability >3
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Table 15.2a Clinical probability score for pulmonary embolism (Wells) (1)

Variable	Points
Clinical signs and symptoms of DVT	+3
PE as likely or more likely than alternative diagnosis	+3
Immobilization or surgery in the past 4 weeks	1.5
Previous PE or DVT	1.5
Heart rate more than 100/min	1.5
Hemoptysis	1
Active cancer	1

Low probability <2, moderate probability 2–6, and high probability >6; PE unlikely ≤4; PE likely >4
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determines whether patients should be evaluated for thrombosis. For the Wells PE criteria, results can be presented as "low," "intermediate," or "high" – alternatively as "PE likely" vs "PE unlikely." Taking a step back, the PERC rule (Table 15.3) evaluates whether the diagnosis of PE should even be considered. Patients who are felt to be at low risk already of PE and who answer negative on all eight questions have low (<1%) rates of being diagnosed with PE, and the evaluation can be halted without further testing. This test performs best in populations at low risk of PE such as young outpatients.

Table 15.2b Clinical probability score for pulmonary embolism (Geneva) (2)

Variable	Points
Previous DVT or PE	+2
Heart rate > 100	+1
Recent surgery	+3
Age	
60–79	+1
>80	+2
$PaCO_2$	
<36 mmHg	+2
36–40 mmHg	+1
PO_2	
<50 mmHg	+4
50–59 mmHg	+3
60–69 mmHg	+2
70–79 mmHg	+1
Atelectasis	+1
Elevated hemi-diaphragm	+1

Low probability 0–4, intermediate probability 5–8, high probability >9
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Table 15.3 PERC rule

Eight questions
1. Age < 50 years
2. Heart rate less than 100 beats per minute
3. Room air oxygen saturations 95% or greater
4. No prior deep DVT or PE
5. No recent trauma or surgery in the past 4 weeks
6. No hemoptysis
7. No exogenous estrogen
8. No clinical signs suggestive of DVT such as unilateral leg swelling

In a population with low risk for PE, patients who answer "no" to all eight have a low (~1%) risk of PE
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D-dimer A major advance in evaluation of patients with DVT/PE is the wide availability of rapid D-dimer assays. Thrombi contain areas which are growing and other areas which are undergoing fibrinolysis. It has been shown that all patients with clinically significant thrombosis will have levels of D-dimers above 500 ng/ml. Two most commonly used rapid assays are the point of care D-dimer and the high-sensitive D-dimer.

"Rapid" point of care D-dimer assays are slide assays (like pregnancy tests) devised to read positive if the D-dimer is above 500 ng/ml. These types of assays are less sensitive (80–90%) than the rapid ELISA but are simple to use and require no special equipment to run. The rapid D-dimer is most effective when used with a clinical prediction rule. Thus, a patient with a negative D-dimer and low probability of thromboembolic event has a remote chance of having thrombosis and need not be evaluated further. If a patient has either a not-low pretest probability or has a positive D-dimer, then they need further workup for DVT/PE.

The "rapid ELISA" or "high-sensitivity" assay for D-dimer offers nearly 100% sensitivity for DVT. Accordingly, a patient with a negative ELISA D-dimer requires no further evaluation unless they have a high pretest probability of thrombosis. The rapid ELISA often requires the test be performed in the central laboratory, increasing turnaround time.

The other drawback of the D-dimer test is its lack of specificity coupled with its high sensitivity. Therefore, patients with positive D-dimer assays require further testing to establish the presence of thrombosis. Patients with recent trauma, recent surgery, and pregnancy or those over age 70 have a higher baseline D-dimer level which greatly limits the use of D-dimers in these patients. There are recent data that an age-adjusted cutoff may improve the ability of D-dimers to exclude thrombosis in older patients. The formula for patients over age 50 is *D-dimer cutoff = age × 10* – so for a 65-year-old, this would be 650 ng/dl.

CT Angiography CT angiography (CTA) has become the diagnostic test of choice for pulmonary embolism. A CTA that is positive for thrombus in a segmental distribution and above pulmonary arteries is highly specific for PE, with it falling to 80% for subsegmental PEs. CTA is now the first-line test for PE, and there is much concern about its overuse since less than 10% of these tests are positive for PE in many institutions. This is why a diagnostic pathway utilizing assessment of clinical probability and D-dimers should be used before CTA to diagnose PE.

Ventilation/perfusion (V/Q) scans are sensitive but not specific for pulmonary embolism unless the result reads high probability. Interpretation is best viewed as "high probability," "negative," and "nondiagnostic." High-probability scans are specific if the patient has not had a previous pulmonary embolism, but specificity falls in patients with previous pulmonary emboli or pre-existing cardiac or pulmonary disease. Less than high-probability scans are not diagnostic unless the result is a normal scan or a low-probability scan in patients with a low pretest probability of thrombosis. V/Q scans are becoming less available as they have been mostly supplanted by CTA.

Leg studies are the definitive diagnostic test in patients with symptoms of deep venous thrombosis. Furthermore, leg studies aid in the patient with a nondiagnostic V/Q scan or in a patient for whom one wishes to defer CTA (pregnancy or renal disease). Deep venous thrombosis will be present in 50–70% of patients with proven pulmonary embolism. If deep venous thrombosis is present, this establishes the need for anticoagulant therapy and eliminates the need for CTA.

Venogram Used to be the gold standard. Venograms visualize both the calf and deep veins. Drawbacks of venography include dye load and a 5% risk of actually causing thrombosis. Given that very few venograms are currently performed, the accuracy and ability to perform technically adequate studies is greatly reduced.

Doppler ultrasound has very high sensitivity and specificity for diagnosing proximal deep venous thrombosis in symptomatic patients and is >90% for the calf veins, so a negative whole leg Doppler rules out DVT. Some institutions only perform Dopplers for proximal vein thrombosis, so if negative, one needs to perform follow-up duplex to rule out clot extension in high-probability patients.

Diagnostic Approach to DVT or PE

1. Assess pretest probability.
2. If high probability, then specific imaging (Doppler for DVT or CTA for PE).

3. If not high probability, then high-sensitivity D-dimer – if negative, no imaging.
4. If positive D-dimer, then specific imaging.

Immediate Therapy

Anticoagulation – See the following section.

Thrombolytic Therapy

PE Given the natural history of pulmonary embolism, the role of thrombolytic therapy is uncertain. The fact that thrombolytic therapy lyses clots faster than heparin was of no clinical significance in the large trials of the early 1980s or in more recent trials. Two trials showed that, in patients with right ventricular dysfunction, thrombolytic therapy failed to improve mortality or prevent long-term complications. Many patients with pulmonary embolism are poor candidates for lytic therapy due to recent surgery or other reasons. Finally of concern is the 1–2% risk of intracranial hemorrhage which accompanies thrombolytic therapy. The vast majority of patients with pulmonary embolism who survive long enough to be diagnosed will survive their thrombosis. Therefore only a small number of patients would benefit from thrombolytic therapy. However, for the patient in extremis due to a pulmonary embolism who is *not* a candidate for embolectomy, fibrinolytic therapy is an option.

If thrombolytic therapy is required, the agent of choice is tPA 100 mg IV over 2 h. There is no agreement on when to start heparin – some practitioners continue it during the tPA or restart after the bolus. In the USA it is more common to wait until the aPTT is less than twice control and then restart the heparin.

There is increasing interest in catheter-directed thrombolytic therapy for pulmonary embolism. Early studies have shown this is feasible, but to date there is little clinical trial data to suggest this is superior to heparin therapy.

DVT Systemic thrombolytic therapy for deep venous thrombosis has little effect on long-term outcomes such as post-thrombotic syndrome and has little role in management of these patients. However, there is increased interest in catheter-directed thrombolytic therapy in massive deep venous thrombosis involving the common femoral or iliac system. This approach uses catheter-guided lytic therapy to recanalize the vessel. Often there are anatomical issues such as May-Thurner syndrome (compression of the left iliac vein by the right iliac artery) that can be corrected with venoplasty and stenting. Unfortunately, data from a large clinic trial show no difference in development of post-thrombotic syndrome with this approach. However, patients with very severe DVT resulting in massive edema leading to arterial compromise (phlegmasia cerulea dolens) or with disabling symptoms despite adequate anticoagulation may benefit from directed thrombolytic therapy.

Embolectomy may be useful in the small subset of patients who are in unresponsive shock. Some series claim up to 70% survival. It has been suggested that if after an hour of medical management, a patient has persistent signs of massive PE such as a systolic blood pressure of less than 90 mmHg, urine output of less than 20 ml per hour, and/or PO_2 of less than 60 mmHg, that patient is a candidate for embolectomy. This approach obviously requires the presence of a qualified cardiac surgeon.

Vena Cava Filter The role of filters in treatment of thromboembolic disease is unclear due to lack of good trials. The clearest indication for filter placement would be PE/proximal DVT in a patient in whom anticoagulant therapy is contraindicated. In patients who can receive anticoagulation, clinical trials show no benefit in survival with filters. One common use of filters is as PE prevention in patients unable to receive prophylactic anticoagulation, but this is discouraged by guidelines and may increase complications. Another group of patients who should not receive filters are

those who have recurrent thrombosis on warfarin. These patients need more aggressive anticoagulation and not another nidus for thrombosis.

Since filters do not protect against thrombosis, the patient needs to resume anticoagulation as soon as possible after filter placement. The risk of deep venous thrombosis is doubled with long-term filter placement, but this alone is not an indication for long-term anticoagulation if the patient had no other indications for long-term treatment.

Most filters placed now are removable filters which allow the filter to be taken out when the patient is back on stable anticoagulation. Unfortunately, many of these filters do not get removed; this can result in filter migration or breakage of the filter and strut embolization. All patients in whom a removable filter is placed need to have a plan for filter removal. Filters can be removed years after placement.

Compression stockings' role in DVT therapy is uncertain – studies have been inconsistent as to whether stockings prevent post-thrombotic syndrome. Some patients do derive relief from stockings so a trial of knee high stockings 30–40 mmHg at the ankle is always worthwhile.

Bed Rest Multiple studies have shown no benefit to bed rest and, in fact, demonstrate a trend for better outcomes the more active the patient with DVT is. Patients with DVT should ambulate as tolerated and be encouraged to exercise.

Home Therapy of PE There is now abundant data that patients at low risk of complications from a PE can be treated at home. There is a scoring system for PE that allows determination of risk of thrombosis (PESI – Table 15.4) with trial data showing patients in Classes I and II (score < 86) can be treated at home. Alternatively, patients who are not hypoxic, have normal blood pressure, and are not at risk of bleeding may be eligible for home treatment.

Table 15.4 PESI score

Add +1: Each year of age
Add +10: Male gender
Add +30: Cancer – active or past history
Add +10: Heart failure
Add +10: Chronic lung disease
Add +20: Heart rate > 110 bpm
Add +30: Systolic blood pressure < 100 mmHg
Add +20: Respiratory rate > 30 bpm
Add +20: Temperature < 36 C
Add +60: Altered mental status
Add +20: Oxygen saturation < 90%
Interpretation: Mortality at 30 days
Score < 65: Class I – Very low mortality risk (0–1.6%)
Score 66–85: Class II – Low mortality risk (1.7–3.5%)
Score 86–105: Class III – Moderate mortality risk (3.2–7.1%)
Score 106–125: Class IV – High mortality risk (4.0–11.4%)
Score > 125: Class V – Very high mortality risk (10.0–24.5%)

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Anticoagulant Treatment of Venous Thromboembolism

There are now multiple options for treatment of DVT and PE with direct oral anticoagulants (DOACs) being recommended as first line in eligible patients.

Unfractionated Heparin

Standard heparin is fading from use – and is not recommended first-line therapy – due to its unfavorable pharmacokinetics and the demonstration of better outcomes with low molecular weight heparin (LMWH). If used, the absolute key in standard heparin use is to give enough. The standard bolus should be 5000 units (10,000 units for larger thrombi or pulmonary embolism). The initial drip should be 1400 units/h. The aPTT or heparin level should be checked 6 h after the bolus and the drip adjusted accordingly. A supratherapeutic aPTT/heparin level may just reflect

the bolus. The drip should never be turned down until two consecutive aPTTs are supratherapeutic. If aPTTs are used to monitor heparin, the laboratory's aPTT must be standardized with heparin levels to determine the proper therapeutic range since the therapeutic range varies with different aPTT reagents. One must be very aggressive in rapidly achieving the proper aPTT when giving heparin. Patients should be on heparin for at least 5 days and have at least 24 h on both heparin and warfarin (in patients started on warfarin) once the INR is greater than 2.

Low Molecular Weight Heparin

The use of low molecular weight heparin (LMWH) for therapy in DVT/PE treatment is recommended because it is both safer and more effective than the use of standard heparin. As noted above, evidence is also clear that stable patients with DVT/PE can be treated at home with LMW heparin. For short courses of therapy, most patients do not need to have LMW heparin levels drawn. Patients who are very obese (greater than two times ideal body weight), pregnant, those with severe liver or heart failure, or those on long-term heparin therapy should have levels performed. Since LMWH is renally cleared, in patients with renal failure, dosing should be once per day. Levels are drawn 4 h after injection and the therapeutic range is 0.7–1.2 anti-Xa units. Like standard heparin, DVT/PE patients need at least 5 days of LMWH for acute thrombosis.

LMWH Options:

- Dalteparin 100 units/kg bid or 200 units/kg daily
- Enoxaparin 1 mg/kg bid or 1.5mg/kg daily (patients with low thrombotic burden)
- Tinzaparin 175 units/kg daily

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin (like heparin). Due to the nature of fondaparinux binding to antithrombin, mainly factor Xa is inhibited. This agent is approved for therapy of DVT and PE. Dosing is 7.5 mg daily – rising to 10 mg in patients who weigh more than 100 kg. Fondaparinux has a half-life of 17–21 h and has high renal clearance so it should not be used in patients with renal disease.

Warfarin

Warfarin is started in the evening with a loading dose of 2.5–10 mg orally. Five milli gram is recommended in most patients. Young (under age 60) healthy patients will need a 10 mg loading dose, while the frail elderly (over age 85) should start with 2.5 mg. Warfarin is titrated to an INR of 2–3. Use of warfarin affects all the vitamin K-dependent proteins. Factor VII falls first, resulting in prolongation of the INR. However, the full antithrombotic effect of warfarin does not occur until factors X and II have fallen. This decrement will take an additional 24 t hours after factor VII levels fall. This explains why patients should overlap heparin and warfarin therapy for 24 h.

Direct Oral Anticoagulants

Four of the new direct oral anticoagulants have been studied as treatment for DVT/PE; all are equal to LMWH/warfarin in effectiveness, and the Xa inhibitors are safer.

In clinical trials, dabigatran and edoxaban were started after heparin therapy, but rivaroxaban and apixaban were started promptly at diagnosis without heparin – but both at initially higher doses. All of these agents are easier to use as they do not require INR monitoring and have no food and few drug interactions.

Direct Oral Anticoagulant Options (See Chapter for More Details).

- Apixaban 10 mg bid × 1 week, then 5 mg bid
- Dabigatran 150 mg bid – started 5 days after LMWH therapy
- Edoxaban 60 mg daily – started 5 days after LMWH therapy
- Rivaroxaban 15 mg bid × 3 weeks, then 20 mg daily.

Special Situations

In Patients with Cancer

Studies had shown that warfarin was inferior to LMWH in patients with cancer so LMWH has previously been recommended as first-line therapy. Clinical trials have shown DOACs to be just as effective to even more effective as LMWH in cancer patients. However, patients with upper GI cancers have a higher incidence of bleeding. One approach would be to offer DOAC to most patients, reserving LMWH for patients with upper GI cancers or other contraindications to DOAC such as mechanical cardiac valves. Patients who have recurrent thrombosis on DOAC should receive LMWH. Patients with recurrence on LMWH should have their dose increased by 20–25%.

In the Pregnant Patient

This is discussed in Chap. 28.

Calf and Muscular Vein Thrombosis

Patients with calf vein thrombosis are at risk for clot extension to proximal veins and subsequent pulmonary embolism. These patients – if safe to anticoagulate – should be anticoagulated for 12 weeks. Patients with calf vein thrombosis at high risk for bleeding on anticoagulation should be observed with serial ultrasounds. Patients with thrombosis in the muscular veins of the calf (soleus, gastrocnemius) can be treated with just 10 days of therapeutic LMWH or simply observed with serial ultrasounds if at high risk of bleeding with anticoagulant therapy.

Superficial Venous Thrombosis

Some superficial venous thrombosis can be treated with heat and anti-inflammatory agents. However, many patients – especially those with greater saphenous vein thrombosis – will go on to have thrombosis of the deep system. Many anticoagulation options exist to treat superficial venous thrombosis; common to all is the fact that prophylactic dosage of LMWH or fondaparinux is sufficient, and treatment duration can range from 12 to 42 days. One approach to treatment is for patients with superficial venous thrombosis over 5 cm or in the greater saphenous vein to be treated for at least 12–14 days with prophylactic-dose LMWH or fondaparinux. If still symptomatic, this treatment can be extended until resolution of symptoms.

"Incidental PE"

Pulmonary emboli may be found in patients receiving CT scans for other reasons. It is clear that in cancer patients, these PEs have the same negative prognostic implications as symptomatic PE and need to be treated aggressively. For other patients, the clinical situation needs to be assessed, but until data prove otherwise, all patients with incidental PE should receive antithrombotic therapy.

Subsegmental PE

The incidence of subsegmental PE has increased with high-resolution CT scans, and there is much controversy about therapy. Some retrospective data indicated a more benign outcome, but prospective studies showed the same natural history as more proximal PE. The diagnosis of subsegmental PE can be reduced by following diagnostic pathways (clinical predication rules, etc.) which allows for CTA only on a higher-risk population. There is a clinical trial underway, but until results of this are available, patients with subsegmental PE should receive the same therapy as any other patient with PE.

Duration of Therapy (Table 15.5)

The key questions to consider when determining duration of therapy are as follows: (1) what was

Table 15.5 Duration of treatment

Superficial venous thrombosis: 10–12-day course of prophylactic-dose LMWH or fondaparinux – repeat if still symptomatic
Muscular calf vein (soleus or gastrocnemius) thrombosis: 10 days of LMWH
Calf vein thrombosis: 12 weeks of therapy
Provoked first DVT or PE: 3 months
Provoking factors: trauma, surgery, bed rest >72 h, pregnancy, estrogen, very long (>10 h) plane flights
Idiopathic first DVT or PE: 3 months of therapy and then strongly consider indefinite therapy for most patients due to high risk of recurrence
Two or more lower extremity proximal DVT or PE: Indefinite anticoagulation
DVT or PE during pregnancy: Duration – the entire course of pregnancy and at least 6 weeks after delivery – total should be at least 3 months. Can use LMWH or warfarin with breastfeeding
Cancer
Use of DOAC or LMWH long-term should be considered especially with lung cancer or pancreatic cancer. Long-term LMWH is mandatory for warfarin/DOAC failures

the location of the thrombosis, (2) what were the circumstances of the thrombosis, and (3) are there any underlying hypercoagulable states?

Patients with thrombosis in unusual sites such as hepatic vein thrombosis or portal vein thrombosis should be indefinitely anticoagulated. An exception would be if there was a clear provoking factor such as an abdominal abscess leading to portal vein thrombosis. In these cases 3 months of therapy would be prudent. Also, as discussed in the next chapter, upper extremity thrombosis needs only limited therapy.

An important factor in determining risk of recurrence is assessing whether the thrombosis was idiopathic or provoked. Most studies indicate that, for a patient to be considered to have an idiopathic thrombosis, they should not have cancer, not have undergone surgery or had trauma in the previous 6 weeks, not be at bed rest, not be pregnant, or not have a major hypercoagulable state. Patients with idiopathic venous thrombosis are at substantial risk of recurrence with a risk that may be as high as 30% in the next 5 years. Many studies have indicated that long-term anticoagulation therapy is of benefit in these patients in preventing recurrent thrombosis. Patients with idiopathic thrombosis, especially large thrombosis or pulmonary embolism, should be considered for indefinite anticoagulation. Trial data does show that warfarin at an INR of 2–3 is just as safe as and more effective than INR 1.5–2; therefore, INR of 2–3 should be the therapeutic range if warfarin is used. Studies have shown low-dose apixaban (2.5 mg bid) or rivaroxaban (10 mg) to be just as effective as standard doses when used for long-term anticoagulation 6–12 months after the initial thrombosis.

There are some data showing that checking a D-dimer 3 weeks after the patient has completed a course of therapy may help predict risk of recurrence. A patient who has a positive D-dimer 3 weeks off anticoagulation has an approximately 10% per year chance of recurrence. The problem is that a negative D-dimer still indicates a 3–5% per year risk of recurrence – which is higher than the risk of anticoagulation in most patients. The high recurrence rate even in low-risk patients plagues other prediction rules; currently the history of provoked vs idiopathic thrombosis remains most predictive of recurrence.

Patients with a provoked first proximal DVT or PE need only 3 months of treatment if the provocation has resolved. Patients who have two or more recurrences need to be treated indefinitely.

As discussed in Chap. 17, patients with inherited hypercoagulable states are at increased risk of first thrombosis but not recurrence. Therefore, the finding of factor V Leiden, etc. does not mandate indefinite therapy.

Prophylaxis of Venous Thromboembolic Disease

Overview

Etiology of Surgical Hypercoagulable States

The etiology of the surgically induced hypercoagulable state is complex. Certainly venous stasis during and after the operation is important. The surgery-induced inflammatory state will cause procoagulant changes in the blood and

vessel endothelium. Direct venous trauma in orthopedic and pelvic surgery plays a role. Patients with a pre-existing hypercoagulable state (acquired or inherited), previous venous thrombosis, heart failure, malignancy, or estrogen use are at higher risk for thromboembolic disease in the operative period. Smokers have an increased risk as well.

The Need for Deep Venous Thrombosis Prophylaxis in Surgery

The first sign of thrombosis in 10–30% of patients is sudden death. The clinical signs of deep venous thrombosis tend to be unreliable. In most large screening studies, only 10–20% of patients with deep venous thrombosis are symptomatic. Prevention is crucial, not only to prevent DVT/PE but because up to 90% of patients with deep venous thrombosis will experience post-phlebitic syndrome. This included patients with asymptomatic thrombosis. Finally, it is better to prevent deep venous thrombosis since treatment in the postoperative period is associated with a higher risk of bleeding. Numerous studies have shown deep venous thrombosis prophylaxis to be medically sound as well as cost-effective. Failure of surgeons to use deep venous thrombosis prophylaxis is the largest cause of preventable operative death in the USA.

Who Is at Risk of Thrombosis?

Low-Risk Patients

- Patients under 40 with no other risk factors (including *negative* family history of deep venous thrombosis)
- Procedures lasting less than 30 min

Medium-Risk Patients

- Patients over 40 years of age with no other risk factors undergoing operations over 30 min long.

High-Risk Patients

- Previous history of venous thrombosis (or strong family history).
- Pelvic or abdominal surgery for malignancy. Lower limb orthopedic surgery.

Very High-Risk Patients

- Lower limb trauma and surgery.
- Surgery in patients with other risk factors – previous thromboembolic disease or cancer.

The Prophylactic Regimens

Intermittent Pneumatic Compression Mechanical means of preventing deep venous thrombosis by squeezing calves. Compression also stimulates fibrinolysis. Disadvantages of compression include patient discomfort, noncompliance, and risk of mechanical breakdown. Compression is effective for prevention of thrombosis in medium- and some high-risk patients.

Subcutaneous Heparin The standard (5000 units B-TID) prophylactic regimen. The dose is started 2–8 h before surgery and given until the patient is ambulatory. Low-dose heparin is effective in medium- but not high-risk patients. Bleeding increases from 3.8% in placebo patients to 5.9% in patients receiving heparin when all studies are considered, but this is far outweighed by prevention of both thrombosis and death.

Aspirin Studies using aspirin have not consistently shown that aspirin prevents deep venous thromboses, but it does lead to wound hematoma in 1 in 50 patients. Unlike heparin and warfarin, aspirin's antithrombotic effects are not reversible. Of additional concern is aspirin's gastrointestinal toxicity and prolonged inhibition of platelet function. Aspirin may be effective in thrombosis prevention when given after a 5-day course of LMWH or DOAC in hip and knee replacement patients.

Warfarin There are several regimens for warfarin in the literature. The "two-step" approach gives low doses of warfarin for 1–2 weeks before the operation to raise PT to 1.5–3 (INR 1.5) seconds above control. Post-op the warfarin dose is increased to raise the INR to 2–3. This approach is particularly effective in preventing deep venous thrombosis after elective hip or knee replacement. The other approach is to give

5 mg of warfarin daily starting immediately after surgery (or in some studies the night before) to achieve an INR of 2.0–3.0 as soon as possible after surgery. Anticoagulation is continued for 3–6 weeks. This was effective in reducing deep venous thrombosis after surgery for hip fractures. The prothrombin INR should be followed to monitor the patient's status and prevent overshooting of the INR. Rates of bleeding are as high as 30%, but most bleeding is seen in patients who are over-anticoagulated. In more recent studies, where therapy was closely monitored, significant post-op bleeding was not a problem.

Low molecular weight heparin is equal to or better than warfarin and subcutaneous heparin for high-risk patients. Low molecular weight heparin can also be given once a day in lower-risk patients and has a lower incidence of heparin-induced thrombocytopenia. Currently, for high-risk patients, LMWH is the standard to which the new anticoagulants are compared.

Fondaparinux is also effective in thrombosis prevention in high-risk patients. It is renally cleared and should not be used in patients with renal insufficiency. Also, given the fixed dose (2.5 mg), it should not be used in patients weighing less than 50 kilograms.

Direct Oral Anticoagulants All of the direct oral anticoagulants have been shown to be effective in thrombosis prevention in knee and hip replacement surgery. They have the benefit of being oral and less expensive than LMWH or fondaparinux.

The Situations

Low-Risk Patients

Patients under 40 and with no other risk factors (including a *negative* family history of deep venous thrombosis) or patients undergoing procedures less than 30 min long do not need prophylaxis.

Medium-Risk Patients

Patients over 40 years of age undergoing operations over 30 min long and with no other risk factors should receive low-dose heparin. Heparin, 5000 units TID, is started 2–8 h before surgery and given until the patient is ambulatory. Compression stockings, LMWH, and fondaparinux are also effective. LMWH or fondaparinux should be considered in patients undergoing surgery for abdominal cancers given their high risk of thrombosis.

High-Risk (Non-orthopedic) Patients

Previous history of venous thrombosis (or strong family history of thrombosis) or pelvic or abdominal surgery for malignancy puts a patient in a high-risk category. Low-dose heparin has been shown to be less effective in patients with previous thrombosis and malignancies (especially gynecological). In patients with a thrombotic history, use of LMWH or fondaparinux is effective. Pneumatic booties have been shown to be effective in patients with gynecological malignancies. Patients with very recent deep venous thrombosis who are ill and who absolutely need surgery require LMWH/fondaparinux along with consideration of an IVC filter.

Knee Surgery

High incidence of calf vein deep venous thrombosis (60%) but low incidence of pulmonary embolism accompanies knee surgery. LMW heparins, fondaparinux, and direct oral anticoagulants have been shown to be the most effective for deep venous thrombosis prevention. There is a high incidence of pulmonary embolism in bilateral knee surgery.

Elective Hip Surgery

In patients undergoing elective hip surgery, there is a high incidence of deep venous thrombosis

(50%), pulmonary embolism (11%), and fatal pulmonary embolism (2%). Low-dose heparin and aspirin are not effective in this situation. Although pneumatic booties are effective for prophylaxis, they have been recently shown to be inferior to two-step warfarin therapy. Effective in *all* patients are one of the warfarin regimens, LMW heparin, fondaparinux, or the direct oral anticoagulants. Prophylaxis should be started 24 h after surgery.

Hip Fractures

This is the highest-risk situation. Risk of deep venous thrombosis is 50–80%; risk of pulmonary embolism is 11–20%; and risk of fatal pulmonary embolism is 5–7%. Again, low-dose heparin and aspirin are *not* effective in this situation. Warfarin has been studied for over 30 years and had been found to be effective in reducing the risk of pulmonary embolism from 5–7% to 1%. Thus, for every two to six patients who have a wound hematoma, one patient's life will be saved. LMW heparin and fondaparinux are also very effective in these patients. There is currently no data at this time for the use of direct oral anticoagulants. The situation of the hip fracture patient is complicated by the fact that as many as 10% of patients have deep venous thrombosis before any hip surgery.

Trauma

These patients are at high risk not only for thromboembolic complications but also for bleeding. Once patients are stable (and if they do not have intracranial hemorrhage), enoxaparin 30 mg every 12 h should be used. Patients with spinal cord injury are at high risk for thrombosis and should receive low molecular weight heparin.

Neurosurgery

Patients are at risk for thrombosis, but until recently pharmacologic prophylaxis was not used due to fear of bleeding. However, studies indicate that enoxaparin 40 mg/day was more effective than pneumatic stockings with no associated higher incidence of bleeding. Patients undergoing neurosurgery for brain tumors are at particular risk of thrombosis and should receive LMW heparin.

Medical Patients

Medical patients are at risk for deep venous thrombosis. The range is from 20% in patients with heart failure or pneumonia to as high as 80% in stroke patients. The risk of deep venous thrombosis is increased in patients who smoke and have heart failure, cancer, and previous venous thrombosis. Studies involving thousands of medical patients have shown that low-dose heparin is effective for prophylaxis of venous thrombosis. It reduces deep venous thrombosis by 66%, pulmonary embolism by 50%, and fatal pulmonary embolism by 0.5%. Pneumatic booties may also be effective in these situations. Recent clinical trials have shown that LMW heparins are equal or superior to standard heparin for prophylaxis of the high-risk medical patient.

Patients over 40 and those with serious illnesses, especially heart failure and pneumonia, benefit from low-dose heparin. ICU patients should receive LMWH due to the high incidence of deep venous thrombosis in this population. Patients with strokes are at high risk for deep venous thrombosis, and consideration should be given to pneumatic booties plus low-dose heparin or LMW heparin.

Several studies have looked at DOACs for extended prophylaxis when patients leave the hospital, but reduction in thrombosis is offset by the increased risk of bleeding.

In Pregnancy

Most experience is with enoxaparin 40 mg every day or with dalteparin 5000 units every 12–24 h. See Chap. 28 for more details.

Suggested Reading

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