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A vast array of information is available to surgeons to aid in the prevention and management of venous thromboembolism (VTE) [1–4], and readers are encouraged to use these and other sources and to stay abreast of the ever-changing body of knowledge related to these conditions. VTE includes deep vein thrombophlebitis (DVT) and pulmonary embolism (PE), and an appreciation of the clotting cascade can serve as a foundation for understanding clot formation and its prevention and treatment (Fig. 2.1). It is also important for foot and ankle surgeons to maintain a high index of suspicion for VTE, since the condition is prevalent and potentially deadly, and even when it is identified and properly treated, the sequelae of post-thrombotic syndrome (PTS) (Fig. 2.2a–d), which occurs in approximately 30% of VTE patients [5], and chronic pulmonary thromboembolic hypertension (CPTH), which occurs in approximately 4% of PE patients [6], are debilitating. PTS is associated with profound lower extremity edema, chronic stasis dermatitis, and cutaneous ulceration in 5–10% patients that suffer with lower extremity DVT. Still further, it has been estimated that 45,000–75,000 patients in the United States die annually as a result of PE [7], whereas <10% of patients with PE die if timely treatment is administered [8].

VTE develops in response to a mixture of acquired and hereditary exposures that promote hypercoagulability or thrombophilia. Virchow's classic triad of venous stasis, damage to the vein wall, and activation of the clotting cascade serve as the foundation for venous thrombosis. Clots that develop in veins are composed primarily of red and white blood cells combined with platelets and fibrin and are particularly prone to localize in the stagnant blood in the perivalvular segments of the veins of the lower extremity. Venous thrombi that remain fixed in the calf or thigh veins eventually undergo thrombolysis and recanalization, whereas those

that break free can migrate with the return of venous blood to the pulmonary arteries where they occlude blood flow to the lungs. Unfortunately, VTE can be difficult to identify, and it can be recurrent. Almost 90% of VTE occur in the lower extremities, and the more proximal the site of VTE in the lower extremity, the greater is the risk of PE. In fact, VTE occurring in the femoral or popliteal veins is associated with a 50% risk of PE if left untreated, whereas the risk of PE is approximately 20–25% for VTE localized to the calf, and, overall, about 15–30% of lower extremity VTE result in PE [9]. PE, in turn, demands compensatory right ventricle inotropism in order to force the blood through the occluded pulmonary artery, which leads to pulmonary artery hypertension and subsequent right heart failure, especially in patients with preexisting cardiac and/or lung disease.

The prevalence of VTE has been estimated to be approximately one million cases per year in the United States [10], and approximately 67% of these cases occur in association with hospitalization, and about half of these patients die as a result of the disease [11]. Risk factors for VTE are present in many hospitalized patients and include comorbidities such as diabetes mellitus, hypertension, hypercholesterolemia, and cigarette smoking, as well as infection, cancer, age >75 years, obesity, and a history of previous VTE [12, 13], surgery, or trauma (Table 2.1) [14]. Following acute myocardial infarction and cerebral vascular accident, VTE is the most common cardiovascular disease [15]. Hereditary conditions, such as protein C and S and antithrombin deficiencies, factor V Leiden, and prothrombin gene mutation, also increase the likelihood of developing VTE.

Diagnosis of Venous Thromboembolism

Clinical Examination

The diagnosis of DVT and/or PE can often be made, or at least strongly suggested, based on the results of the historical review and clinical examination, and combinations of

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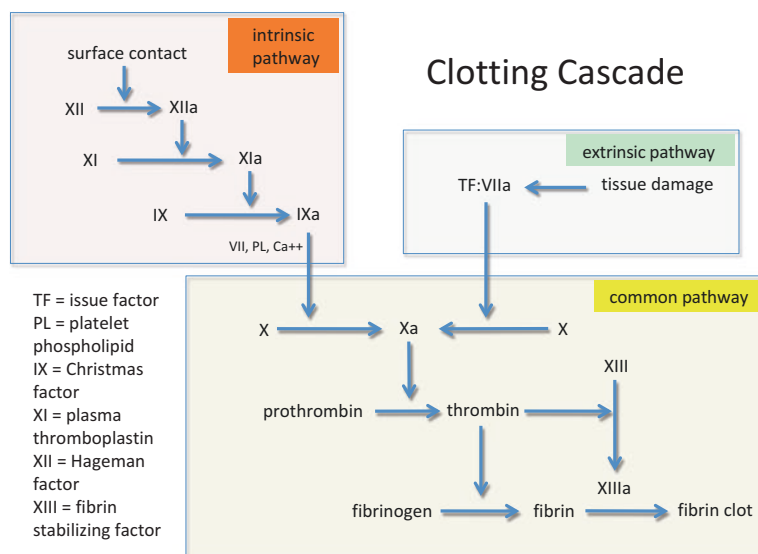
Fig. 2.1 The clotting cascade

Fig. 2.2 (a) Chronic right lateral lesser saphenous venous stasis ulcer in patient with post-thrombotic syndrome. (b) Chronic post-thrombotic stasis dermatitis and scarification right lower extremity, lateral view. (c) Chronic post-thrombotic stasis dermatitis and scarification right lower extremity, medial view (same patient as viewed in b). (d) Bilateral postphlebotic stasis dermatitis with post thrombotic syndrome



diagnostic criteria have been shown to be more or less suggestive of DVT (Table 2.2) [14, 16]. Clinically, DVT of the lower extremities is commonly associated with pain localized to, and swelling in the extremity distal to, the site

of the thrombus. The involved extremity can also be warm, with cutaneous erythema, and regional varicosities may be evident. Homan's sign, which is pain in the calf upon dorsiflexion of the ankle, is commonly thought to be evidence of

Table 2.1 Risk factors for venous thromboembolism

| | |
|------------------------|--|
| Inherited risk factors | Antithrombin deficiency |
| | Dysfibrinogenemia |
| | Elevated levels of factor VIII |
| | Factor V Leiden mutation |
| | Hyperhomocysteinemia |
| | Protein C or S deficiency |
| | Prothrombin gene mutation |
| Acquired risk factors | Air travel |
| | Antiphospholipid syndrome |
| | Body mass index >30 |
| | Cancer or certain cancer treatments |
| | Cardiovascular risk factors (smoking, hypertension, hyperlipidemia, diabetes mellitus) |
| | Heparin-induced thrombocytopenia |
| | Immobilization ^a |
| | Indwelling central venous catheter or pacemaker |
| | Inflammatory bowel disease |
| | Medical illness (heart failure, chronic obstructive pulmonary disease) |
| | Myeloproliferative disorder |
| | Pregnancy, oral contraceptive use, hormone replacement therapy |
| | Presence of an inferior vena cava filter |
| | Previous episode of venous thromboembolism |
| | Surgery ^a |
| | Trauma ^a |

^aAcquired risk factors related to most, if not all, foot and ankle surgical patients

Table 2.2 The Wells [14, 16] diagnostic criteria suggestive of deep vein thrombosis^a

| Risk factor criteria | Points |
|---|--------|
| Active cancer | 1 |
| Recently bedridden >3 days or major surgery within 4 weeks | 1 |
| Calf swelling >3 cm compared to contralateral calf measured 10 cm distal to tibial tuberosity | 1 |
| Presence of collateral non-varicose superficial veins | 1 |
| Entire ipsilateral lower extremity (leg) swollen | 1 |
| Ipsilateral tenderness localized to deep venous system | 1 |
| Pitting edema greater in the symptomatic lower extremity | 1 |
| Paralysis, paresis, or recent immobilization of symptomatic lower extremity | 1 |
| History of previously documented DVT | 1 |
| Alternative diagnosis to DVT as or more likely | -2 |

^aInterpretation: A score ≥ 2 indicates that the probability of DVT is likely, whereas a score < 2 indicates that probability of DVT is unlikely

calf DVT; however, this has been shown to be an unreliable assessment for calf DVT [17]. Multiple thrombosed deep and collateral veins in an extremity can result in a severely edematous, inflamed extremity known as phlegmasia cerulea dolens, which can be limb threatening due to ischemia, and may be associated with prothrombotic disorders such as heparin-induced thrombocytopenia (HIT), myeloproliferative disease,

factor V Leiden mutation, polycythemia vera, and paroxysmal nocturnal hemoglobinuria (PNH). As for PE, signs and symptoms include chest pain; tachypnea and dyspnea, along with a sense of impending doom; tachycardia; hyperpyrexia; cough; hemoptysis; syncope; and, frequently, evidence of an associated DVT. Unfortunately, DVT can be clinically silent until the clinical signs of PE become evident.

Diagnostic Laboratory Tests for Venous Thromboembolism

Coagulation Tests

The *partial thromboplastin time* (PTT) is a reliable coagulation screening test, although it may not be sensitive enough to detect subtle coagulopathies. The PTT is also used to monitor heparin anticoagulation therapy, although it is not suitable for monitoring factor VII or platelet factors. The normal range for the PTT is 25–35 s, and it remains normal in von Willebrand's disease, platelet dysfunction, and thrombocytopenia. The PTT is prolonged by defects in clotting factors I, II, V, VIII, IX, X, XI, and XII. The *prothrombin time* (PT) can be used to monitor long-term warfarin anticoagulation therapy. The normal range for the PT is 11–16 s, and it is prolonged with defects in factors I, II, V, VII, and X, as well as in vitamin K deficiency, fat malabsorption (steatorrhea, colitis, jaundice), salicylate or warfarin therapy, and advanced hepatic disease. The *bleeding time* is a simple clinical examination used to assess the overall ability to stop bleeding following a cutaneous prick, and it is particularly sensitive to platelet defects. The normal range (Duke) for the bleeding time is 1–4 minutes, and it is prolonged in thrombocytopenia, abnormal platelet function, and von Willebrand's disease. The *clotting time* is a nonspecific, in vitro screening test used to determine the presence of a major clotting deficiency. The normal range (Lee-White) clotting time is 3–6 min in a capillary tube and 6–17 min in a test tube. The *international normalized ratio* (INR) is a test that was established by the World Health Organization (WHO) and the International Committee on Thrombosis and Hemostasis so that the results of blood clotting tests could be reported by any lab by virtue of the fact that all of the results are standardized with the international sensitivity index for the particular thromboplastin reagent and instrument combination used to perform the test. For warfarin, the usual optimal therapeutic prothrombin time is INR = 2–3.

Platelet Count

The normal range for the *platelet count* is 140,000–340,000/mm³, and platelets are commonly diminished in pregnancy, leukemia, myelodysplasia, hepatic cirrhosis, aplastic anemia, iron deficiency, vitamin B12 deficiency, HIV/AIDS, Epstein-Barr virus infection, chicken pox, and various toxicities (chemotherapy, alcohol, radiation, other chemicals),

hypersplenism, autoimmune diseases, septicemia, idiopathic or thrombotic thrombocytopenic purpura, hemolytic uremia, and disseminated intravascular coagulation. Thrombocytosis, which can predispose to VTE, can be caused by acute hemorrhage and blood loss, surgery, trauma, burn wounds, allergic reactions, cancer, chronic kidney disease, exercise, myocardial infarction, coronary artery bypass, infection, iron deficiency, vitamin deficiency, splenectomy, hemolysis, systemic inflammatory disease (rheumatoid arthritis, inflammatory bowel disease, celiac disease), pancreatitis, and certain medications, including epinephrine, tretinoin, vincristine sulfate, and heparin sodium.

D-Dimer Test

As a result of fibrinolysis, some of the fibrin in a thrombus degrades to form the D-dimer protein, which consists of two cross-linked D fragments of fibrin and which is elevated in the blood in the presence of VTE, rheumatoid arthritis with elevated rheumatoid factor, myeloproliferative disorders, infection, hemorrhage, trauma, and surgery. So, the D-dimer assay is not very specific for VTE, since it is also elevated in several other conditions; nonetheless, when combined with a symptomatic leg and even more so a symptomatic leg and venous Doppler ultrasound imaging of the involved extremity, elevation of the D-dimer can be very specific. The normal value for D-dimer units is ≤ 250 ng/mL or ≤ 0.5 mcg/mL fibrinogen equivalent units. As a rule, patient with a low pre-test probability of DVT or PE with a negative D-dimer test should undergo further testing, typically imaging evaluation, if VTE is still suspected.

Imaging Studies for Venous Thromboembolism

Duplex Doppler Ultrasound (DDUS)

Duplex Doppler ultrasound (DDUS) imaging of the lower extremity veins is the mainstay diagnostic imaging examination used to identify lower extremity DVT. DDUS is noninvasive, usually readily available and, in comparison to other imaging modalities, relatively inexpensive in terms of the crude cost of the study. Venous DDUS is highly sensitive (95%) and specific (98%) for the diagnosis of DVT in the symptomatic lower extremity, although it is less sensitive in the asymptomatic extremity and in very obese patients [18, 19].

Other Venographic Methods

Contrast, magnetic resonance, and computerized axial tomographic venography can also be used to identify DVT in the lower extremity. The routine use of contrast venography has dwindled over the past 20–30 years, due to the potentially hazardous nature of invasive contrast media (nephrotoxicity), limitations related to inadequate deep vein filling with the

contrast dye, and the steady improvement and availability of noninvasive magnetic resonance venography (MRV) and computerized axial tomographic venography (CATV).

Diagnostic Tests for Pulmonary Embolism

When PE is suspected, either with or without a prior diagnosis of DVT, a number of diagnostic laboratory, imaging, and functional tests can be helpful. As previously mentioned above, elevation of the D-dimer units present in the blood can be suggestive of VTE and is most useful in terms of specificity. Hypoxia secondary to diminished pulmonary perfusion related to PE results in an arterial blood gas with a $\text{PaO}_2 \leq 80$ mmHg in about 84% of patients with confirmed PE and no previous cardiopulmonary disease [20]. Measured levels of urine prothrombin fragment F1 + 2 can also potentially be used to assess the individual risk of vascular thrombotic complications, including VTE, following total hip arthroplasty and to test for noninvasive detection of sustained coagulation activation [21]. Right heart failure secondary to PE and pulmonary artery hypertension can also lead to elevation of cardiac troponin, as well as elevation of brain natriuretic peptide in patients without renal failure [22]. Radiographic images of the chest might reveal nonspecific signs of atelectasis, consolidation, and pleural effusion, in association with PE; electrocardiography might reveal several findings commonly associated with PE, including the $\text{S}_1\text{Q}_3\text{T}_3$ waveform pattern [23]; and transthoracic as well as transesophageal echocardiography can reveal evidence of right heart failure as a result of PE. The use of a ventilation-perfusion (V-Q) scan, where radiopharmaceutical (a gamma ray emitting xenon or technetium compound) is injected and lung ventilation and perfusion monitored, can be helpful in cases where contrast medium cannot be administered due to allergy or kidney disease or in certain obese or pregnant patients, and it is strongly suggestive of PE when it is abnormal and observed in conjunction with strongly indicative clinical findings. Pulmonary angiography, by means of contrast medium injection or magnetic resonance angiography (MRA), can also be useful, although computerized tomographic pulmonary angiography with contrast, while being expensive and invasive in terms of contrast medium and radiation exposure, has been shown to be more sensitive for PE than VQ scanning [24] and may be more sensitive and more specific than classic contrast pulmonary angiography [25].

Methods of VTE Prophylaxis and Treatment

Patient Education, Mechanical Prophylaxis, and Non-general Anesthesia

Prevention of VTE is a worthwhile and potentially lifesaving endeavor. The basic elements of VTE prophylaxis include patient education, mechanical methods that promote venous blood flow in the extremities, chemoprophylactic measures

that inhibit thrombus formation, and variations in anesthesia and fluid management. Nurses [26] and surgeons, as well as house and office staff, can play an important role in teaching patients the basic physiology and warning signs of VTE, both DVT and PE, and this can go a long way in regard to compliance with prophylactic measures and even early diagnosis should a complication develop. As a rule, combined prophylactic modalities decrease significantly the incidence of VTE, in particular DVT [27]. Of course, lower extremity movement, in particular ambulation with active contraction and relaxation of the crural musculature and resultant knee and ankle motion, is an important deterrent to VTE. In fact, most VTE prophylaxis protocols in otherwise healthy individuals are discontinued once regular knee and ankle motions are resumed following foot and ankle surgery. When lower extremity range of motion cannot be implemented, such as when complete bed rest is a required element of treatment or when the extremity is immobilized, then graduated compression stockings (GCS), and intermittent pneumatic compression (IPC) devices on one or both extremities can be employed (Fig. 2.3). A 2010 review of the literature pertaining to the use of GCS revealed that their use reduced the incidence of DVT from 26% to 13% ($p < 0.0001$) in comparison to patients treated without GCS [28]. IPC devices applied to any extremity can also provide beneficial fibrinolytic activity, as evidenced by elevated blood-borne fibrinolytic activity in assays procured from sites distant to the location of the IPC device [29, 30], and this could be particularly useful to foot and ankle surgical patients when both lower extremities have to be in the surgical field [31]. In general, when foot and/or ankle surgery is undertaken on one lower extremity, an IPC device is typically applied to the contralateral lower extremity during the operative procedure and throughout the course of hospitalization.

In regard to anesthesia and its potential adverse influence on venous stasis and the development of VTE, it is generally considered favorable to avoid cessation of the calf muscle pump influence on venous return from the lower extremities, and, therefore, avoidance of skeletal muscle paralysis and general anesthesia, when possible, is likely to decrease the risk of DVT [32–35]. In fact, the American Association of Plastic Surgeons has recommended that when possible, the use of non-general anesthesia, such as monitored anesthesia care, local anesthesia with sedation, or neuraxial anesthesia instead of general anesthesia, should be used in order to diminish the risk of VTE [31].

Pharmacological Prophylaxis (Chemoprophylaxis) and Treatment of VTE

Naturally occurring, physiologic anticoagulants such as antithrombin III and activated protein C prevent widespread thrombosis and localize clot formation to sites of vascular



Fig. 2.3 Intermittent pneumatic compression (IPC) device on the left lower extremity of a patient about to undergo right foot surgery

injury. The clotting cascade is also balanced by plasmin-mediated fibrinolysis, resulting in the formation of D-dimers and other fibrin degradation products. When the body's intrinsic anticoagulation system requires bolstering to prevent or treat VTE complicating surgery or medical care, a wide range of therapeutic agents are available (Table 2.3), including unfractionated heparin (UFH), which is typically administered subcutaneously (SC) or via intravenous (IV) infusion; low-molecular-weight (fractionated) heparins (LMWHs), which are administered via subcutaneous injection or IV infusion and include agents such as enoxaparin, dalteparin, and tinzaparin; vitamin K antagonists like warfarin, which can be administered orally or via IV infusion; factor Xa inhibitors, which are administered via subcutaneous injection or IV infusion and include agents such as fondaparinux, rivaroxaban, apixaban, and edoxaban; direct thrombin inhibitors like dabigatran, which can be administered orally; and combined factor Xa and thrombin inhibitors like danaparoid, which can be administered via subcutaneous injection or IV infusion. The decision to choose one anticoagulant over another varies by indication and patient-specific factors, and surgeons are always encouraged to use their clinical judgment in order to tailor evidence-based guidelines for VTE prophylaxis or treatment to the particular needs of their individual patients. Useful guidelines for VTE prophylaxis and treatment are available, and readers are encouraged to review these [31, 36–38]. Surgeons are also encouraged to read the clinical pharmacology

Table 2.3 Anticoagulants used for venous thromboembolism prophylaxis and treatment

| Category | Agent | Prophylaxis ^{a, b} | Treatment ^a |
|---|--------------|---|---|
| Unfractionated heparin (UFH) | Heparin | 5000 units SC 2 h preoperative | 80 u/kg bolus followed by 18 u/kg/hr IV infusion, or initial IV bolus of 5000, followed by 17,500 u SC twice daily |
| Low-molecular-weight heparin (LMWH) | Enoxaparin | 40 mg SC 2 h preoperative | 1.5 mg/kg/day SC once daily or 1 mg/kg SC every 12 h |
| | Dalteparin | 2500 u SC starting 4–8 h after surgery, then 5000 u daily; or 2500 u SC starting 2 h preoperative, then 2500 u SC 4–8 h postoperative on the day of surgery, then 5000 u SC daily; or, 5000 u SC 10–14 h presurgery, then 5000 u SC 4–8 h postoperative on the day of surgery, then 5000 u SC daily | 200 u/kg SC daily or 100 u/kg SC every 12 h |
| | Tinzaparin | 50–75 u/kg 2 h preoperative, then 50 u/kg daily for 7–10 days, or 75 u/kg daily postoperative for 7–10 days | 175 units/kg SC for 6–7 days |
| Factor Xa inhibitor | Fondaparinux | 2.5 mg SC once daily starting 6–8 h postoperative, for 5–32 days after surgery | 5 mg (body weight < 50 kg), 7.5 mg (body weight 50–100 kg), or 10 mg (body weight > 100 kg) SC once daily for 5 days and until a therapeutic oral anticoagulant effect is established |
| | Rivaroxaban | 10 mg orally once daily with or without food | The 15 mg and 20 mg tablets are taken with food, whereas the 10 mg tablets can be taken with or without food. For the treatment of DVT, PE, and reduction in the risk of recurrence of DVT and of PE, 15 mg orally twice daily for the first 21 days for the initial treatment of acute DVT or PE. After the initial treatment period, 20 mg orally once daily with food for the remaining treatment |
| | Apixaban | 2.5 mg orally twice daily | 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily, for treatment of DVT and PE, or 2.5 mg taken orally twice daily for reduction in the risk of recurrent DVT and PE following initial therapy |
| | Edoxaban | Not indicated for prophylaxis | 60 mg once daily or, if creatinine clearance, 15–50 mL/min or body weight less than or equal to 60 kg or who use certain <i>P</i> -glycoprotein inhibitors, 30 mg once daily |
| | | | |
| Direct thrombin inhibitor | Dabigatran | For patients with creatinine clearance >30 mL/min, 110 mg orally first day, then 220 mg once daily | For patients with creatinine clearance >30 mL/min, 150 mg orally, twice daily after 5–10 days of parenteral anticoagulation and for reduction in the risk of recurrence of DVT and PE for patients with creatinine clearance >30 mL/min, 150 mg orally twice daily after previous treatment |
| Combined factor Xa, heparinoid thrombin inhibitor | Danaparoid | For nonvascular surgery, if ≤90 kg, 750 u SC 1–4 h preoperative repeated ≥6 h postoperative then 750 u SC twice daily for 7–10 days starting the first postoperative day; and if >90 kg, then 750 u SC 1–4 h preoperative repeated ≥6 h postoperative then 1250 u SC twice daily or 750 u SC three times daily for 7–10 days starting the first postoperative day. In patients with current HIT, body weight ≤ 90 kg, 750 u SC two or three times daily for 7–10 days, following initial IV bolus of 1250 u SC; if >90 kg, then 1250 u SC two or three times daily for 7–10 days after an initial. In patients with past HIT, ≤90 kg, 750 u SC two or three times daily for 7–10 days; and if >90 kg then 1250 u SC two or 750 u SC three times daily for 7–10 days | For a thrombosis <5 days old and weight ≤ 55 kg, 1250–1500 u IV bolus then 400 u/h next 4 h then 300 u/h next 4 h then 150–200 u/h for 5–7 days or maintenance of 1500 u SC twice daily for 4–7 days; if weight 55–90 kg, 2250–2500 u IV bolus then 400 u/h next 4 h then 300 u/h next 4 h then 150–200 u/h for 5–7 days or maintenance of 2000 u SC twice daily for 4–7 days; and if weight > 90 kg, then 3750–2500 u IV bolus then 400 u/h next 4 h then 300 u/h next 4 h then 150–200 u/h for 5–7 days or maintenance of 1750 u SC twice daily for 4–7 days. For thrombosis ≥5 days old and weight ≤ 90 kg, 1250 u IV bolus the 750 u SC two or three times daily; if >90 kg, then 1250 u IV bolus then 750 u SC three times daily or 1250 u SC two or three times daily |

(continued)

Table 2.3 (continued)

| Category | Agent | Prophylaxis ^{a, b} | Treatment ^a |
|--------------------------|--------------------------------|--|---|
| Vitamin K antagonist | Warfarin | Warfarin is available as scored tablets of 1, 2, 2.5, 3, 4, 5, 6, 7.5, or 10 mg and as a vial of 5 mg of reconstituted lyophilized powder for injection. Individualized dosing of warfarin is administered orally (or IV) when heparin or heparinoid therapy is already in effect, and it can usually begin (or be resumed if a 5-day overlap, bridging protocol is in effect) on the night of surgery, after which therapy is guided by the INR for at least 10 days and continued up to 4–6 weeks depending on patient-specific factors. Patients that have discontinued their maintenance warfarin therapy preoperatively can typically resume their usual dose beginning the night of surgery or the first postoperative day | After initiation of oral (or IV) administration, aiming for an INR of 2–3, warfarin is usually continued for 3–6 months |
| Cyclooxygenase inhibitor | Aspirin (acetylsalicylic acid) | 325 mg daily for 4–6 weeks, starting the night of surgery, always in combination with physical measures such as GCS and ICD, as well as patient education and avoidance of GA whenever possible | Not indicated for treatment |

Abbreviations: *GA* general anesthesia; *GCS* gradient compression stockings; *ICD* intermittent compression device; *IV* intravenous; *SC* subcutaneous, *u* international units

^aDuration of prophylaxis is usually continued until the involved extremity is mobilized and the duration of treatment is typically 3–6 months post identification of the clot

^bProphylaxis entails chemoprophylaxis combined with patient education, mechanical methods, and avoidance of general anesthesia when possible; surgeons and anesthesiologists need to use caution if neuraxial (spinal, epidural) anesthesia is to be used since the risk of spinal or epidural hematoma increases with VTE prophylaxis; and dosage recommendations are based primarily on VTE prophylaxis associated with hip and/or knee surgery or general medical patient care

information contained in the package insert specific to each of these medications in order to review the details related to their proper use for VTE prophylaxis, treatment, and reversal (which is beyond the scope of this text). Surgeons are also encouraged to recruit the medical expertise of other experienced clinicians in the management of acute DVT and/or PE, since the care of such patients can be complicated and requires a wide range of expertise and intervention. Although the primary adverse effect of anticoagulant pharmacological agents is hemorrhage, parenteral administration and patient and surgeon nonadherence to treatment and guidelines are important limitations of their use [39].

Prophylaxis is generally continued until the risk factors are such that VTE is not likely, and this is typically at a time when lower extremity immobilization is discontinued and surgeons need to individualize the duration of prophylaxis based on the needs of each individual patient. The duration of treatment for confirmed DVT and/or PT depends to a large degree on the risk of recurrence. Patients at a high risk for recurrence include those with idiopathic DVT or PE, malignancy, antiphospholipid syndrome, an inferior vena cava filter, obesity, the elderly, and males. As always, the risk of prolonged anticoagulation is hemorrhage.

Anticoagulants that are commonly used for VTE prophylaxis include unfractionated heparin, fractionated heparins

such as dalteparin and enoxaparin, the factor Xa inhibitor fondaparinux, and the heparinoid danaparoid, which is particularly useful in patients with a history of heparin-induced thrombocytopenia (HIT). Aspirin can also play a role in prophylaxis [40], although it is not considered to be a sole method of prophylaxis. Warfarin can also be used and is often initiated after surgery using a bridging protocol that also employs heparin or another anticoagulant.

The main goals of treatment for DVT include prevention of PE, postphlebotic syndrome, and recurrent thrombosis. Once VTE is suspected, anticoagulation should be started immediately unless there is a contraindication. In their review of the treatment of VTE, Wells et al. [4] divided therapies into acute (first 5–10 days), long-term (from the end of acute to 3–6 months), and extended (beyond 3–6 months) phases. And, despite the potentially lethal and acutely morbid nature of DVT and PE, they found that low-molecular-weight heparin (LMWH) along with vitamin K antagonists or the use of two oral agents without LMWH, along with ambulation and other physical measures, allows for outpatient management of most cases of DVT and some cases of PE, in the acute phase. Unless there is a specific contraindication, anticoagulation should be initiated as soon as VTE is diagnosed. Beyond the use of LMWH and/or oral therapies combined with physical measures, the use of thrombectomy

is reserved for severe VTE threatening limb loss or stroke, and retrievable inferior vena cava (IVC) filters are indicated when anticoagulation is contraindicated. Typically, adequate treatment of DVT and PE entails 3 months of use of anticoagulants, such as single or combinations of LMWH, vitamin K antagonists, or direct factor Xa or factor IIa inhibitors, after which additional therapy used over the long-term and extended phases of VTE is based on the risk of recurrence, cause of the initial thrombus, and the risk of a serious bleeding event over time.

Although prevention of the development of VTE is generally considered a worthwhile aspect of foot and ankle surgery, hemorrhage, particularly bleeding related to methods of anticoagulation and clot prevention, can be problematic and lead to wound as well as systemic complications. Patients with a platelet count $<100,000/\text{mm}^3$; those with active or a history of heparin-induced thrombocytopenia; those taking aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs; and those with renal or hepatic disease may not be satisfactory candidates for VTE chemoprophylaxis. In such patients, non-pharmacologic methods of prophylaxis, including GCS and ICDs, early active motion with activation of the calf muscle venous pump, and avoidance of general anesthesia if possible are likely to be the mainstays of VTE prophylaxis.

Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparin (LMWH)

Unfractionated heparin (UFH) occurs naturally and is contained in mast cell granules and released via degranulation in response to numerous stimuli, including hypersensitivity and tissue injury, in particular blood vessel disruption. Fractionated heparins (enoxaparin, dalteparin, tinzaparin), which are derived from depolymerization of long-chain polysaccharide heparin, are categorized as low molecular weight and useful as anticoagulants if their molecular weights average ≤ 8000 Daltons. The clotting cascade (Fig. 2.1), via sequential protease activity, amplifies conversion of soluble fibrinogen to insoluble strands of fibrin that combine with platelets to form a thrombus. Antithrombin is a serine protease inhibitor that disrupts the clotting cascade and, as such, serves as the key plasma inhibitor of coagulation. Heparins bind to antithrombin and inhibit factor Xa (activated factor X), thereby impeding the clotting cascade. Interestingly, LMWHs can only bind to and inhibit antithrombin, whereas heparin can bind to antithrombin and inhibit both antithrombin and thrombin. UFH also binds other plasma proteins, whereas LMWH is limited in its binding activity, and as such LMWH is associated with a more consistent dose-response and fewer non-hemorrhagic adverse effects. Heparins can be neutralized by protamine if problematic hemorrhage develops. Moreover, immune-mediated heparin-induced thrombocytopenia

(HIT)) can develop in response to administration of heparin, and this can lead to devastating thrombosis. The incidence of HIT in patients that have been heparinized for more than 7 days is approximately 1% [41], and the 30-day incidence of mortality associated with HIT is 16.6% [42].

Factor Xa Inhibitors, Direct Thrombin Inhibitors, and Heparinoids

A number of factor Xa inhibitors can be used for VTE prophylaxis and/or treatment, including fondaparinux, rivaroxaban, apixaban, and edoxaban. Although specific indications may be more broadly defined than just prophylaxis or treatment of DVT and/or PE, all of these agents can potentially be used in the realm of foot and ankle surgery. Fondaparinux is indicated for VTE prevention in patients undergoing hip fracture surgery, hip replacement surgery, knee replacement surgery, and abdominal surgery and for the treatment of acute DVT and/or PE when administered in conjunction with warfarin. Rivaroxaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE, for the reduction in the risk of recurrence of DVT and of PE, and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery. Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery, for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. Edoxaban is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation and for the treatment of DVT and PE following 5–10 days of initial therapy with a parenteral anticoagulant. The direct thrombin inhibitor dabigatran is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days, to reduce the risk of recurrence of DVT and PE in patients who have been previously treated, and for the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery. The combined factor Xa-thrombin inhibitor danaparoid, a heparinoid, is indicated for the treatment of patients with an acute episode of heparin-induced thrombocytopenia (HIT) and for prophylaxis in patients with a history of HIT.

Warfarin

Warfarin remains a very prevalent anticoagulant in the clinical realm, and foot and ankle surgeons routinely encounter patients that use this drug. Warfarin inhibits the synthesis of

vitamin K-dependent clotting factors, including factors II, VII, IX, and X, and proteins C and S, which naturally prevent coagulation. Anticoagulation generally occurs within 24 h, and peak antithrombotic effects occur 72–96 h after administration of warfarin. As a rule, the antithrombotic effects of warfarin multiply over time, and regular monitoring of coagulation using the INR or the prothrombin time is required. The pharmacokinetics of warfarin are influenced by a wide range of physiologic conditions (malnutrition, dehydration, old age) and the effects of concomitantly administered medications, in particular certain antibiotics. Generally, the use of warfarin can begin on the night of surgery and guided thereafter by the INR. Patients previously on chronic warfarin therapy prior to their surgery can resume their regular dosage the night of the operation. An INR > 3 warrants cessation of warfarin administration, and 1 mg of vitamin K should be administered orally or SC for an INR > 6 in the absence of active hemorrhage, and even higher doses may be used in the presence of bleeding. Fresh frozen plasma can also be administered if active bleeding occurs. Importantly, warfarin should not be administered in conjunction with aspirin or COX-1 inhibiting nonsteroidal anti-inflammatory drugs, although concomitant use of COX-2 inhibitors like celecoxib can be used if needed. For VTE prophylaxis, warfarin should be administered from 10 days to 4–6 weeks, depending on patient-specific factors, whereas, for the treatment of VTE, warfarin is generally administered for 3–6 months, aiming for an INR 2–3.

Aspirin

Historically, aspirin seems to be a prevalent method of VTE prophylaxis in bone and joint surgery, although its efficacy has been questioned by many clinicians due to a limitation of quality evidence. Over the 7–10 day lifespan of a platelet, aspirin (acetylsalicylic acid) irreversibly inactivates cyclooxygenase (COX) by means of acetylation, thereby preventing catalytic oxygenation of arachidonic acid to prostaglandin G₂ and the formation of thromboxane A₂, a mediator of platelet aggregation and vasoconstriction. Although aspirin is not recommended as a sole option for the prevention of VTE, in patients undergoing elective TKR or who have a contraindication to pharmacologic prophylaxis and undergo a THR or hip fracture surgery, aspirin in conjunction with compression devices as part of a multimodal approach can be acceptable; and existing evidence does not support the hypothesis that aspirin is less likely to cause adverse bleeding events than other anticoagulants [40]. Patients who have given aspirin as postoperative VTE prophylaxis typically receive 325 mg daily for 4–6 weeks, starting the night of surgery, and this is combined with physical measures such as GCS and IPC, as well as patient education and avoidance of general anesthesia when indicated. Surgeons also need to keep in mind that platelet inhibition diminishes the cytoprotective function of

prostaglandin in the stomach, thereby predisposing to gastritis, peptic ulcer, and gastrointestinal bleeding, so surgeons employing aspirin for VTE prophylaxis need to take these potential complications into consideration.

Thrombolytic Therapy

Therapeutic thrombolysis, either by means of systemic administration or catheter-directed infusion of the thrombolytic agent, can be used in certain patients, although the risk of bleeding, including intracranial hemorrhage, is higher with thrombolytic therapy than it is with generalized anticoagulation. Two agents, namely, streptokinase (250,000 units infused as a loading dose, then 100,000 units/h over the ensuing 24 h) and recombinant tissue plasminogen activator (TPA, 100 mg infused over 2 h), are commonly used for clot lysis. Thrombolysis, in particular catheter-directed infusion aimed at the clot, may diminish the risk of PTS, so it may be a preferred approach in patients with a severe proximal clot or multiple clots, or a previous history of DVT or PTS, and those at risk for limb gangrene but at low risk for hemorrhage [43]. Thrombolytic therapy may also be beneficial for patients with hemodynamically unstable PE with right heart failure.

Pulmonary Embolectomy

In patients with severe PE, who fail to respond favorably to anticoagulation and supportive therapies, including thrombolytic therapy, pulmonary embolectomy may be indicated. The incidence of mortality associated with pulmonary embolectomy is approximately 20% [44].

Inferior Vena Cava (IVC) Filter

There are a number of indications for IVC interruption, including severe PE, thrombosis in the iliac veins or the distal vena cava, inability to adequately anticoagulate or complications related to anticoagulation, and DVT in the presence of preexisting cardiac or pulmonary disease. Alone, an IVC filter is not an adequate therapy for DVT or prevention of PE, so anticoagulation is generally used in conjunction with the filter, if it is not contraindicated. IVC filters can be permanent or retrievable devices, the selection of which is based on the expected duration of use.

Risk Stratification Schemes for VTE Prophylaxis

Long ago, Thomas Bayes pointed out the importance of the baseline probability of a condition (the prevalence of a condition in a specific population) as it relates to the probability of a test being positive for that condition [45]. Since Bayes' famous essay was written, clinical decision rules based on pretest probability have been developed for many diagnostic tests, including those used to identify the presence of

VTE. Such clinical decision rules can be used to classify individuals into high-, medium-, and low-risk categories for the probability of DVT [46–49]. Since the clinical examination of DVT can be unreliable in and of itself, risk stratification of patients based on clinical decision rules that combine clinical and laboratory and imaging tests can increase the accuracy of a diagnosis. In fact, the use of the Wells rules (Table 2.2) [14, 16], combined with the use of the D-dimer test [47], can help surgeons decide when noninvasive imaging of the lower extremity veins is indicated and increases the likelihood of an accurate diagnosis of lower extremity VTE [48]. The Wells criteria [49] for the diagnosis of DVT were determined based on analysis of 1096 outpatients suspected of having DVT. The use of the D-dimer test imparts a negative predictive value (NPV, the probability that the individual does not have the disease of interest if the test result is negative) of 99.1% (95% confidence interval 96.7, 99.9) in patients with a low pretest probability of DVT (a Wells criteria score < 2). In patients with a high pretest probability of DVT (a Wells criteria score \geq 2), the NPV of the D-dimer test was 89.0% (95% confidence interval 80.7, 94.6).

Overall, it is understood that all patients admitted to the hospital, including those undergoing inpatient or outpatient surgery, are at risk of developing VTE. Of the 38 million hospital discharges in the United States in 2003, 20% were surgical inpatients, and using the American College of Chest Physicians' guidelines for risk stratification [50], it was estimated that 15%, 24%, and 17% were at moderate, high, or very high risk for VTE [51]. Interestingly, PE has been described as the most common cause of preventable hospital death [52–56] and accounts for approximately 150,000–200,000 deaths per year in the United States [57, 58]. Since DVT often precedes PE, its prevention and treatment, once it has been diagnosed, are important aspects of the care of foot and ankle surgical patients, and effective and safe prophylactic measures are available for most high-risk patients [59–62]. Furthermore, numerous evidence-based guidelines have been published for the prevention of VTE in general medical [63, 64] and cancer [65] patients.

VTE Prophylaxis in Hospitalized Patients

One risk stratification scheme that has been found to be useful in the management of a wide range of patients is the Padua Prediction Score, which was developed based on a prospective cohort study that involved 1180 consecutive hospitalized patients who were followed for 90 days following their admission [66]. The Padua Prediction Score was based on the summation of risk factor scores, and a score \geq 4 was considered to indicate a high risk for venous thromboembolism (VTE), whereas a score < 4 was considered to

Table 2.4 Padua [66] prediction score for VTE risk assessment in hospitalized patients^a

| Risk factor | Score |
|--|-------|
| Active cancer (patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months) | 3 |
| Previous VTE (excluding superficial vein thrombosis) | 3 |
| Reduced mobility (bedrest with bathroom privileges, either due to patient's limitations or on physicians order, for at least 3 days) | 3 |
| Known thrombophilia (carrier of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome) | 3 |
| Recent (\leq 1 month) trauma and/or surgery | 2 |
| Elderly age (\geq 70 years) | 1 |
| Heart and/or respiratory failure | 1 |
| Acute myocardial infarction or ischemic stroke | 1 |
| Acute infection and/or rheumatologic disorder | 1 |
| Obesity (BMI \geq 30) | 1 |
| Ongoing hormonal therapy | 1 |

^aA score \geq 4 indicates a high risk for venous thromboembolism (VTE), whereas a score < 4 is considered a low risk for VTE

indicate a low risk for VTE (Table 2.4). Of the patients, 469 (39.7%) were labeled as being at a high risk for thrombosis, and VTE developed in 4 (2.2%) of 186 who received thromboprophylaxis and 31 (11%) of 283 who did not (HR of VTE = 0.13; 95% CI, 0.04–0.40). Furthermore, VTE developed in 2 (0.3%) of 711 low-risk patients (HR of VTE in high-risk patients without prophylaxis as compared with low-risk patients, 32.0; 95% CI, 4.1–251.0), and bleeding occurred in 3 (1.6%) of 186 high-risk patients who had thromboprophylaxis. The authors concluded that their risk assessment model (the Padua Prediction Score) discriminated between medical patients at high and low risk of VTE and that adequate thromboprophylaxis in high-risk patients during hospitalization could result in long-standing (up to 90 days) protection against thromboembolic events with a low risk of bleeding.

VTE Prophylaxis in Non-orthopedic Surgical and Nonsurgical Patients

Also in 2001, Caprini and colleagues published a risk stratification scheme for VTE in surgical (non-orthopedic) and nonsurgical patients [67], and later in 2010, Caprini and colleagues published a review of VTE risk assessment scoring systems and the results of a validation study of a risk assessment tool for VTE prophylaxis in non-orthopedic surgical patients [68]. In these reports, various risk factors for VTE were categorized and weighted with point values (Table 2.5). In order to determine an individual patient's risk stratum,

Table 2.5 Caprini [67, 68] score risk factors and point values

| Risk factor | Score |
|--|-------|
| Age 41–60 years | 1 |
| Current swollen leg | 1 |
| Varicose veins | 1 |
| Obesity (BMI > 25) | 1 |
| Minor surgery planned | 1 |
| Sepsis (<1 month) | 1 |
| Acute myocardial infarction | 1 |
| Congestive heart failure (<1 month) | 1 |
| Medical patient currently at bed rest | 1 |
| History of inflammatory bowel disease | 1 |
| History of prior major surgery (<1 month) | 1 |
| Abnormal pulmonary function (COPD) | 1 |
| Serious lung disease, pneumonia (<1 month) | 1 |
| Oral contraceptive or hormone replacement therapy | 1 |
| Pregnancy or postpartum (<1 month) | 1 |
| History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant | 1 |
| Other risk factor | 1 |
| Age 61–74 years | 2 |
| Central venous catheter | 2 |
| Arthroscopic surgery | 2 |
| Major surgery (>45 minutes) | 2 |
| Malignancy (present or previous) | 2 |
| Laparoscopic surgery (>45 minutes) | 2 |
| Patient confined to bed (>72 h) | 2 |
| Immobilizing plaster cast (<1 month) | 2 |
| Age ≥ 75 years | 3 |
| Family history of thrombosis (this is most frequently missed risk factor) | 3 |
| History of DVT or PE | 3 |
| Positive prothrombin 20210A | 3 |
| Positive factor V Leiden | 3 |
| Positive lupus anticoagulant | 3 |
| Elevated serum homocysteine | 3 |
| Heparin-induced thrombocytopenia (HIT) | 3 |
| Elevated anticardiolipin antibodies | 3 |
| Other congenital or acquired thrombophilia (if yes, type should be specified) | 3 |
| Stroke (<1 month) | 5 |
| Multiple trauma (<1 month) | 5 |
| Elective major lower extremity arthroplasty | 5 |
| Hip, pelvis, or leg fracture (<1 month) | 5 |
| Acute spinal cord injury (paralysis, <1 month) | 5 |

the various risk factor points were added to arrive at the patient's Caprini score. It should be pointed out that the Caprini score, as compared to the Wells criteria (Table 2.2), focuses on risk stratification and not the likelihood of a diagnosis of VTE. Based on prospective risk factor modeling in a large cohort of patients, the Caprini score can be used to determine a patient's risk for VTE, which is used to guide the approach to thrombosis prophylaxis (Table 2.6).

Table 2.6 Recommended prophylaxis for non-orthopedic (not hip or knee arthroplasty) general and abdominal pelvic surgery including gastrointestinal, genitourinary, bariatric, vascular, reconstructive, cardiothoracic, and gynecologic surgery hospitalized surgical patients

| VTE risk score ^a | Low risk of bleeding | High risk of bleeding |
|-----------------------------|--|--|
| 0 (very low risk) | Early ambulation | Early ambulation |
| 1–2 (low risk) | Intermittent pneumatic compression | Intermittent pneumatic compression |
| 3–4 (moderate risk) | Low-molecular-weight heparin or low-dose unfractionated heparin or intermittent pneumatic compression | Intermittent pneumatic compression |
| ≥ 5 (high risk) | Low-molecular-weight heparin or low-dose unfractionated heparin and intermittent pneumatic compression | Intermittent pneumatic compression until risk of bleeding diminishes, the chemoprophylaxis |

^aBased on the Caprini score [67, 68]

VTE Prophylaxis in Hip, Knee, and Orthopedic Trauma Surgery

In regard to hip replacement surgery, which carries a high risk of VTE, LMWHs, namely, enoxaparin, tinzaparin, and reviparin, can be used as prophylaxis. These agents behave as separate, noninterchangeable compounds that cannot be therapeutically substituted based upon anti-factor Xa levels, and the choice of LMWH used should be based on clinical experience with each agent [69]. The occurrence of pulmonary embolism and deep venous thrombosis within 30 days after elective primary total hip or knee arthroplasty was more frequent in patients with a body mass index >30 kg/m² and in patients with moderate or severe systemic disease resulting in some functional limitation as defined by an American Society of Anesthesiologists (ASA) physical status classification ≥ 3 [70]. Interestingly, a systematic review of thromboprophylaxis in trauma patients, published in 2013, concluded that there was only weak evidence to recommend the use of DVT prophylaxis for people with severe trauma, that there was some evidence that thromboprophylaxis prevents DVT, and that there was no quality evidence that thromboprophylaxis actually reduced PE or mortality related to trauma [71]. Still further, in a multicenter, non-inferiority design randomized controlled trial, the report for which was published in 2013 [72], the authors concluded that extended prophylaxis for 28 days with aspirin was non-inferior to and as safe as dalteparin for the prevention of VTE after THR in patients who initially received dalteparin for 10 days, and they further speculated that aspirin's low cost and greater convenience could make it a reasonable alternative for extended thromboprophylaxis after THR.

In regard to hip and knee surgery, the American Academy of Orthopaedic Surgeons' expert opinion clinical guideline entitled *Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty: Evidence-Based Guideline and Evidence Report*, published in 2011 by the American Academy of Orthopaedic Surgeons [73], makes the following ten recommendations for surgeons performing hip or knee arthroplasty:

1. We recommend against routine postoperative duplex ultrasonography screening of patients who undergo elective hip or knee arthroplasty.
2. Patients undergoing elective hip or knee arthroplasty are already at high risk for venous thromboembolism. The practitioner might further assess the risk of venous thromboembolism by determining whether these patients had a previous venous thromboembolism.
3. Patients undergoing elective hip or knee arthroplasty are at risk for bleeding and bleeding-associated complications. In the absence of reliable evidence, it is the opinion of this work group that patients be assessed for known bleeding disorders like hemophilia and for the presence of active liver disease which further increase the risk for bleeding and bleeding-associated complications.
4. We suggest that patients discontinue antiplatelet agents (e.g., aspirin, clopidogrel) before undergoing elective hip or knee arthroplasty.
5. We suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty and who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding.
6. In the absence of reliable evidence, it is the opinion of this work group that patients undergoing elective hip or knee arthroplasty, and who have also had a previous venous thromboembolism, receive pharmacologic prophylaxis and mechanical compressive devices.
7. In the absence of reliable evidence, it is the opinion of this work group that patients undergoing elective hip or knee arthroplasty, and who also have a known bleeding disorder (e.g., hemophilia) and/or active liver disease, use mechanical compressive devices for preventing venous thromboembolism.
8. In the absence of reliable evidence, it is the opinion of this work group that patients undergo early mobilization following elective hip and knee arthroplasty. Early mobilization is of low cost, minimal risk to the patient, and consistent with current practice.
9. We suggest the use of neuraxial (such as intrathecal, epidural, and spinal) anesthesia for patients undergoing elective hip or knee arthroplasty to help limit blood loss, even though evidence suggests that neuraxial

anesthesia does not affect the occurrence of venous thromboembolic disease.

10. Current evidence does not provide clear guidance about whether inferior vena cava (IVC) filters prevent pulmonary embolism in patients undergoing elective hip and knee arthroplasty who also have a contraindication to chemoprophylaxis and/or known residual venous thromboembolic disease. Therefore, we are unable to recommend for or against the use of such filters.

VTE Prophylaxis in Foot and Ankle Surgery

For the purposes of this chapter, foot and ankle surgical patients include any and all inpatients and outpatients managed by surgeons, including patients that undergo surgery localized to the forefoot and toes, mid- and hindfoot, ankle and leg distal to the tibial tuberosity, regardless of whether or not the surgery is undertaken for elective reconstructive interventions, emergent or planned operations, limb salvage or wound care, amputations, and the repair of traumatic injuries. Since immobilization, bed rest, and surgery, as well as trauma, are common elements of many foot and ankle surgical patients, the presence of clinical findings suggestive of DVT in conjunction with just two of these risk factors, according to the Wells criteria [16] (Table 2.2), is highly likely to be associated with the presence of DVT (and possibly PE). Unfortunately for foot and ankle surgeons, in comparison to VTE in association with knee and hip surgery, rigorous study of its association with foot and ankle surgery has not been as thoroughly documented in the peer-reviewed scientific literature. As such, there remains considerable debate as to the routine need for VTE prophylaxis in association with foot and ankle surgery, and definitive methods, in terms of the agents and methods used, dosages, and duration of intervention, have yet to be clearly defined in regard specifically to foot and ankle surgery. Foot and ankle surgeons are encouraged to become familiar with the existing literature, their hospital's institutional protocols, to carefully consider each patient on an individual basis in regard to the risk of developing VTE, and to use the methods that, based on one's experience and understanding of the evidence, prevent the development of VTE. What follows, is a review of the literature related to VTE prophylaxis in foot and ankle surgery.

In a prospective multicenter study published in 1998, Mizel et al. aimed to identify patients with symptomatic thromboembolic disease and to evaluate potential risk factors for VTE in 2733 foot and/or ankle surgery patients [74]. They observed that six (0.22%) patients with clinically significant VTE were identified, four (0.15%) nonfatal pulmonary emboli were identified, and significant risk factor covariates included non-weight bearing and immobilization after surgery. Based on their observations, the investigators concluded that routine prophylaxis

laxis for thromboembolic disease after foot and ankle surgery probably was not warranted. Then, in 2002, Solis and Saxby [75] undertook a prospective study to establish the incidence of DVT in patients who had undergone foot and/or ankle surgery, by performing bilateral calf duplex ultrasound examinations at the first postoperative visit. Of 201 consecutive patients, deep calf clots were found in seven (3.5%) patients, but none of these showed progression on follow-up ultrasound or extension proximal to the calf. By the authors' criteria, none of the studied patients required treatment, and they concluded that the rate and progression of DVT after foot and ankle surgery were low and did not require routine prophylaxis. They also noted that risk factors associated with DVT formation were postoperative immobilization, hindfoot surgery, tourniquet use, and advancing age. Also in 2002, Lassen et al. [76] published the results of a prospective, double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous reviparin (1750 anti-Xa units given once daily during the course of immobilization) in 371 patients who required immobilization in a plaster cast or brace for at least 5 weeks after a leg fracture or rupture of the Achilles tendon, and they performed venography of the injured leg within 1 week after removal of the plaster cast or brace, or earlier if there were symptoms suggesting deep vein thrombosis. They observed that DVT was diagnosed in 17 (9.3%) of the 183 patients randomly assigned to receive reviparin and 35 (18.7%) of 188 patients randomly assigned to receive placebo (odds ratio = 0.45; 95% confidence interval, 0.24–0.82). Most of the thromboses that they observed were distal (14 in the reviparin group and 25 in the placebo group), and there were two (1.1%) cases of PE in the placebo group who also had proximal DVT. There were no differences between the two groups with respect to bleeding or other adverse events. Based on these findings, the authors concluded that DVT was common in persons with leg injury requiring prolonged immobilization and that reviparin given once daily was effective and safe in reducing the risk of VTE.

In 2003, Slaybaugh, Beasley, and Massa [77] published a clinical protocol, a risk assessment tool based on their modification of the previously published Caprini risk stratification tool [67], and prophylaxis and treatment guidelines for DVT and PE that occur in association with foot and ankle surgery. Interestingly, the Slaybaugh, Beasley, and Massey (SBD) risk stratification system for VTE prophylaxis (Tables 2.7 and 2.8) is a system that the authors developed based on their interpretation of the Caprini score as it would, in theory, relate to patients undergoing foot and ankle surgery. Although the SBD foot and ankle risk stratification system has not been validated by means of prospective factor analysis or reliability testing and the precise rationale for their modification of the Caprini risk factor point system was not explicitly defined in the published report, the system has face validity (in this author's opinion).

Table 2.7 SBM^a venous thromboembolism point system for risk stratification in foot and ankle surgery^b

| Risk factor | | Points | |
|--------------------|--|---|---|
| Clinical situation | OR time > 105 min | 1 | |
| | Tourniquet time > 90 min | 1 | |
| | Rearfoot or ankle sugary | 1 | |
| | Immobilization in a BK or AK cast >1 week | 2 | |
| | Medical or surgical patients confined to bed for >72 h | 2 | |
| | Central venous access | 2 | |
| | Congestive heart failure | 3 | |
| | Sever sepsis/infection | 3 | |
| | Ankle, pilon, or tibial fracture | 3 | |
| | Multiple trauma | 5 | |
| | Acute spinal cord injury | 5 | |
| Medical condition | Clinical status | 40–60 years of age | 1 |
| | | Pregnancy or postpartum | 1 |
| | | Varicose veins | 1 |
| | | Obesity defined as >20 pounds > ideal body weight | 1 |
| | | Diabetes mellitus | 1 |
| | | Hypertension | 1 |
| | | Hyperlipidemia | 1 |
| | | Smoker | 1 |
| | | Polycystic ovary syndrome | 1 |
| | | >60 years of age | 2 |
| | | Oral contraceptive or receiving hormone replacement therapy | 2 |
| | | Inflammatory bowel disease | 2 |
| | | Currently treated or history of malignancy | 2 |
| | | History of deep venous thrombosis or pulmonary embolism | 5 |
| | Inherited | Factor V Leiden/activated protein C resistance | 3 |
| | | Antithrombin III deficiency | 3 |
| | | Protein S and C deficiency | 3 |
| | | Dysfibrinogenemia | 3 |
| | | Homocysteinemia | 3 |
| | | 20210A prothrombin mutation | 3 |
| | Acquired | Lupus anticoagulant | 3 |
| | | Antiphospholipid antibodies | 3 |
| | | Myeloproliferative disorders | 3 |
| | | Disorders of plasminogen and plasmin activation | 3 |
| | | Heparin-induced thrombocytopenia | 3 |
| | | Hyperviscosity syndromes | 3 |
| | | Homocysteinemia | 3 |

^aSBM = Slaybaugh-Beasley-Massa [77]

^bRisk factor points are added to determine risk stratum, which is used to guide prophylaxis (see Table 2.8)

In a 2006 retrospective analysis of 602 foot and ankle surgical patients from two separate practices, 24 (4% incidence) patients experienced a postoperative VTE complication, the risk factors for which were rheumatoid arthritis, a recent

Table 2.8 SBM^a pharmacologic venous thromboembolism prophylaxis recommendations by risk stratum for foot and ankle surgery^b

| Patient status and duration of prophylaxis | Risk stratum ^c | | | |
|--|------------------------------|---|--|--|
| | Low (0–1 risk factor points) | Medium (2 risk factor points) | High (3–4 risk factor points) | Very high (≥ 5 risk factor points) |
| Inpatient | No prophylaxis | Beginning first day postoperative and continue throughout hospitalization: enteric coated ASA 325–650 mg orally every 12 h, if ASA contraindicated, then UFH 5000 u SC every 12 h | Beginning first day postoperative and continue throughout hospitalization: enteric coated ASA 325–650 mg orally every 12 h, if ASA contraindicated, then UFH 5000 u SC every 12 h or LMWH SC daily | Beginning preoperative or within 12 h postoperative, UFH 5000 u SC every 8 h, or LMWH SC daily |
| Outpatient surgery or upon discharge | No prophylaxis | Enteric-coated ASA 325–650 mg orally every 12 h, if ASA contraindicated, then no pharmacologic prophylaxis | Enteric-coated ASA 325–650 mg orally every 12 h or UFH or LMWH preoperative or immediately postoperative, or LMWH beginning the first postoperative day | LMWH SC daily or immediate total or partial weight bearing with ankle range of motion and ASA 325–650 mg orally every 12 h |
| Duration | No prophylaxis | While hospitalized up to first postoperative visit, then decide whether to extend 7–14 days | While hospitalized up to 7–14 days postoperative, then reassess | While hospitalized up to 10–14 days postoperative, continued while immobilized |

Abbreviations: ASA acetylsalicylic acid, LMWH low-molecular-weight heparin, SC subcutaneous, UFH unfractionated heparin

^aSBM = Slaybaugh-Beasley-Massa [77]

^bEarly range of motion and mechanical methods (venous compression stockings and intermittent pressure devices) are recommended in conjunction with pharmacological methods

^cRisk stratum determined based on the sum of risk factor points described in Table 2.7

history of air travel, previous DVT or PE, and limb immobilization [78]. The authors of that study concluded that the incidence of symptomatic VTE complications could be higher than what had been previously reported (prior to 2006) and that further scientific investigation was needed in order to guide clinical practice.

In a 2007 report of the results of an e-mail-based survey aimed at determining current trends in VTE prophylaxis among 142 American and British foot and ankle surgeons, 27 (19%) of the surgeons indicated that they routinely used VTE prophylaxis in both elective and trauma foot and ankle surgery [79]. The surveyed surgeons in that report indicated that the most common situation in which VTE prophylaxis was used involved postoperative immobilization of the lower extremity, or when postoperative non-weight-bearing ambulation was employed. The respondents also indicated that the most common reasons for not using VTE prophylaxis on a routine basis were the known low incidence of VTE following foot and ankle surgery and the lack of published evidence indicating that it was beneficial. The investigators concluded that further clinical research was required in order to adequately guide practice.

In 2008, Wukich and Waters [80] reviewed a cohort of 1000 patients that had been treated over a 1.5-year period, and identified 4 (0.4%) cases of DVT and 3 (0.3%) cases of nonfatal PE. They also observed that the patients who developed DVT had ≥ 2 identifiable risk factors. Based on the $<1\%$ incidence of VTE following foot and ankle surgery, Wukich and Waters concluded that routine prophylaxis in association with foot and ankle surgery was not supported by their evidence.

In a 2010 survey focusing on VTE prophylaxis practices in elective foot and ankle surgery amongst 159 members of the British Orthopaedic Foot and Ankle Society (BOFAS), 84 (53%) respondents, accounting for 33,500 foot and ankle operations per annum, estimated the incidence of DVT, PE and fatal PE to be 0.6%, 0.1% and 0.02, respectively [81]. Furthermore, and despite recognized biases, they concluded that 10,000 patients would have to be treated (number needed to treat) in order to prevent a single fatal PE and, based on their observations, they questioned guidelines that called for routine VTE chemoprophylaxis in elective foot and ankle surgery.

In a retrospective cohort study of English National Health Service patients, published in 2011, symptomatic VTE, PE, and mortality within 90 days following fixation of an ankle fracture (45,949 patients), first metatarsal osteotomy (33,626 patients), hindfoot fusion (7033 patients), and total ankle replacement (TAR, 1633 patients), observed over a 42-month period, revealed the following incidences of DVT, PE, and mortality, respectively: after fixation of an ankle fracture—0.12%, 0.17% and 0.37%; after first metatarsal osteotomy—0.01%, 0.02% and 0.04%; after hindfoot fusion—0.03%, 0.11% and 0.11%; and after TAR—0, 0.06%, and 0. The risk factors that were significantly associated with VTE were older age and multiple comorbidities following ankle fracture repair [82]. Based on these national data, the investigators concluded that VTE, PE, and death following foot and ankle surgery were extremely rare, and although the fracture subset was at a higher risk, there was no evidence that VTE prophylaxis reduced the risk and, for most patients, prophylaxis was not required.

In a review of the incidence of VTE and PE following surgical repair of acute Achilles tendon rupture in 88 patients

who underwent surgery without VTE prophylaxis, 5 (5.7%) cases of VTE and 1 (1.1%) case of PE were identified [83]. Based on their retrospective observations, the authors recommended routine VTE prophylaxis for patients undergoing acute repair of a ruptured Achilles tendon.

Using the 2007–2009 National Trauma Data Bank, Shibuya et al. [84] showed that the incidence of VTE and PE associated with foot and ankle trauma was 0.28% and 0.21%, respectively. They also observed that older age (DVT, odds ratio [OR] 1.02, 95% confidence interval [CI] 1.01–1.03; PE, OR 1.02, 95% CI 1.01–1.03), obesity (DVT, OR 2.35, 95% CI 1.33–4.14; PE, OR 3.06, 95% CI 1.68–5.59), and higher injury severity score (DVT, OR 1.22, 95% CI 1.16–1.28; PE, OR 1.21, 95% CI 1.14–1.29) were statistically and clinically significant risk factors for DVT and PE following foot and ankle trauma. Based on the observed low incidence of DVT and/or PE, the authors concluded that routine pharmacologic thromboprophylaxis might be contraindicated in foot and ankle trauma, and clinicians were encouraged to undertake careful, individualized assessment of the risk factors associated with DVT/PE in order to decide when chemoprophylaxis was indicated.

In a retrospective study that focussed on the incidence of symptomatic VTE complications observed in a consecutive series of 2654 patients that underwent elective foot and ankle surgery, of whom 1078 (40.62%) received 75 mg aspirin as VTE prophylaxis between 2003 and 2006 and 1576 (59.38%) patients received no form of chemical thromboprophylaxis between 2007 and 2010, the overall incidence of VTE was 0.42% (DVT, 0.27%; PE, 0.15%) and 27 (1.01%) patients were lost to follow-up [85]. Assuming that those lost to follow up developed VTE, the overall incidence of VTE was 1.43%. Based on this worst-case scenario incidence of VTE of 1.43%, the authors concluded that routine VTE chemoprophylaxis was not indicated for foot and ankle surgery unless the patient was categorized at high risk for VTE.

Interestingly, in regard to major lower extremity amputation, the authors of a systematic review concluded that there was insufficient evidence to make any meaningful conclusions regarding VTE prophylaxis [86].

In a comparison of 130 patients that underwent foot and/or ankle surgery and treated with a below-the-knee cast for 4 weeks and non-weight-bearing ambulation for up to 6 weeks to 88 patients that underwent hallux surgery and treated without a cast or non-weight bearing, none of whom were administered any form of VTE prophylaxis, and all of whom underwent venous compression ultrasonography between 2 and 6 weeks postoperative; the overall incidence of VTE was 5.09% and that of PE was 0.9% [87]. Since none of the cases of VTE or PE in this particular study occurred in the hallux surgery group, the incidence of VTE or PE was 8.46% in the cast/non-weight-bearing group. Interestingly, 90.9% of patients in the VTE group had a total risk factor score of ≥ 5 ,

and 73.7% of patients in the non-VTE group had a total risk factor score of ≥ 5 , and the mean time to the diagnosis of VTE was 33.1 days. Based on their findings, the investigators recommended that VTE prophylaxis be routinely used for patients that undergo foot and/or ankle surgery requiring the use of a short-leg cast and non-weight bearing and that it should be carried out until weight bearing is resumed either with or without immobilization or until immobilization is discontinued whether with or without non-weight bearing, between 28 and 42 days following the surgery.

Even though it is generally known that the incidence of venous thromboembolism (VTE) is lower following foot and ankle surgery, in comparison to hip or knee surgery, it is important to consider the potential complications secondary to VTE, including pulmonary embolism (PE), in comparison to the costs, risks, and effectiveness of venous thromboembolism (VTE) prophylaxis. An e-mail-based survey of 100 active American Orthopaedic Foot and Ankle Society (AOFAS) committee members (80% of which responded) inquired as to the use, type, and duration of VTE prophylaxis following elective ankle fusion surgery in three different clinical scenarios, including a 50-year-old female with no risk factors, a 50-year-old female with a history of PE, and a 35-year-old female on birth control pills [88]. In response to the first scenario, 45 (57%) of the respondents said that no prophylaxis was required, and in response to the second scenario, 78 (97.5%) said that prophylaxis was required, whereas in response to the third scenario, 49 (61.3%) said that they would employ some form of prophylaxis. Among the respondents, the most common forms of prophylaxis were aspirin, 49% (24/49), and LMWH, 47% (23/49); and the recommended duration of VTE prophylaxis ranged from 1 day to more than 6 weeks. These investigators concluded that wide variation existed in regard to VTE following foot and ankle surgery, and further research was needed in order to more precisely define guidelines for VTE following foot and ankle surgery.

As noted earlier, in comparison to VTE in association with knee and hip surgery, rigorous study of its association with foot and ankle surgery has not been as thoroughly documented in the peer-reviewed scientific literature. As such, there is considerable debate as to the routine need for VTE in association with foot and ankle surgery, and definitive methods, in terms of the agents and methods used, dosages, and duration of intervention, have yet to be clearly determined. In still another systematic review of English language literature, up to 2012, the overall incidence of symptomatic VTE associated with foot and ankle surgery was $\leq 0.55\%$, and there was an increased incidence in foot and ankle trauma patients with the highest incidence reported in tendo-Achilles surgery [89]. In that review, moreover, the reported risk factors included previous history of VTE, immobilization, high BMI, age, comorbidities, contraceptive pill, and air travel,

and there was a cumulative effect resulting in higher risk when two or more risk factors are present.

Finally, in an analysis of 200 consecutive patients treated with plaster cast immobilization for ankle fracture, wherein oral anticoagulant therapy was administered for prevention of venous thromboembolism in those patients that were deemed to be at high risk for thrombosis, only one (0.5%) patient developed a DVT [90]. Based on this observation, they concluded that oral anticoagulation prophylaxis was suitable for ambulatory trauma patients temporarily immobilized for the nonsurgical treatment of an ankle fracture.

Since 2008, ten reports [78, 80–85, 87, 88, 90], describing results based on 211,067 foot and ankle surgical patients, observed the incidence of DVT to range from 0.01% to 8.46%, the incidence of PE to range from 0.02% to 0.9%, and the incidence of mortality to be 0.02–0.37% (the incidence of mortality based on observations in 88,241 patients). Of note, the highest incidences of DVT were 8.46% and 5.7%, observed in patients that were immobilized in a below-the-knee cast for 4–6 weeks non-weight bearing [87] and those that underwent acute surgical repair of Achilles tendon rupture, respectively. It is also interesting to note that 61.3% of orthopedic surgeons responding to a survey indicated that they would use VTE prophylaxis in a 35-year-old female on birth control pills who was undergoing elective ankle arthrodesis and that aspirin was the chemoprophylaxis of choice in 49% of these surgeons [88]. Unfortunately, further research is required in order for surgeons to be able to know for sure whether or not routine VTE prophylaxis is truly beneficial in foot and ankle surgery. In fact, in their position statement approved July 9, 2013 [91], the American Orthopaedic Foot and Ankle Society said “There is currently insufficient data for the American Orthopaedic Foot & Ankle Society (AOFAS) to recommend for or against routine VTED [venous thromboembolic disease] prophylaxis for patients undergoing foot and ankle surgery. Further research in this field is necessary and is encouraged.” Still further, in their clinical consensus statement [92], the American College of Foot and Ankle Surgeons claimed “The decision to prescribe chemical prophylaxis during nonoperative or operative management of foot and ankle disorders should be based on each patient’s unique risk benefit-analysis. This involves weighing the risks and consequences of bleeding against those of developing VTED. Exactly what constitutes sufficient risk to warrant chemical prophylaxis is not clear. Factors associated with the greatest risk include a personal history of VTED, active or recent cancer, a hypercoagulable state, and prolonged lower extremity immobilization.” As such, surgeons are encouraged to pursue VTE prophylaxis based on the recommendations that they believe are meaningful, in conjunction with their own experience and knowledge of their individual patient’s needs.

In conclusion, VTE is prevalent in surgical patients, and it can result in substantial morbidity as well as mortality. There are well-established risk assessment models that can be used to stratify the risk of VTE in hospitalized patients and others that focus on patients undergoing total hip or total knee arthroplasty. And even though there have been numerous peer-reviewed publications that focus on VTE in association with foot and ankle surgery, to date, a specific foot and ankle surgical VTE risk assessment model has not been validated. As such, foot and ankle surgeons are in the position of having to extrapolate the information in general medical and hip and knee VTE prophylaxis guidelines and combine this with their knowledge of their individual patient’s needs in order to determine how to minimize the risk of VTE.

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Complications in Foot and Ankle Surgery
Management Strategies

Lee, M.S.; Grossman, J.P. (Eds.)

2017, XIII, 452 p. 114 illus., 99 illus. in color., Hardcover

ISBN: 978-3-319-53684-2