Perioperative Venous Thromboembolism

4

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Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a multifactorial disease process that refers to the formation of a blood clot in a deep vein. PE occurs when the clot then travels to the pulmonary arteries, thereby preventing effective gas exchange. All hospitalized patients are at risk for a VTE. There are measures to pharmacologically and mechanically prevent VTE while in hospital. Unfortunately, studies demonstrate that 50% of thromboembolic events are healthcare-related, occurring during or soon after a hospital stay. In fact, up to 20% of hospitalized patients will develop a VTE [1].

Risk Factors and Epidemiology of VTE

In a review of 1231 patients treated for VTE, 96% had one or more recognized risk factor [15]. Major surgery as a risk factor for VTE has been extensively studied, with trauma, hip or knee replacement, and spinal cord injury reported as strong risk factors among hospitalized patients [16]. One-third of VTE-associated deaths occur after surgical procedures. Additional risk factors demonstrating a moderate to low risk consist of chemotherapy, hormone replacement therapy, malignancy, and thrombophilia, with the likelihood of a VTE proportionally increasing with the number of risk factors present [16] (Table 4.1). The two most common genetic hypercoagulable disorders that predispose to VTE are factor V Leiden and prothrombin G20210A. A systematic review found that approximately 20% of patients

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Table 4.1 Risk factors for the development of venous thromboembolism

Strong risk factors (odds ratio >10)	Moderate risk factors (odds ratio 2–0)	Weak risk factors (odds ratio <2)
Fracture (hip or leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Immobility (long travel times)
Major general surgery	Chemotherapy	Age
Major trauma	Congestive heart or respiratory failure	Laparoscopic surgery
Spinal cord injury	Hormone replacement therapy	Obesity
	Malignancy	Varicose veins
	Oral contraceptive therapy	
	Paralytic stroke	
	Pregnancy	
	Previous thromboembolism	
	Thrombophilia	

experienced a first-ever VTE compared to 10% of patients with prothrombin G20210A [17]. Additional hematologic disorders associated with VTE include heparin-induced thrombocytopenia, disseminated intravascular coagulation (DIC), antiphospholipid antibody syndrome, and hemolytic uremic syndrome (HUS). First-time VTEs have a higher incidence in African-American populations when compared to Caucasians and Asian/Pacific Islanders [12]. A primary DVT occurs in the absence of known risk factors, and is also referred to as an "unprovoked" DVT. Conversely, secondary DVTs refer to thromboses in the presence of a recognized risk factor, and are referred to as "provoked" DVT.

VTE is a major health and financial burden on a national and global scale. The exact incidence of VTE is unknown as VTE remains underdiagnosed. However, approximately 900,000 people are estimated to develop a VTE in the United States. One-third of this population will experience recurrence within 10 years. VTE recurrence has been shown to be dependent on the original mode of presentation. This means that a patient who originally presented with a DVT is more likely to develop another DVT instead of a PE [11]. Research has shown that the risk of a developing a recurrent PE is three times greater in patients who initially presented with a PE [11].

Despite recent advancements in diagnosis, treatment, and prophylaxis of VTE over the last decade, the disease continues to be the third most common vascular pathology after myocardial infarction and stroke. VTE is responsible for approximately 250,000 hospitalizations per year [28]. PE is directly responsible for or associated with 100,000 deaths annually in the United States [28]. Mortality associated with PE is as high as 30% if untreated compared to an 8% mortality with appropriate treatment [27]. Acutely, up to 10% of patients will succumb to the PE and die suddenly, and two-thirds will die within 2 h of presentation [27]. After the acute event, 3-month mortality sits 17.5% [27]. To put it in perspective, more deaths annually can be owed to VTE than car crashes and breast cancer combined [27]. Thus, it is of utmost importance to recognize risk factors that lead to VTE and be familiar with initial diagnosis and treatment to further minimize morbidity and mortality.

Pathophysiology

Virchow's triad represents three discrete groups of risk factors that serve to describe the pathophysiology behind the formation of a thrombus: stasis of flow, a hypercoagulable state, and intravascular endothelial injury. Each of these factors in isolation may be responsible for VTE. However, it is the synergy between the three factors which can exponentially increase one's risk of VTE.

Damage to the wall of a vessel results in local alterations of blood flow and exposes endothelial cell and subendothelial proteins that promote the activation and circulation of coagulation pathways and enzymes. Such damage can occur from smoking, iatrogenic instrumentation, and trauma. Venous stasis occurs during times of immobility and trauma and in medical conditions such as arrhythmias, valvular heart disease, and congestive heart disease. Stasis increases the duration of contact between coagulation factors with each other and the endothelium, subsequently inducing endothelial damage and reducing fibrinolysis. Research has implicated smoking in various coagulation abnormalities mainly related to inflammation and increased fibrinogen. Fibrinogen is an acute phase reactant, and part of its contribution as a risk factor is by virtue of producing a vascular endothelial inflammatory state. It also plays an essential role in thrombus formation as fibrinogen is a thrombin substrate in the formation of fibrin [18]. Additional studies have demonstrated a rapid decline in fibrinogen concentration after the cessation of smoking. Fibrinogen levels are nearly equal in previous smokers and never smokers after 2 weeks of smoking cessation [19].

The delicate balance between clot formation and breakdown generally shifts toward thrombus generation in hereditary and acquired hypercoagulable conditions. It is important to note, however, that thrombophilias can be distinguished by associated risk for venous thrombus versus arterial thrombus versus both. Factor V Leiden and prothrombin G20210A, the most common inherited thrombophilias, have increased risk of venous thromboembolism with no consistent association with arterial thrombosis [20]. This pattern is also seen in protein C and S deficiencies and antithrombin deficiency. In contrast, antiphospholipid syndrome has a propensity for both venous and arterial thromboses, while homocysteinemia has been demonstrated to predispose patients to arterial thrombosis only [20]. Acquired hypercoagulable states seen in chemotherapy, cancer, pregnancy, oral contraceptives and hormone replacement therapy, and obesity further change coagulation pathways and create a thrombogenic state. There are few tests that qualitatively assess the ongoing clotting process in a patient. Conventional plasma tests such as prothrombin time, partial thromboplastin time, and INR are plasma-based studies that are inadequate in assessing coagulopathies. Thromboelastography (TEG) is a point-of-care test that evaluates the viscoelastic properties of whole blood, providing information about initial clot formation, fibrinolysis, and platelet aggregation. Studies have found that a collection of individual TEG parameters can be used as a marker for hypercoagulability and help identify patients at risk for VTE [32]. Subsequently, goal-directed therapies for intervention can be initiated and precision medicine practiced.

Deep Vein Thrombosis

Lower Extremity

The vast majority of DVTs are distal, occurring in the veins of the calf, while proximal DVTs, located in thigh veins, are less common. Up to half of all DVT patients are asymptomatic [25]. Symptomatic patients classically complain of a unilateral, dull ache in the leg, swelling, or erythema [24]. There may be significant swelling, cyanosis, and non-varicose, dilated superficial veins in patients with extensive iliofemoral DVT [24]. This classic presentation remains rare – less than 50% of cases [25]. Hence, physicians should remain vigilant in spite of the absence of the classic presentation, especially if other risk factors are present. With prompt recognition and anticoagulation therapy, some DVT may dissolve and recede within weeks to months, particularly those in the lower leg. Without appropriate anticoagulation, however, DVTs may extend and/or embolize.

Burdensome and lifestyle limiting sequelae include chronic venous insufficiency secondary to post-thrombotic syndrome. Post-thrombotic syndrome develops in up to 20–50% of patients within 7 years after the initial VTE [23]. While the pathophysiology is complex, most studies suggest that ambulatory venous hypertension is a result of outflow obstruction and/or valvular insufficiency. The sustained venous hypertension leads to structural and biochemical abnormalities that damage the vein walls and create a state of chronic inflammation, which results in pathologic skin and subcutaneous tissue effects. The most important risk factor for developing PTS is recurrent ipsilateral DVT, resulting in a sixfold increase in one study [29]. Additionally, DVT in multiple segments with iliac involvement increased the risk for developing PTS. Additional studies demonstrated that patients with popliteal vein abnormalities were also at an increased risk to develop PTS compared to those without popliteal vein involvement [29].

However, even with appropriate and timely treatment of DVT, the resulting inflammatory process can lead to permanent scarring and valvular dysfunction, ultimately leading to venous reflux and chronic venous hypertension [23]. The Villalta score diagnoses and stratifies the severity of post-thrombotic syndrome by assessing clinical signs and symptoms [22]. The higher the score, the greater the severity and disability [22]. The ATTRACT trial, a multicentered, randomized control trial, showed that the occurrence of moderate to severe post-thrombotic syndrome was greatly dependent on the location of the primary thrombosis. Patients had a greater risk of developing post-thrombotic syndrome after an iliofemoral DVT than following isolated femoropopliteal DVT [20]. Post-thrombotic syndrome can greatly reduce patient health-related quality of life and subjects patients to lifelong lower extremity pain, edema, venous ulceration, and lipodermatosclerosis [3] (Fig. 4.1).

A less frequent complication, seen in massive pelvic DVT, is the development of phlegmasia alba dolens and phlegmasia cerulea dolens, which occur when venous hypertension due to clot and edema obstructs arterial inflow, inducing tissue ischemia [2] (Fig. 4.2). Although this is not a common sequela, it is acutely life- and

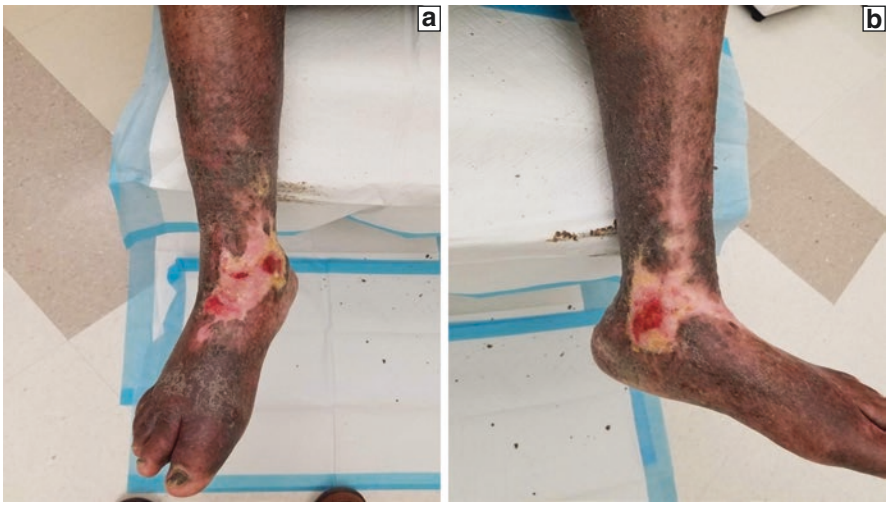

Fig. 4.1 Physical findings consistent with chronic venous insufficiency on the anterior (**a**) and medial aspect of the lower leg, ankle, and foot (**b**). Note the areas of hemosiderin deposition, resulting in hyperpigmentation, or rust-colored discoloration of the skin. Note also the medial location of both ulcers, which are in various stages of healing, typical for venous stasis ulceration

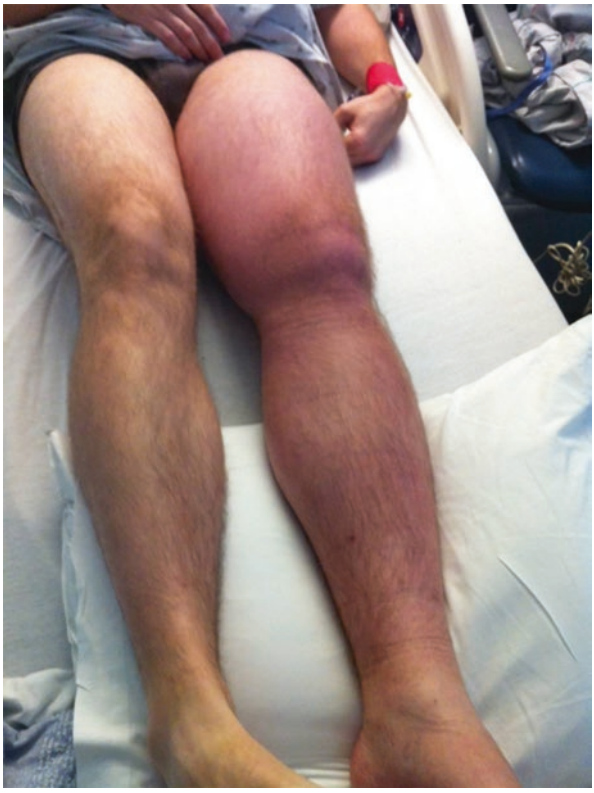

Fig. 4.2 Phlegmasia cerulea dolens of the left lower extremity

limb-threatening, and represents a surgical emergency. In phlegmasia alba dolens (white leg or milk leg), venous drainage is present but significantly decreased since the thrombosis spares collateral veins. Therefore, cyanosis will be absent. In contrast, in those with phlegmasia cerulea dolens, the thrombosis extends into the collateral veins, resulting in hydrostatic pressure that is exceedingly higher than the oncotic pressure. Consequently, there is an abundance of interstitial fluid sequestration that rapidly increases venous pressure [30]. When the interstitial pressure exceeds that of the capillary pressure, arterial ischemia ensues, potentially leading to compartment syndrome and so-called venous gangrene. These patients will present not only with severe edema, pain, and cyanosis but also absent pulses, signs and symptoms not found in individuals with uncomplicated DVT. While both are surgical emergencies, phlegmasia alba dolens is associated with a much lower risk of major amputation than phlegmasia cerulea dolens [33]. If not treated promptly and aggressively, venous gangrene can develop, which carries a 20–50% amputation rate and a 20–40% mortality rate [21]. Patients who present with phlegmasia alba or phlegmasia cerulean dolens are best treated with therapeutic anticoagulation and thrombus removal [30].

The optimal approach to diagnosing DVT is a combination of risk stratification, laboratory testing, and, if appropriate, diagnostic imaging. One highly validated model that stratifies the risk for VTE and provides recommendations regarding prophylaxis during the hospital stay and upon discharge is the Caprini score (Table 4.2). A meta-analysis published by Pannucci et al. in 2017 demonstrated that patients with a higher Caprini score were more likely to develop a VTE and those with a Caprini score >7 had a significant VTE risk reduction in the perioperative period with chemoprophylaxis. Individualizing medicine by risk stratifying patients ensures that chemoprophylaxis is used only in appropriate surgical patients, thereby minimizing bleeding complications.

With high sensitivity and specificity, duplex ultrasound continues to be the initial diagnostic test of choice to diagnose DVT. One study reported duplex ultrasound had a sensitivity of 96% in a proximal DVT, sensitivity of 71% in a distal DVT, and

Table 4.2 Risk of venous thromboembolism as stratified by the Caprini score, with the attendant recommendations for adequate prophylaxis

Caprini score	Risk category	Risk percent	Recommended prophylaxis	Duration of prophylaxis
0–2	Low	Minimal	Early ambulation, pneumatic compression devices, +/− graduated compression stockings	During hospitalization
3–4	Moderate	0.7%	Pneumatic compression devices, +/− graduated compression stockings	During hospitalization
5–8	High	1.8–4%	Pneumatic compression devices *AND* low-dose heparin *OR* low molecular weight heparin	7–10 days
≥9	Highest	10.7%	Pneumatic compression devices *AND* low-dose heparin *OR* low molecular weight heparin	30 days

an overall specificity of 94% [34]. It is easily reproducible, noninvasive, painless, cost-effective, and safe to use during pregnancy. Even though it is thought to be less accurate in assessing veins below the knee, it is still a widely accepted technique.

In cases of iliofemoral DVT, the duplex ultrasound shows loss of respiratory variation at the common femoral vein [25]. Recognizing this finding is important since treatment of iliofemoral DVT differs compared to distal DVT due to higher risk of post-thrombotic syndrome. In the absence of flattened common femoral waveforms, one can safely assume that the proximal iliofemoral veins are patent (Fig. 4.3). Hence, an accurate negative duplex justifies withholding intervention (thrombolysis, balloon venoplasty, and/or stenting) for a suspected iliofemoral DVT. If a duplex is indeterminate, treatment administration can be decided based on other risk factors and laboratory testing. Duplex is limited in obese patients, those with marked edema, and areas not amenable to compression like the subclavian veins, iliac veins, and femoral vein at the adductor canal and is notoriously user-dependent.

Additional imaging includes contrast venography, computed tomographic venography, and magnetic resonance imaging. These modalities can be considered when DVT diagnosis remains uncertain after a duplex ultrasound or when the DVT in question is located in the pelvis or an upper extremity. CTV and MRV are useful diagnostic tools for overcoming anatomic limitations or diagnosing inferior vena caval thrombosis when other imaging is contraindicated or inadequate. It is important to highlight the fact that the most common etiology of a massive iliofemoral DVT arises from extrinsic compression, whether from compression of the left iliac vein between the right iliac artery and a vertebral body (May-Thurner syndrome), trauma, or, most commonly, compression via tumor [26]. In these scenarios, note that an MRV or CTV is necessary to diagnose and evaluate the mass effect. Overall, however, CTV and contrast venography are less preferred due to cost, invasiveness, and risk of renal dysfunction, and MRI is time-consuming and contraindicated in patients with certain hardware.

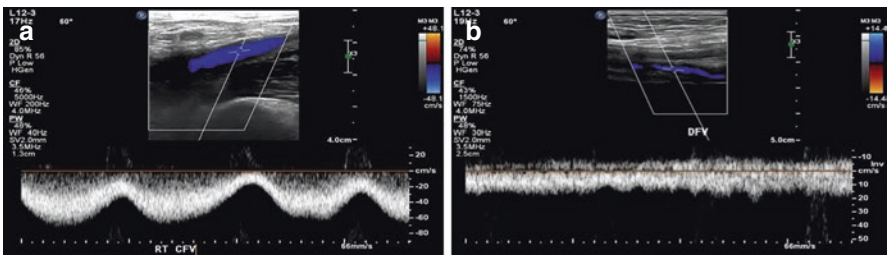

Fig. 4.3 Note the normal, respire-phasic waveforms with the gentle undulation with expiration and inspiration in (**a**). With proximal obstruction, the ability for changes in intra-abdominal pressure to influence the flow is obliterated, resulting in a non-phasic, flattened, or continuous Doppler venous waveform (**b**). (**a**) Normal phasic waveform in the common femoral vein that varies with respiration during the cardiac cycle. (**b**) Abnormal waveform in the common femoral vein. The absence of phasicity indicates an iliocaval venous obstruction. (Images courtesy of J. Chung)

Wells et al. created a scoring system based on risk factors and physical presentation that can be utilized to exclude the diagnosis of DVT without the need for a duplex ultrasound. A negative D-dimer in a patient combined with a low or intermediate Wells score has a negative predictive value of nearly 100%. However, use of the Wells score becomes more problematic when assessing patients categorized as high risk with a negative D-dimer. In these cases, it is recommended to proceed with duplex ultrasound. A resulting negative duplex is sufficient for ruling out a DVT, while a positive duplex warrants treatment with anticoagulation.

Upper Extremity

Thrombosis in upper extremity veins is far less common, accounting for 4% of all VTE cases. The most common locations of upper extremity DVT are the subclavian and axillary veins [3], though the jugular, brachiocephalic, distal brachial, ulnar, and radial veins are all possible sites. Although primary axillary and subclavian DVTs are rare, 10–15% cause PE.

Primary axillary/subclavian thrombosis is typically due to Paget-Schroetter syndrome (PSS), a venous form of thoracic outlet syndrome sometimes seen in young athletes or workers who use their arms repetitively. This occurs due to compression of the exiting vein in the thoracic outlet in the presence of anatomic abnormalities. Primary upper extremity DVT can also be a consequence of hypercoagulability. Secondary axillary/subclavian thromboses are more common, partly owing to the frequency of indwelling devices such as central venous catheters, pacemaker, or defibrillator leads [4]. Other risk factors include congestive heart failure and mediastinal tumors. As with lower extremity thrombosis, these clots may be occult or symptomatic. Suspicion for DVT should arise in patients presenting with unilateral upper extremity edema, pain, and cyanosis.

These veins can be difficult to directly visualize with duplex due to location and the shadowing of the clavicle. Nevertheless, duplex remains the dominant diagnostic test. If the duplex is indeterminate, CT or MRI can be used.

Pulmonary Embolism

A pulmonary embolism is a devastating and potentially fatal complication of DVT, occurring in up to 40% of patients with DVT and accounting for a majority of DVT-related deaths [13]. Clot from a DVT embolizes and travels into the pulmonary arteries, causing occlusion. These clots may range from small, sub-segmental emboli to massive emboli that lead to cardiogenic shock or cardiac arrest. Presentation is usually nonspecific; signs and symptoms include tachypnea, tachycardia, shortness of breath, dyspnea, pleuritic chest pain, and hemoptysis. Left untreated, PE carries a mortality rate of up to 25% [13]. The PIOPED II trial investigated the diagnostic accuracy of a CTA and indicated a 96% specificity in

diagnosing a PE. Consequently, CTA became the modality of choice in assessing pulmonary vasculature [14].

V/Q scans and pulmonary arteriography have fallen out of favor due to inferior specificity and invasiveness, respectively.

Prophylaxis

VTE prophylaxis includes limiting venous stasis, reducing coagulability, or a combination of both. Mechanical prevention with graduated compression stockings or sequential compression devices (SCDs) compresses the leg compartments, resulting in an increase in venous return and fibrinolytic activity. Employing mechanical prophylaxis reduces the risk for DVT in surgical patients by two-thirds when used alone and by an additional 50% when used in conjunction with drug prophylaxis [6]. A Cochrane review found that monotherapy with graduated compression stockings reduced the risk of a DVT from 27% to 13% and, if added to any other prophylactic measure, further reduced the risk of a DVT from 15% to 2% [5]. In most hospital settings, utilization of SCDs is prevalently preferred over static graduation compression stockings. A meta-analysis demonstrated that sequential compression devices decrease the relative risk of DVT by 62% compared to placebo and 47% compared to graduated compression stockings [7].

In addition to sequential compression devices, other means of counteracting venous stasis have been investigated, such as physical exercises. One study aimed to identify forceful foot exercises that engaged the calf muscle pump, thereby increasing venous return [31]. Six exercises were performed, and peak systolic velocity was measured via Doppler ultrasound and recorded. While all exercises resulted in a marked increase in peak systolic velocity, the highest was achieved by forceful dorsiflexion with toe extension followed by plantar flexion with 250 Newtons and forceful flexion of all toes [31]. These simple maneuvers can be taught to patients prior to long periods of immobilization or during hospital admission stays.

The value of anticoagulation in the prevention of DVT has long been established. Studies have shown that unfractionated heparin (UFH) and low molecular weight heparin (LMWH) each reduce the risk of DVT and PE by approximately 60%. Notably, LMWH carries a lower risk of major bleeding compared to UFH due to its decreased ability to bind and inhibit thrombin [8]. Although the risk of complications from prophylactic levels of anticoagulation remains low, platelet counts should be closely monitored in any patient receiving heparin for the development of heparin-induced thrombocytopenia (HIT). This is a dose-independent reaction that should be suspected when platelet counts fall below 100,000 or where there $\geq$50% drop in platelet count occurs following the administration of heparin. When suspected, heparin should be immediately stopped and an alternate form of anticoagulation initiated. It is important to note, however, there are two types of HIT. Type I HIT is a nonimmune-mediated reaction resulting from platelet aggregation that is more common than type II and is of mild consequence. It can be seen as soon as

after 1 day of therapy, and the platelet counts will spontaneously normalize even if heparin is continued [35]. Type II HIT is an immune-, antibody-mediated reaction and will therefore usually occur 5–14 days after receiving heparin [35]. The resulting hypercoagulable state can lead to life-threatening complications. As such, calculating the "4 T score" is the first step in diagnosing type II HIT. A score of 0–3 points indicates that HIT is unlikely and heparin therapy may precede as the other causes of thrombocytopenia are explored. A score of 4–5 corresponds to an intermediate probability, while a score of 6–8 is a high probability of HIT [35]. A score of 4+ warrants immediate discontinuation of all forms of heparin with the initiation of a direct thrombin inhibitor for further anticoagulation.

Treatment

Anticoagulation is the mainstay of treatment for DVT and should be initiated promptly when there is high suspicion for a DVT, regardless if there is a delay in diagnosis. Patients will be placed on an anticoagulation regimen for at least 3–6 months, depending on the absence or presence of propagating factors. Traditionally, treatment of a DVT began with the administration of heparin and then bridged to warfarin after 2–3 doses which typically places the INR between 2.5–3.0. Although heparin does not have thrombolytic activity, it is effective in preventing the propagation of the thrombus. It is relatively safe, is easy to administer, has a quick onset of action, has a relatively short half-life, and can be monitored.

Warfarin creates a hypercoagulable state in the first several days of its administration due to its inhibition of anticoagulant proteins C and S. Therefore, unopposed warfarin will exacerbate thrombus extension and can lead to warfarin-induced skin necrosis, a rare complication occurring in 1:10,000 [34]. For these reasons, warfarin therapy is always initiated in conjunction with parenteral anticoagulation until there is effective reduction of coagulation factors, which usually requires several days because of the varying half-lives of the vitamin-K dependent factors. Because of warfarin's narrow therapeutic window and drug and dietary interactions, patients will also require ongoing monitoring of their INR, aiming for an INR range between 2.0 and 3.0.

Novel oral anticoagulants (NOACs) such as direct-acting oral anticoagulants (apixaban, rivaroxaban, edoxaban) and direct factor IIa inhibitors (dabigatran) have recently been introduced as options for long-term anticoagulation. Both classes have been shown to be non-inferior to LMWH and warfarin. Instead of being bridged to warfarin, patients can now be transitioned to a DOAC/NOAC and sent home. The lack of requirement for routine laboratory monitoring is an added benefit of DOACs.

Anticoagulants alone are sufficient to prevent thrombus extension and recurrence in most DVTs. However, in cases of iliofemoral DVT or severe obstruction (Fig. 4.4), as seen in phlegmasia, where edema threatens limb viability, there is a marked increase in long-term morbidity. Studies show 95% of patients with iliofemoral DVT have valvular dysfunction 5 years after the initial DVT and 30% developed venous ulceration or claudication [9]. Therefore, in these patients intervention should be strongly considered. Suction thrombectomy and rheolytic thrombectomy

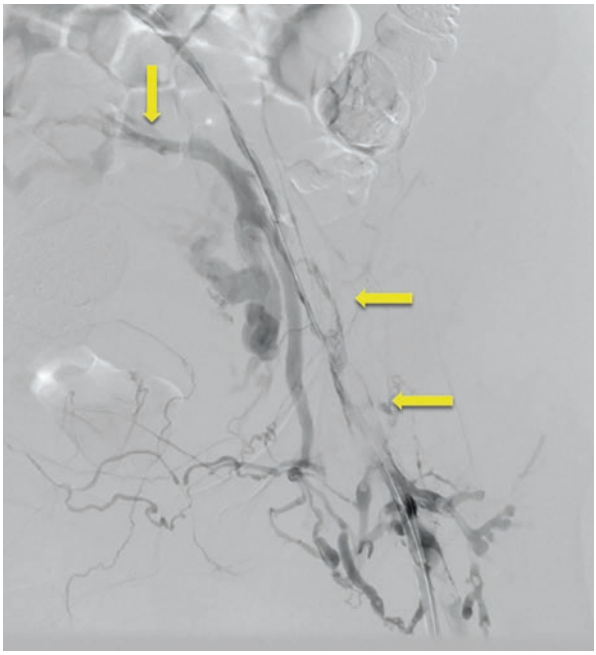

Fig. 4.4 Venogram of an extensive iliofemoral vein deep venous thrombosis. The areas free of thrombus show contrast partially filling the lumen of the vein segment. Areas of flow defects, as seen in the common femoral vein, and the external iliac vein, show where the acute thrombus is present (yellow arrows)

are two procedures designed to retrieve clots via catheter aspiration. The primary purpose of the ATTRACT trial was to investigate the risk of post-thrombotic syndrome development after treatment of DVT with either pharmacomechanical thrombolysis followed by anticoagulation or oral anticoagulation only [20]. Of the patients in the treatment arm who underwent catheter-directed thrombolysis, 46.7% went on to develop post-thrombotic syndrome, while 48.2% of patients who received anticoagulation alone went on to develop post-thrombotic syndrome [20]. The study concluded that there was no difference in prevalence of post-thrombotic syndrome between the two treatment arms ($p = 0.56$). However, the arm receiving pharmacomechanical thrombolysis had less moderate/severe post-thrombotic syndrome compared to the arm receiving thrombolysis alone ($p = 0.04$).

Thrombolysis using agents such as urokinase, streptokinase, and tissue plasminogen activator is commonly delivered through a catheter instead of systemically. This catheter-directed thrombolysis (CDT) is a minimally invasive endovascular approach that has become increasingly popular over the past decade. The 2011 CaVent trial revealed that long-term occurrence of post-thrombotic syndrome is reduced in patients who receive CDT compared to those who received traditional treatment with anticoagulation and compression stockings. However, CDT was associated with increased risk of bleeding [10] (Table 4.3).

While studies favor the addition of CDT, especially for iliofemoral DVT, it is important to be aware that not all patients are suitable candidates for this approach. Absolute contraindications to CDT include active internal bleeding and recent stroke [36]. Relative contraindications involve recent eye surgery, major surgery, or trauma [36].

Table 4.3 Relative and absolute contraindications for the administration of thrombolytic therapy

Absolute contraindications	Relative contraindications	Minor contraindications
Cerebrovascular events, including TIA, in the last 3 months Active bleeding diathesis Recent GI bleeding within the last 10 days Neurosurgery within the last 3 months	Cardiopulmonary resuscitation within the last 10 days Major nonvascular surgery or trauma within the last 10 days Uncontrolled hypertension of systolic >180 mmHg or diastolic >100 mmHg Intracranial tumor Recent eye surgery	Hepatic failure Bacterial endocarditis Pregnancy Diabetic hemorrhagic retinopathy

In addition to pharmacologic agents, multiple percutaneous mechanical devices exist to remove clot. Percutaneous aspiration thrombectomy devices rely upon a steady flow of suction via an aspiration catheter to remove the clot. Rheolytic aspiration devices utilize the Bernoulli principle by creating a vacuum with high-pressure hypotube, which engages and fragments the thrombus before aspiration through a catheter. Other devices incorporate three self-expanding nitinol disks that, when deployed, capture the thrombus and retract it into the aspiration catheter [37].

Future Investigation

Clinical investigation is ongoing in the areas of pharmacologic and mechanical prophylaxis, venous stenting, and prosthetic venous valves. Additionally, the quest to determine the optimal duration of anticoagulation after discharge using the safest and most efficacious medication is a top priority.

With the wider adoption of the direct oral anticoagulants, the management of VTE in the acute and long-term setting has been simplified. Direct thrombin (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) are first-line oral anticoagulants in nonpregnant patients without renal insufficiency or active cancer [37]. Unlike warfarin, routine lab testing and dose adjustments are not required for these medications. In nonpregnant patients with renal dysfunction, warfarin is the medication of choice for long-term anticoagulation [37]. However, warfarin does require bridging with heparin as it does not reach its full therapeutic effect until 5–7 days after beginning therapy. Premature discontinuation of heparin prior to warfarin reaching a full therapeutic effect can result in insufficient protection against DVT [37]. In patients without renal insufficiency who are unable to tolerate oral medications, low molecular weight heparin can be used, as it is as effective as warfarin in the prevention of VTE [39].

When assessing duration of anticoagulation, it is of utmost importance to individualize therapy based on risk factors and bleeding risks. In general, current guidelines recommend a minimum of 3 months of anticoagulation in patients with a first episode of VTE [37]. In patients with transient risk factors that are no longer present, isolated distal DVT, or if the bleeding risk is high, extending anticoagulation for longer than 3 months is not recommended [37]. The populations that are likely to

benefit from indefinite anticoagulation include those who experience an unprovoked proximal DVT or PE and recurrent unprovoked VTE, patients with active cancer, and those with antiphospholipid antibody syndrome.

Advances in prophylactic strategies have led to the development of game-based exercises that augment blood flow in the deep venous system. A pilot study demonstrated that a series of foot exercises increases the average volume flow volume, flow velocity, and peak systolic velocity in the femoral vein by approximately 50% [38]. In doing so, patients can help mitigate the risk of clot formation.

In recent years, the role of venous stenting in acute and chronic venous insufficiency has received increased attention as treatment in patients with proximal venous disease, especially those with compressive pathologies, such as May-Thurner syndrome or pelvic tumors. One of the first large studies to look at stenting in chronic venous disease found an overall improvement in pain and swelling and healing of half of venous ulcers after venoplasty and stenting, suggesting a role for stenting in chronic venous disease [40]. Stenting has also attracted attention in the setting of acute venous disease for the alleviation of symptoms. Research has been focused on assessing the efficacy of invasive management versus anticoagulation alone. Park et al. conducted a study looking at venous stent placement following CDT. A venogram was used to evaluate the degree of stenosis after completion of CDT, and in patients that continued to have severe stenosis or those with May-Thurner syndrome, a stent was placed. At 5 years, those that received a stent had a venous patency rate of 77.8% compared to 42.1% in non-stented patients [41]. Additionally, DVT recurrence was markedly increased in the non-stented arm [41]. Regardless, stenting in acute DVT warrants further investigation as there is a paucity of studies examining the long-term efficacy of this intervention. (Insert venogram pictures here.)

Currently there are no FDA-approved thrombolytics approved for the treatment of DVT. However, alteplase, urokinase, and streptokinase have been well-studied and are FDA-approved for the treatment of PE [42]. Utilization of newer thrombolytics, such as tenecteplase, for DVT has been reported in small case studies. Development of agents that are increasingly specific and effective at dissolving clot continues to be one such area of future investigation [42].

In the last several decades, there has been experimental work regarding prosthetic and autogenous valve replacement in the treatment of chronic venous insufficiency. One study showed autogenous valve transplants to be patent and competent for up to 3 months, and while these short-term results appeared to be promising, long-term results remain disappointing [42]. Percutaneous prosthetic or autogenous venous valves may prove to be a minimally invasive treatment, but further studies are required to document their success.

Summary

Venous thromboembolism (VTE) continues to be a significant source of inhospital morbidity, complicating up to 20% of hospital admissions. The most recent epidemiologic data shows that approximately 900,000 patients suffer VTE per

year in the United States, and is responsible for approximately 100,000 deaths. This makes VTE the third most lethal cardiovascular disease in America. Virchow's triad, comprised of stasis, hypercoagulability, and endothelial cell damage, underpins the risk factors for the development of VTE. The Caprini score has been validated to help practitioners risk stratify patients for the potential to develop VTE, and hence their need for prophylactic measures. Most VTE occurs in the lower extremity and pelvic veins, though a significant minority may develop in the upper extremities. Duplex ultrasound, D-dimer, and application of Wells criteria remain the mainstays of the diagnosis of deep vein thrombosis (DVT). Identification of pulmonary embolus hinges mostly upon computed tomographic angiography. Physicians continue to rely upon systemic anticoagulation to manage DVT. Novel oral anticoagulants (NOACs) have been rapidly supplanting more traditional means of anticoagulation with similar efficacy. Thrombolysis and other devices to remove thrombus are reserved for more extensive thrombus burdens and in the setting of phlegmasia cerulean dolens and massive PE. Future investigations abound in the areas of pharmacologic and mechanical prophylaxis, venous stenting, and prosthetic valves.

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