

age of these patients and the absence of atherosclerotic risk factors. The prevalence of ACD has been variously reported as 1 in 1200 patients with claudication, regardless of age, and 1 in 1000 diagnostic angiograms.<sup>46</sup> These reports include predominantly symptomatic patients, so the incidence of ACD in the general population is unknown.

## Pathogenesis

### Etiology

The precise cause of ACD remains unclear and controversial. Five theories of etiology and pathogenesis have been proposed: repetitive trauma, ganglion, systemic disorder, developmental, and articular theories.<sup>45,46</sup> Although convincing data to support the validity of the first three theories are scarce, they are briefly described below.

### Repetitive trauma theory

Proponents of this theory suggest that repeated flexion and extension of the knee joint result in chronic injury of the popliteal artery that is characterized by cystic degeneration.<sup>42,45,47</sup> This repetitive distraction movement of the popliteal artery causes intramural hemorrhage between the adventitia and media. Subjecting the knee joint to repetitive movement and stress leads to joint degeneration and changes in the surrounding connective tissue, which in turn secretes hydroxyproline that acts on the intramural hemorrhage to result in adventitial cyst formation.<sup>47</sup>

Although this theory is simple and relatively intuitive, scientific data to support it is scarce. Repetitive trauma as a causative factor does not explain cases occurring in arteries that are not subjected to such stress or in younger patients who have not been subjected to the same duration of this stimulus. Furthermore, one would expect more cases of adventitial cystic disease in athletes, and there would be a positive correlation between age and incidence of the disease. Such trends, however, have not been observed.

### Ganglion theory

Proponents of this theory have been prompted by the similar content of simple ganglia and popliteal artery cysts.<sup>42,45,48</sup> Both types of cystic structures contain high levels of hyaluronic acid. Additionally, there have been case reports of synovial cystic structures and Baker cysts directly involving adjacent vascular structures.<sup>49</sup> Presumably, in the case of the popliteal artery, these synovial cysts enlarge and track along arterial branches, where they implant in the adventitia of the popliteal artery.<sup>50</sup> However, there is no evidence of histologic similarities between the lining and chemical content of the cystic fluid in the synovium and popliteal artery cysts. In fact, fluid from adventitial cysts has a much higher hyaluronic acid content than synovial cysts.<sup>51</sup>

### Systemic disorder theory

This theory postulates that a systemic mucinous or myxomatous degenerative condition leads to development of ACD. Despite being proposed in 1967,<sup>52</sup> no systemic disorder has

been identified to support this theory. In addition, reports of bilateral disease are very rare,<sup>53</sup> as are cases of synchronous or metachronous cysts in different vascular locations that one would expect with a systemic disorder.

### Developmental theory

Also known as the cellular inclusion theory, this theory proposes that ACD occurs when mesenchymal mucin-secreting cells are implanted in the adventitia of the vessel during development. Levien and Benn noted that non-axial arteries form from vascular plexuses between 15 and 22 weeks of embryologic development adjacent to developing joints.<sup>42</sup> During this time, mesenchymal cells that form these joints can be incorporated into closely adjacent vessels and may be responsible for subsequent cyst formation when these mesenchymal cells start to secrete mucoid material.

### Articular (synovial) theory

Connections between the knee joint capsule and an adjacent popliteal artery adventitial cyst have been identified both intraoperatively and by preoperative imaging.<sup>36,45,50,52,54–57</sup> The articular (synovial) theory postulates that synovial fluid from a neighboring joint egresses and dissects along the adventitia of an articular (capsular) branch to the parent vessel.<sup>57–59</sup> Proponents of this theory argue that ligation of the joint connection along with simple cyst incision and drainage provides definitive treatment and decreases the need for vein harvest.<sup>38</sup>

On the one hand, the presence of such a connection lends support to the ganglion theory of development, with the connection representing a direct communication between the joint capsule and the arterial adventitial layer through which synovial cysts can migrate.<sup>50,54,56</sup> Alternatively, proponents of the developmental theory claim that these communications represent a residuum of the embryologic process, when mesenchymal cells of the adjacent joint are included in the adventitia of the nearby developing artery.<sup>42,50</sup>

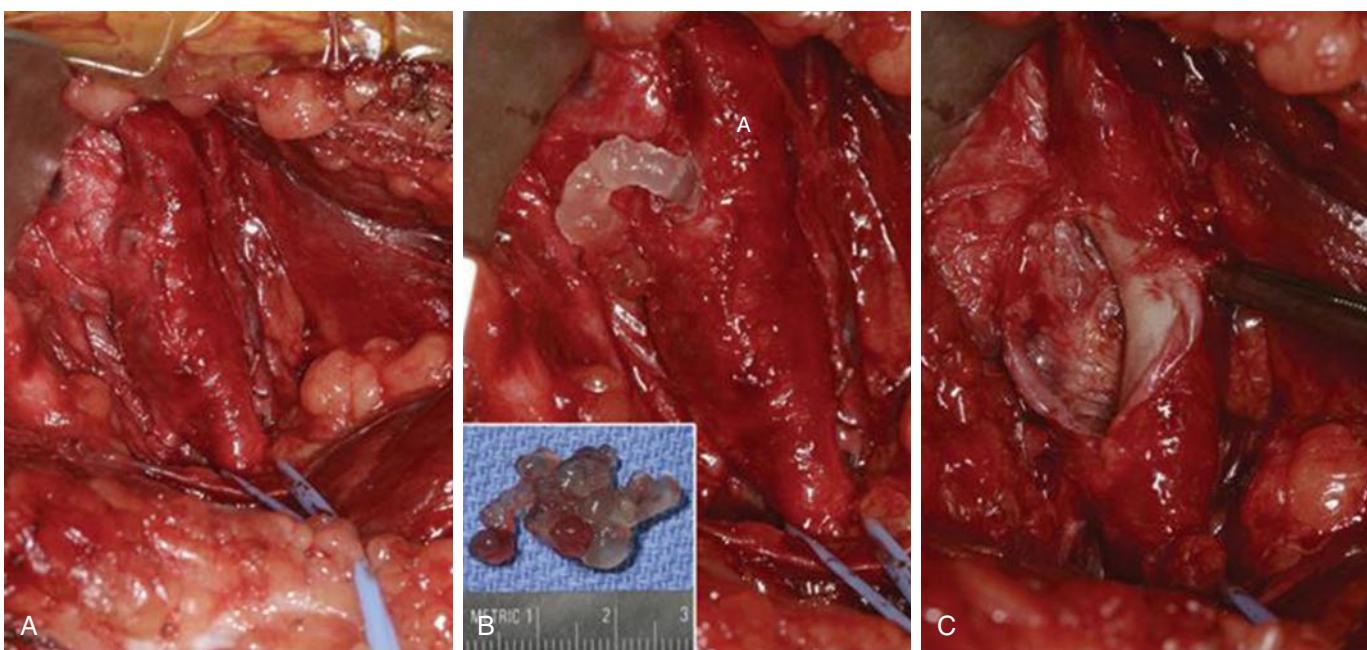
### Pathology

Popliteal artery adventitial cysts are filled with a gelatinous mucoid material. Microscopic examination reveals a simple cuboid cell lining in the adventitial layer, with a notable absence of any coexisting microscopic features of atherosclerotic disease. Grossly, the popliteal artery may appear enlarged and sausage-like, connected by adhesions to adjacent structures (Fig. 144.7). The cyst is usually uni-locular but can be multi-locular. Cyst contents are usually clear or yellow, but can be dark red following hemorrhage. Intraoperatively, these cysts are apparent following incision of the adventitial layer, although a case of ACD located only in the media has been described.<sup>60</sup>

## Clinical Presentation

### Arterial

The typical patient with ACD of the popliteal artery is a young male who complains of sudden onset of short-distance calf claudication.<sup>46</sup> The disease can present in all ages, however, and has been described in young children.<sup>61</sup> The duration of



**Figure 144.7** Adventitial cystic disease of the popliteal artery opened and evacuated. (A) Cystic adventitial disease of the popliteal artery. (B) Incision of adventitia with drainage of mucoid material (inset). (C) The popliteal artery after evacuation of mucoid cyst. (From Spinner RJ, Desy NM, Agarwal G, et al. Evidence to support that adventitial cysts, analogous to intraneurial ganglion cysts, are also joint-connected. *Clin Anat.* 2013;26(2):267–281.)

symptoms is generally relatively short (weeks to a few months) and unilateral. Claudication symptoms may completely resolve for a period of time and then recur, or they may progress rapidly. Recovery time is often prolonged, up to 20 minutes, compared with that of typical claudicants.<sup>62</sup>

Given the focality of these cysts, the young age of patients, and the otherwise normal status of inflow and outflow vessels, progression to CLTI is unusual with ACD, although the severity of claudication can progress and become disabling. It appears that the cysts need to be present and slowly enlarging for extended periods before patients enter the symptomatic phase. These enlarging cysts lead to progressive compression of the arterial lumen and can result in a “functional” occlusion of the artery without causing complete thrombosis. In cases of apparent arterial occlusion without thrombosis, evacuation of cyst contents can restore arterial patency. Nonetheless, prolonged compression of a compromised lumen can lead to popliteal artery thrombosis and a fixed occlusion.

Approximately two-thirds of patients present with popliteal artery stenosis rather than occlusion. On physical examination, this may be demonstrated by normal or diminished pedal pulses and by an audible bruit in the popliteal fossa. Pedal pulses that are present at rest may disappear with flexion of the hip and knee (Ishikawa sign),<sup>63</sup> representing a functional stenosis that progresses to vessel occlusion with this physical manipulation. This is in contradistinction to popliteal artery entrapment, in which pedal pulses disappear with gastrocnemius muscle contraction caused by active plantar flexion or passive dorsiflexion of the foot.<sup>46</sup>

There have been case reports of spontaneous cyst resolution,<sup>64–68</sup> possibly because of cyst rupture into the popliteal

fossa. However, this is extremely unusual and should not be considered a feature of this disorder. Furthermore, Zhang and colleagues described a recurrence of the disease after an apparent spontaneous cyst resolution in a female patient who eventually required surgery.<sup>69</sup>

### Venous

Venous ACD of the lower extremities is very rare.<sup>44,70</sup> As with arterial ACD, it occurs predominantly in young males and has been described in children.<sup>71</sup> However, it most commonly involves the iliofemoral rather than the popliteal segments. Typically, the diagnosis is made when a young, previously healthy male presents with painless swelling of the lower extremity and is investigated for deep venous thrombosis. Venous ACD should be considered when there is evidence of extrinsic compression on venous duplex imaging or a filling defect on venography. The optimal method of management is not well defined, but most authors advocate operative exploration with venotomy and evacuation of the cyst contents, followed by cyst wall excision to minimize the risk of recurrence. A recurrence rate of 11.5% has been reported.<sup>70</sup>

### Diagnostic Evaluation

The differential diagnosis for ACD includes synovial, ganglion, and intraneurial ganglion cysts, as well as synovial sarcomas.<sup>72</sup> Ankle–brachial indices in patients with ACD are unaffected at rest and drop following exercise. This pattern should raise the suspicion of an arterial cause of the patient’s symptoms and prompt further investigation.

As with all other arterial pathologies, there has been a steady progression of diagnostic modalities from standard

angiography and Doppler ultrasound technologies to cross-sectional imaging with CT and MRI. Although each method has advantages and disadvantages, current recommendations advocate the use of duplex ultrasound scanning followed by CT or MRI.<sup>46</sup>

### Noninvasive Testing

Duplex ultrasound should be the initial diagnostic tool.<sup>73,74</sup> The number of cysts and their dimensions can be easily evaluated. Elevated Doppler velocities and cystic extra-luminal compression of the affected popliteal artery segment is considered diagnostic. The boundary between the cyst and the arterial lumen is depicted by a fine bright line that pulsates. Ultrasound can also differentiate these cysts from popliteal artery aneurysms by an absence of flow within the cysts. Following intervention, duplex scanning is a useful postoperative surveillance tool to exclude cyst recurrence and residual or recurrent stenosis.

### Angiography

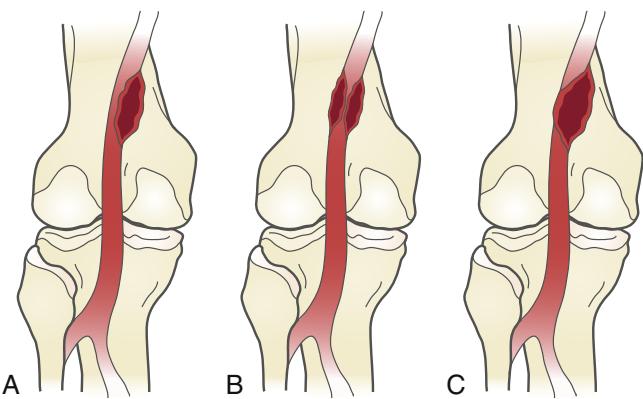
Traditionally, angiography was the gold standard for diagnosing ACD, but this has now been largely replaced by noninvasive methods. Complete popliteal artery occlusion is demonstrated with angiography in up to one third of cases, and the remaining studies demonstrate an eccentric compression of the popliteal artery lumen known as the “scimitar” sign, or an “hourglass” sign secondary to concentric compression (Figs. 144.8 and 144.9).<sup>73</sup> These imaging features can be detected with CT and MRI as well.

Angiography lacks sensitivity compared with other imaging modalities because stenosis can be missed on anteroposterior views and may be evident only with lateral projections. Angiograms that demonstrate eccentric stenosis in the absence of thrombosis and post-stenotic dilatation are specific for ACD. However, the diagnostic capability of conventional angiography is limited in patients with arterial occlusion and provide little information about arterial wall pathology and the surrounding soft tissues.<sup>46</sup>

### Computed Tomography and Magnetic Resonance Imaging

CT is being used more extensively in cases of popliteal artery disease. It allows for the differentiation of ACD from PAES and aneurysmal disease, especially in cases of popliteal artery occlusion or thrombosis. CT also has the ability to demonstrate the size of the cysts and their relationship to surrounding structures (Fig. 144.10).<sup>75</sup>

At some institutions, MRI is frequently used for the work-up of ACD (Fig. 144.11).<sup>76</sup> Advantages of MRI include the avoidance of ionizing radiation and intravascular contrast agents. MRI clearly depicts the extent of cystic involvement, and many authors consider it essential during the planning of surgical intervention.<sup>38</sup> Some authors recommend protocolling the MRI to include T2-weighted and gradient-echo sequences for suspected cases of ACD.<sup>46</sup> Others have described the use of T3 high spatial resolution MRI imaging, but there are concerns that significant increases in spatial



**Figure 144.8** Adventitial cysts can occur in variable locations on the popliteal artery. The expanding cyst may indent the artery, resulting in the “scimitar” sign (A); encircle the artery, resulting in the “hourglass” sign (B); or completely occlude the vessel (C).

resolution may adversely affect the image signal-to-noise ratio and limit the study’s usefulness.<sup>77,78</sup>

Despite the lack of convincing evidence to support the use of MRI over CT, most investigators recommend some cross-sectional imaging for the diagnosis of ACD and subsequent treatment planning. Duplex ultrasound remains useful as an initial diagnostic test and for postoperative surveillance. Emerging diagnostic technologies such as intravascular ultrasound and optical coherence tomography (Fig. 144.12) might also play an important role in the vascular surgeon’s diagnostic toolbox as they become more widely available.<sup>79</sup>

### Treatment

Given its rarity, ACD treatment recommendations are based on single-center experiences. Management options for ACD can be divided into nonresectional and resectional interventions.<sup>38,46</sup> In the majority of instances where non-occlusive stenoses are encountered, nonresectional methods are recommended. Resection, with subsequent arterial reconstruction, is more commonly used in cases of complete popliteal artery occlusion secondary to thrombosis or in the presence of extensive degeneration of the arterial wall.

#### Nonresectional Methods

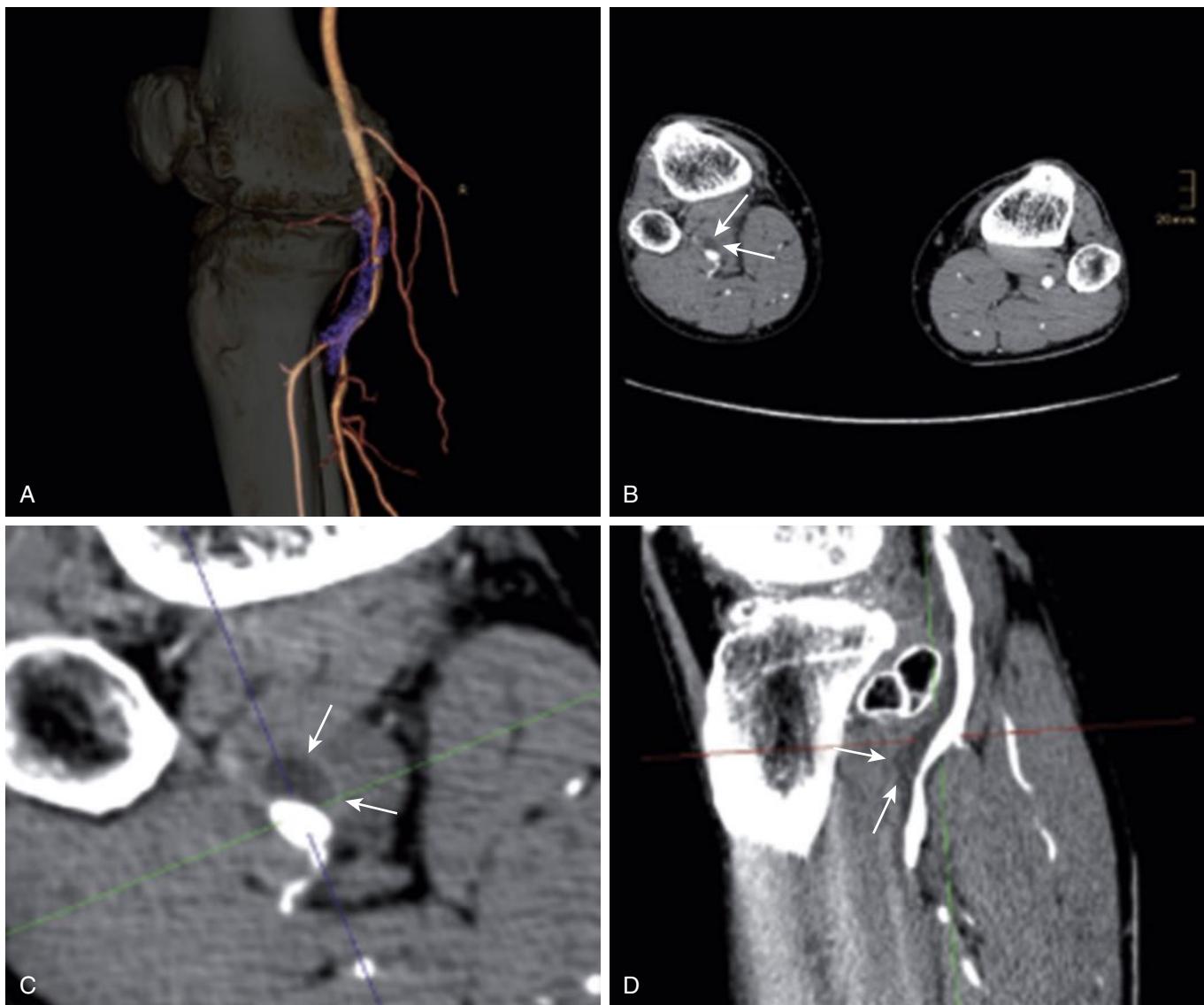
Nonresectional methods of treatment include percutaneous transluminal angioplasty (with or without stenting), CT- or ultrasound-guided percutaneous cyst aspiration, and cyst evacuation (with or without cyst excision). These treatment methods are described below in order of increasing chance of initial success and decreasing recurrence rate.

#### Transluminal angioplasty

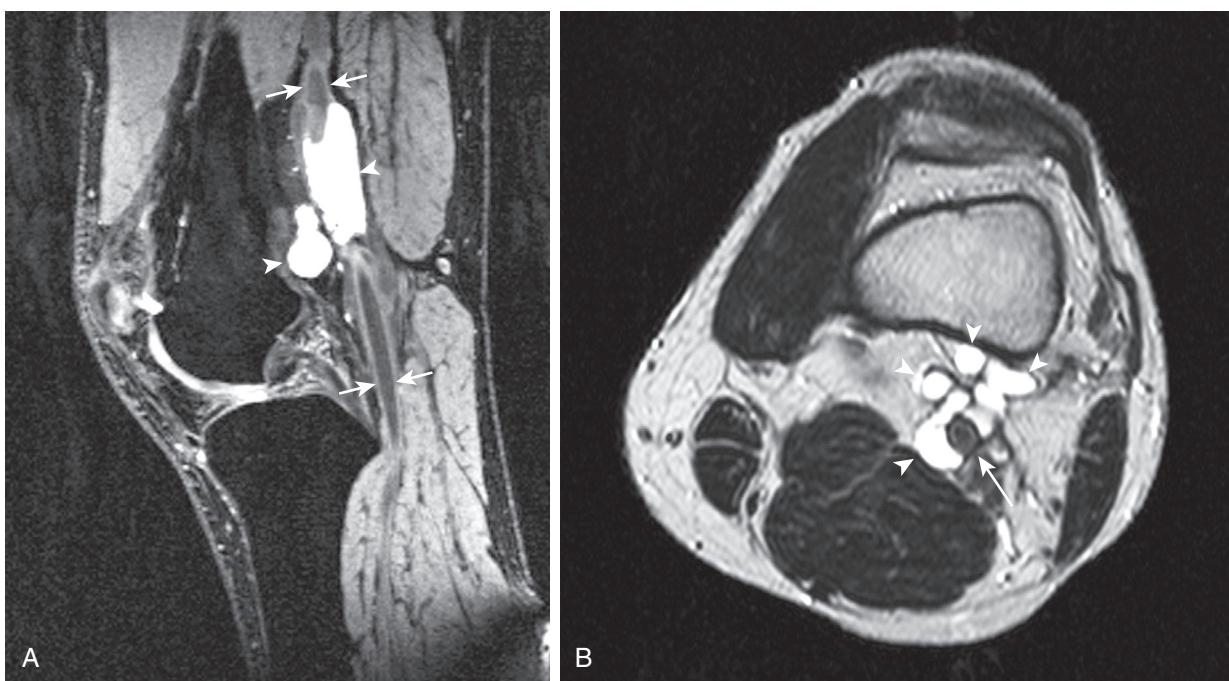
Angioplasty, with or without stenting, has been largely discarded as a treatment option. It is ineffective because the normal intimal layer of these arteries and the compliant arterial segment can recoil and restenose as early as 24 hours following balloon dilatation.<sup>80</sup>



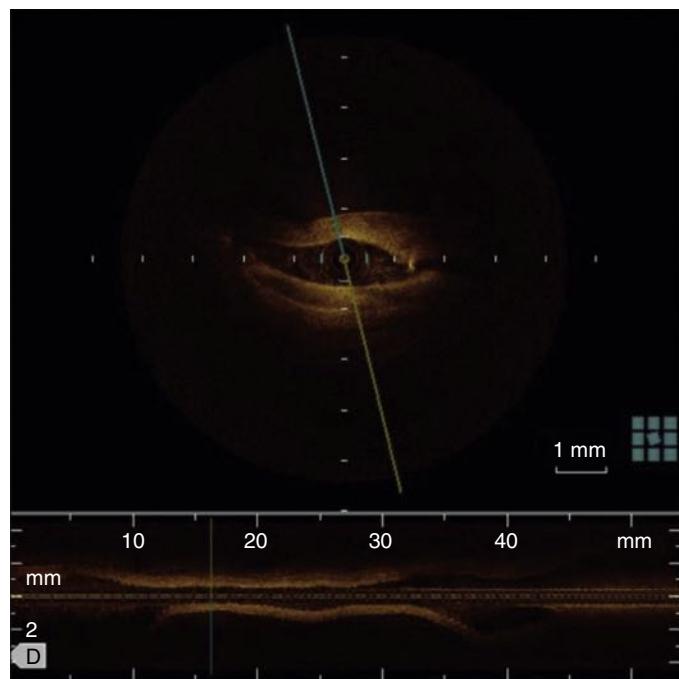
**Figure 144.9** (A) Femoral angiogram shows compression of the right popliteal artery by an adventitial cyst. (B) Lateral view of another patient shows anterior compression of the popliteal artery above the knee.



**Figure 144.10** Contrast medium-enhanced CT angiography with three-dimensional reconstructions (A) shows a cystic extraluminal mass along and around the popliteal artery (B and C, arrows) extending to the tibiofibular trunk (D, arrows). (From Wick MC, Tauscher T, Rieger M. Claudication due to cystic adventitial degeneration: a classical differential diagnosis of atherosclerotic peripheral artery disease. *Circulation*. 2012;125(15):1926–1927.)



**Figure 144.11** (A) Cystic structures (arrowheads) in close contact with the popliteal artery (arrows). (B) Cystic structures (arrowheads) in close proximity to popliteal artery (arrow). (From van Rutte PW, Rouwet EV, Belgers EH, et al. In treatment of popliteal artery cystic adventitial disease, primary bypass graft not always first choice: two case reports and a review of the literature. *Eur J Vasc Endovasc Surg*. 2011;42(3):347–354.)



**Figure 144.12** Optical coherence tomography cross-sectional images showing ACD of the popliteal artery extending from the 11 to 8 o'clock position. Multi-loculated anechoic lesions around the stenosis area are more evident than by intravascular ultrasound. (From Takasawa Y, Mizuno S, Maekawa N, et al. Diagnosis of adventitial cystic disease of the popliteal artery by optical coherence tomography. *Int J Cardiol*. 2016;203:653–655.)

### Cyst aspiration

Promising short-term outcomes have been achieved with CT- or ultrasound-guided cyst aspiration. The technique requires precise positioning of the needle tip in order to avoid the popliteal

vein and the tibial and peroneal nerves.<sup>46,81–83</sup> Despite the simplicity of this treatment modality, failures are not unusual in cases of multiple loculations and highly viscous cyst fluid. Spontaneous cyst resolution has been described after an unsuccessful attempt at aspiration, highlighting a possible role for disrupting the cyst wall in cyst resolution.<sup>84</sup> However, treatment failure and rapid recurrence has also been described.<sup>85</sup> Given the risk of incomplete evacuation and recurrence, cyst aspiration should be limited to patients who are not operative candidates and who agree to close imaging surveillance and probable re-intervention.

### Cyst excision and evacuation

Operative exposure of the involved popliteal artery is best achieved via a posterior approach with the patient prone. In the case of a stenotic popliteal artery, incision into the cyst and evacuation of its contents is usually sufficient to restore arterial patency.

### Resectional Methods

In instances of popliteal artery thrombosis or extensive arterial degeneration, a resectional treatment approach is preferred. The affected popliteal artery is explored through a posterior approach, and the extent of resection is determined by the length of arterial involvement on preoperative cross-sectional imaging and intraoperative findings. Arterial reconstruction is performed with an autogenous venous conduit or prosthetic graft of the surgeon's choice.

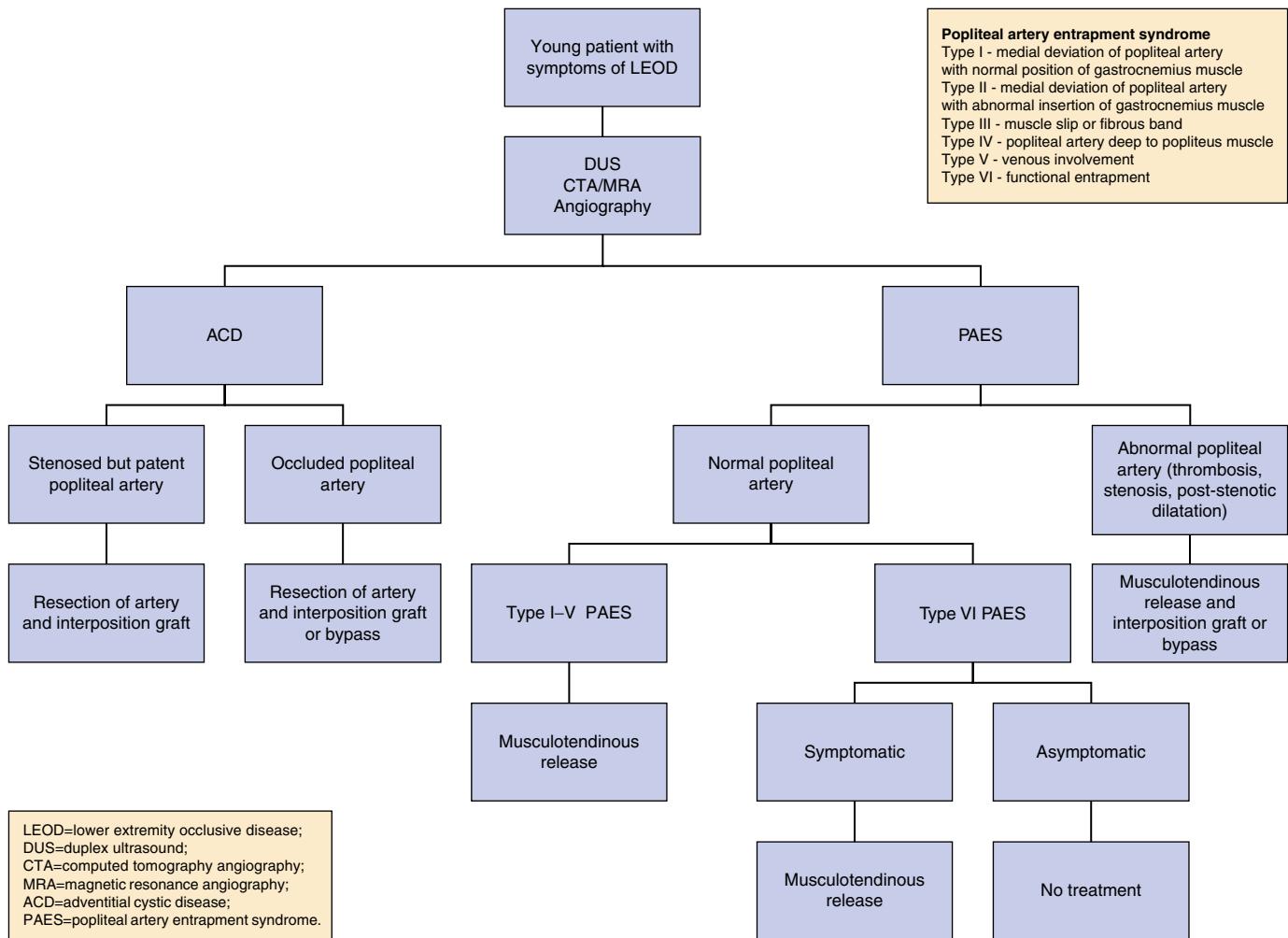
Choice of therapy is determined by the luminal status of the popliteal artery. In non-occluded arteries, nonresectional methods, including imaging-guided cyst aspiration or operative cyst evacuation and excision, offer good short-term outcomes. In instances of popliteal artery thrombosis, resection is advocated, with excision of the involved artery and reconstruction with an autogenous conduit.

## Treatment Outcomes

Recurrence of popliteal ACD has been described following all methods of therapy, although it is less likely with resection of the cyst or the involved artery.<sup>86</sup> Symptoms recur in 10% to 30% of patients undergoing cyst aspiration at a mean follow-up period of 15 months.<sup>62,87</sup> Treatment failure or recurrence has also been reported in 15% of patients undergoing cyst evacuation and 6% to 10% of those undergoing resection.<sup>46,88</sup> Arterial segment revascularization with

autogenous venous conduit is associated with the highest success rate,<sup>39</sup> although disease recurrence has been reported in the vein graft after popliteal bypass surgery.<sup>89,90</sup> Conversely, short-term failure of treatment after endovascular therapy has been reported in 37.5% of patients undergoing percutaneous transluminal angioplasty and 50% of patients undergoing angioplasty and stenting.<sup>91</sup> Given the recurrence risk with all of these therapies, indefinite and periodic postoperative duplex surveillance is necessary.

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# Infected Arterial Aneurysms

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Management of infected arterial aneurysms remains a daunting surgical challenge. These infections can occur in any named vessel and often affect elderly patients with multiple medical comorbidities. Medical treatment alone with culture-directed antibiotics rarely eradicates the infection, and excision of the involved vessel with anatomic or extra-anatomic arterial reconstruction is usually required. Reports of using endovascular stent grafts as the primary treatment or a bridging therapy to arterial reconstruction have been published; however, the specific role of endovascular devices in the treatment of this difficult problem remains to be defined.

## HISTORY AND EPIDEMIOLOGY

Osler in 1885 was the first to publish a comprehensive discussion of infected aneurysms.<sup>1</sup> His series described infected peripheral arterial aneurysms in patients with endocarditis. In addition, his proposed pathogenesis included embolism of bacteria-laden material from infected heart valves to peripheral arteries resulting in destruction of the arterial wall. He termed the resulting aneurysm “mycotic,” since the eccentric saccular configuration resembled a mushroom. Unfortunately, this term led to confusion, with some assuming that it applied only to infections caused by fungi, and others applied the term to all

infected aneurysms rather than just those associated with bacterial endocarditis. For these reasons, the term is best avoided.

In 1923, Stengel and Wolferth demonstrated that infected aneurysms could result from a variety of blood-borne septic conditions, not just endocarditis.<sup>2</sup> Sommerville in 1959 reported a third type of arterial infection, one that occurred in preexisting atherosclerotic aneurysms.<sup>3</sup> Later, infected pseudoaneurysms due to illicit drug use or iatrogenic arterial trauma were described. The overall incidence of infected arterial aneurysms has risen in recent decades with the increasing prevalence of immunosuppressed patients, invasive hemodynamic monitoring, catheter-based procedures, increasing use of cross-sectional imaging, and illicit drug abuse.<sup>4–17</sup>

## PATHOGENESIS AND ETIOLOGY

Infected arterial aneurysms are classified into four types based on etiology: (1) microbial arteritis with aneurysm formation due to noncardiac origin bacteremia or contiguous spread of a localized infection; (2) posttraumatic infected pseudoaneurysms, most commonly related to illicit drug abuse; (3) infection of a preexisting atherosclerotic aneurysm from bacteremia or contiguous spread; and (4) infected aneurysms from septic emboli, as classically described by Osler (Table 145.1).<sup>1</sup>

**TABLE 145.1** Clinical Characteristics of Infected Aneurysms

	Microbial Arteritis	Post-Traumatic Infected Pseudoaneurysms	Infection of Preexisting Aneurysms	Infected Aneurysms from Cardiac Source
Etiology	Bacteremia, contiguous spread	Narcotic addiction, trauma	Bacteremia, contiguous spread	Endocarditis
Age	>50 years	<30 years	>50 years	30–50 years
Incidence	Common	Common	Unusual	Rare
Common location	Aorta Iliac artery Intimal defects	Femoral Carotid	Infrarenal Aorta	Aorta Visceral Intracranial Peripheral
Common bacteriology	<i>Salmonella</i> Others	<i>Staphylococcus aureus</i> Polymicrobial	<i>Staphylococcus</i> Others	Gram-positive cocci

Adapted from Wilson SE, Van Wagenen P, Passaro E Jr. Arterial infection. *Curr Probl Surg*. 1978;15:1–89.

## Microbial Arteritis

Bacterial seeding can occur in nonaneurysmal arteries with preexisting wall irregularities caused by atherosclerosis or congenital abnormalities (e.g., aortic coarctation, patent ductus arteriosus).<sup>18,19</sup> Additionally, normal arteries can be infected by adjacent spread of a locally invasive infection. Once established, inflammation, suppuration, localized perforation, and/or pseudoaneurysm can result. Alternatively, more diffuse infection can result in rapid development of a true aneurysm, although often the aneurysm is saccular rather than a typical fusiform degenerative aneurysm. All named arteries are at risk, but the aorta is most commonly involved, likely due to its large intraluminal surface area and propensity for atherosclerotic involvement.<sup>15,20–23</sup>

Conditions associated with microbial arteritis include diabetes, cirrhosis, chronic hemodialysis, posttransplant immunosuppression, human immunodeficiency virus infection, alcoholism, chronic glucocorticoid therapy, chemotherapy, and malignancy.<sup>11,16–19,24–29</sup> In a study of 43 patients with infected aneurysms, Oderich et al.<sup>7</sup> found that 70% of patients had at least one of the aforementioned immunocompromised conditions.

## Post-Traumatic Infected Pseudoaneurysms

Arterial trauma leading to direct bacterial inoculation of the arterial wall can result in an infected arterial aneurysm. Bacteria can be introduced at the time of endovascular access or during drug abuse with inadvertent or intentional intra-arterial injection (Fig. 145.1A and B). Notably, the use of percutaneous closure devices for endovascular procedures has been reported to be associated with infected pseudoaneurysms.<sup>30,31</sup> Not surprisingly, the common femoral artery is the most common location, but posttraumatic infected pseudoaneurysms involving the carotid, brachial, external iliac, and subclavian arteries have also been reported.<sup>10,24,25</sup>

## Infection of Preexisting Aneurysms

Preexisting aneurysms can be secondarily infected by hematogenous or contiguous spread. Aneurysms are susceptible to

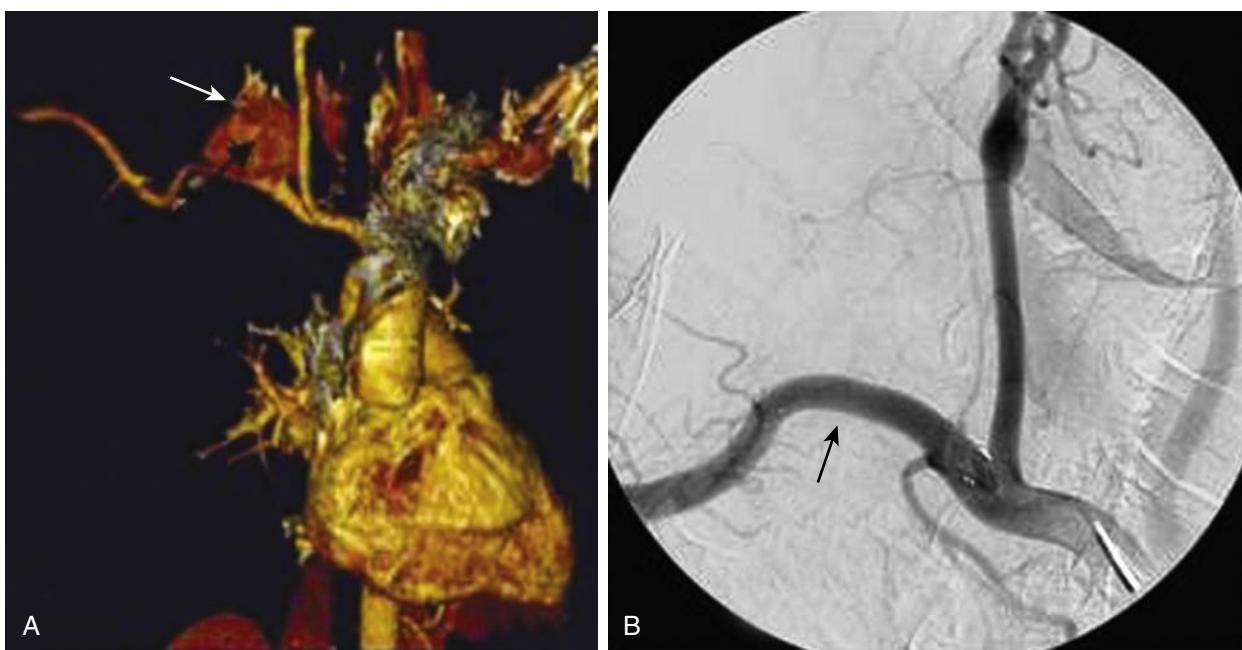
infection, because the diseased intima or intraluminal thrombus presents a nidus for bacterial seeding (Fig. 145.2A and B).<sup>3</sup> Interestingly, several studies have found that bacteria can be cultured from thrombus associated with asymptomatic degenerative aneurysms in up to 4% of patients and that aneurysms associated with bacterial growth in the thrombus may be more apt to rupture.<sup>3,19,20</sup> Furthermore, Ernst<sup>32</sup> showed that a greater number of positive cultures were found in patients with ruptured aneurysms compared with asymptomatic or symptomatic aneurysms (38% vs. 9% and 13%, respectively). Recent research has suggested the possibility that multi-bacterial infection in the aortic wall may be a contributor to the development of degenerative aortic aneurysms.<sup>33</sup>

## Infected Aneurysms Due to Endocarditis

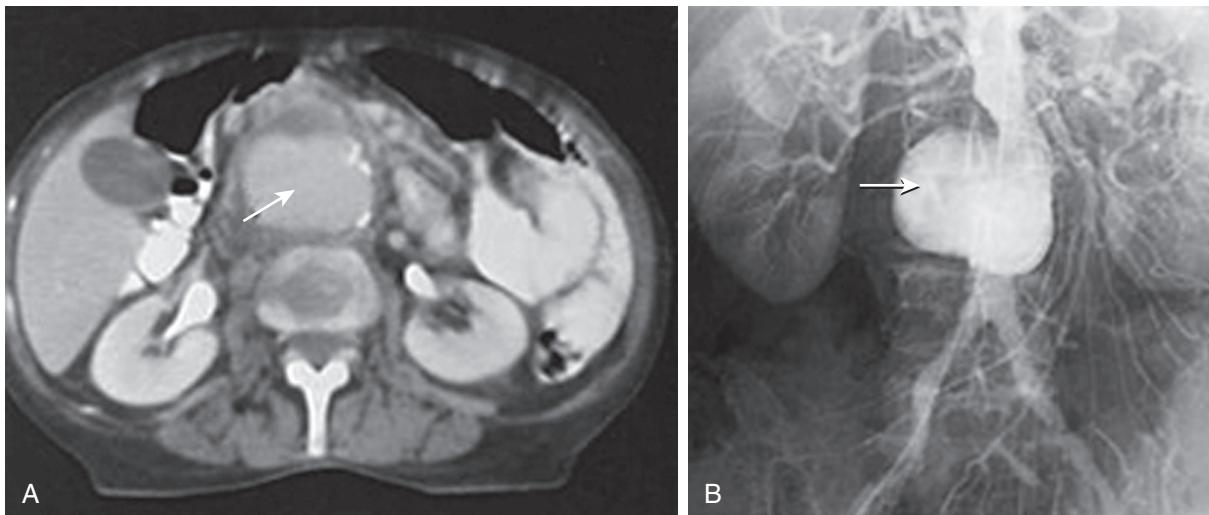
Currently, less than 10% of infected arterial aneurysms originate from endocarditis as classically described by Osler.<sup>15,34,35</sup> Septic cardiac emboli may lodge in the lumen or occlude the vasa vasorum of the arterial wall, leading to ischemia and arterial wall infection. Once the artery is infected, rapid, focal, and progressive deterioration occurs and results in the characteristic saccular or multi-lobulated “mushroom-like” aneurysms. This process often leads to a locally contained rupture and formation of a false aneurysm.<sup>14,21</sup> Infected aneurysms associated with cardiac emboli are frequently multifocal, involving the aorta, intracranial circulation, and splanchnic and femoral arteries, typically at arterial bifurcations.<sup>1,2,36</sup>

## MICROORGANISMS

The predominant microorganisms found in infected aneurysms depend on the type and etiology of the aneurysm, the patient's geographic location and travel history, and their immune system. The bacteriologic spectrum is extensive and may be broader than was once believed.<sup>37</sup> *Staphylococcus* species, of which many are methicillin resistant, are the most common organisms and account for 28% to 71% of cases. *Salmonella* species are the second most common and have been reported in 15% to 24% of patients. *Streptococcus* species account for less than 10% of the cases in the postantibiotic era.<sup>8,13,38</sup> Overall,



**Figure 145.1** (A) Three-dimensional reconstruction computed tomographic angiography image in a patient with a polymeric posttraumatic false aneurysm of the right subclavian artery caused by repeated percutaneous cervical injection of illegal narcotics (arrow). (B) Treatment with a covered stent graft for control of hemorrhage (arrow). Adjuvant therapy included open debridement and irrigation along with intravenous antimicrobial therapy.



**Figure 145.2** Diagnostic radiology studies of a patient with *Salmonella* infection of a preexisting small atherosclerotic aneurysm. (A) Contrast-enhanced computed tomography scan showing a saccular aneurysm with calcification (arrow). (B) Transfemoral aortogram showing a saccular atherosclerotic infrarenal aneurysm (arrow).

blood cultures are positive in 50% to 85% of infected aneurysm patients, and organisms have been isolated from aneurysmal tissue in up to 76% of patients with a suspected infected aneurysm.<sup>7,15,39–43</sup> As endoluminal device implantation has increased, infection in an existing aneurysm and microbial arteritis has also increased.<sup>44,45</sup>

### Specific Organisms

Although less common, Gram-negative infections are more virulent than Gram-positive infections as demonstrated by rates of aneurysm rupture (84% vs. 10%) and patient mortality (84%

vs. 50%).<sup>19</sup> The increased virulence is postulated to occur due to the ability of Gram-negative organisms such as *Pseudomonas aeruginosa* to release alkaline protease along with a variety of elastases that cause vascular wall necrosis.<sup>46</sup> Furthermore, Gram-negative organisms are commonly implicated in graft disruption and arterial stump hemorrhage after reconstruction. Consequently, the presence of Gram-negative organisms is an important consideration when contemplating repair strategies.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an important public health problem. New strains of *S. aureus* with multiple resistant traits have been associated with high morbidity and mortality, and several recent series

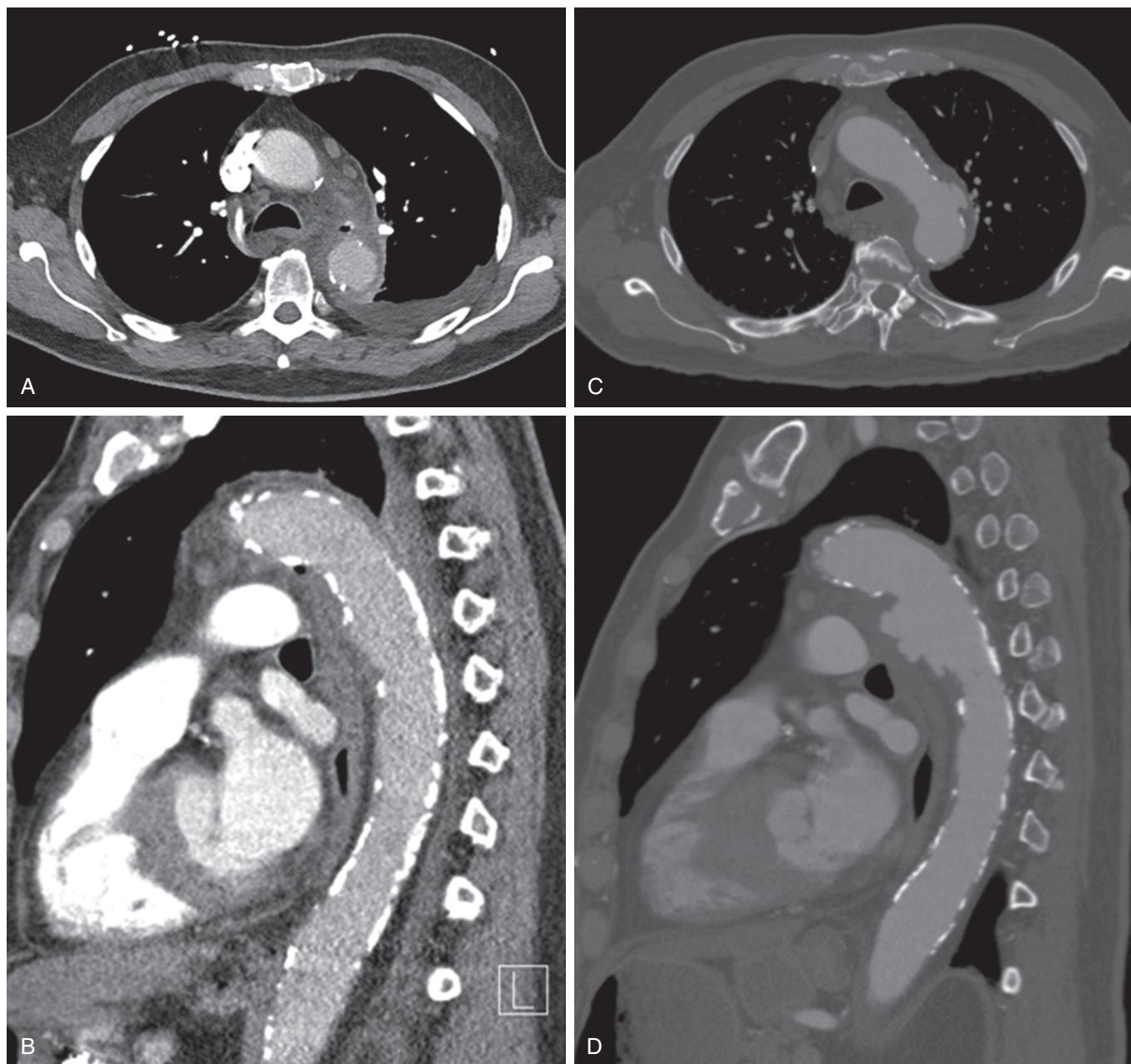
report MRSA as the predominant organism in infected aneurysms.<sup>47–49</sup> In particular, infected arterial aneurysms with MRSA have been reported as the primary organism found in patients due to illicit drug abuse.<sup>50,51</sup>

The diseased aorta appears to be particularly vulnerable to seeding by *Salmonella* species, and this pathogen is frequently found in infected preexisting aneurysms and in the infected atherosclerotic nonaneurysmal aorta. Specifically, *Salmonella enterica* accounts for more than half of reported cases of *Salmonella* aortitis.<sup>34,52</sup>

Clostridia infections of the aorta have been reported as well. One species, *Clostridium septicum*, has a propensity

to cause fulminant infected aortic aneurysms. *C. septicum* aortitis is often related to a gastrointestinal or hematological malignancy.<sup>53</sup> The proposed pathogenesis involves microperforation of the gastrointestinal malignancy leading to hematogenous seeding in areas of the aorta with existing abnormalities, such as ulcerated plaque.<sup>54,55</sup> If not aggressively managed by wide debridement and reconstruction, the overall prognosis is poor with rapid deterioration of the aortic wall leading to rupture and death in 64% to 100% of patients (Fig. 145.3).<sup>54–56</sup>

Fungal infections, although rare, have been reported in patients with diabetes mellitus, immune suppression, and those



**Figure 145.3** *Clostridium septicum* aortitis of the proximal descending thoracic aorta. (A and B) Proximal descending thoracic aorta with periaortic gas formation, and thickened wall. (C and D) Interval computed tomographic angiography in 10 days showing rapid enlargement of the aortic pseudoaneurysm. Patient underwent open aortic debridement via posterolateral thoracotomy, and *in situ* reconstruction.

with a history of systemic fungal disease.<sup>4,57,58</sup> Reported fungal pathogens include *Candida*, *Cryptococcus*, *Aspergillus*, and *Pseudallescheria boydii*.<sup>59–62</sup>

*Treponema pallidum* and *Mycobacterium* species have also been found in infected aneurysms.<sup>32,63–65</sup> *T. pallidum* (syphilis) once caused up to 50% of infected aneurysms but has become much less common since the advent of penicillin. Finally, tuberculosis (TB) is a rare cause and is generally secondary to erosion of TB-infected periaortic lymph nodes into the aortic wall.<sup>66</sup> More recently, it has been reported that the use of Bacillus Calmette–Guérin (attenuated bovine TB bacillus) as an intravesical treatment for superficial bladder cancer has led to remote arterial infections involving the infrarenal aorta and popliteal artery.<sup>67,68</sup>

## DIAGNOSIS

### Clinical Findings

The patient presentation of an infected aneurysm will depend on the anatomic location, the virulence of the organisms, and the duration of infection. General symptoms can include malaise, fever, and/or chills. Although some patients can manifest more dramatic signs of overt sepsis, most have a nonspecific clinical picture that can be associated with back or abdominal pain, distal embolization, a pulsatile tender abdominal mass, or pulsatile peripheral mass with overlying cellulitis.<sup>16,19,69–71</sup> Hemodynamic instability due to rupture can be the initial clinical event.

### Laboratory Studies

Leukocytosis and an elevated erythrocyte sedimentation rate and/or C-reactive protein are common but nonspecific findings in patients with an infected aneurysm.<sup>72</sup> Positive blood cultures without an obvious source in patients with a known arterial aneurysm should raise diagnostic suspicion, but negative blood cultures are not sufficient to rule out the diagnosis of an infected aneurysm.<sup>12</sup> The diagnostic utility of blood cultures is limited if patients have been treated with antibiotics.<sup>58</sup>

### Imaging

Radiological imaging is essential to establishing the diagnosis and planning the appropriate surgical management. Ultrasoundography and arterial duplex are helpful for initially assessing potentially infected peripheral aneurysms, but they are of limited value for infections of the aorta.<sup>16</sup> Computed tomography angiography (CTA) is the imaging modality of choice when an infected aneurysm is suspected. Typical CTA findings include saccular, multi-lobulated, or eccentric true and false aneurysms; adjacent soft tissue inflammation and fluid; air within the aneurysm or arterial wall; or evidence of aneurysm rupture. Serial scans obtained days to weeks apart can be particularly valuable when the initial clinical and CTA findings are suspicious but not diagnostic. The findings of a rapidly enlarging aneurysm or the interval development of aneurysms in

previously uninvolved aorta are highly suggestive of infection (see Fig. 145.3).<sup>73–76</sup>

Positron emission tomography (PET) alone or in combination with CTA has also been used effectively, given the often avid uptake of the radionuclide tracer by infected tissues.<sup>77–79</sup> Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are highly sensitive for inflammation and can also be helpful in patients with contraindications to iodinated contrast or when the CTA is equivocal.<sup>80,81</sup> Finally, indium 111-labeled white blood cell scanning has been used to identify prosthetic graft infections, but its use has not always been accurate in infected aneurysms.<sup>82,83</sup> Although neither sensitive nor specific, these studies can be of assistance when other imaging studies are equivocal.

## MANAGEMENT

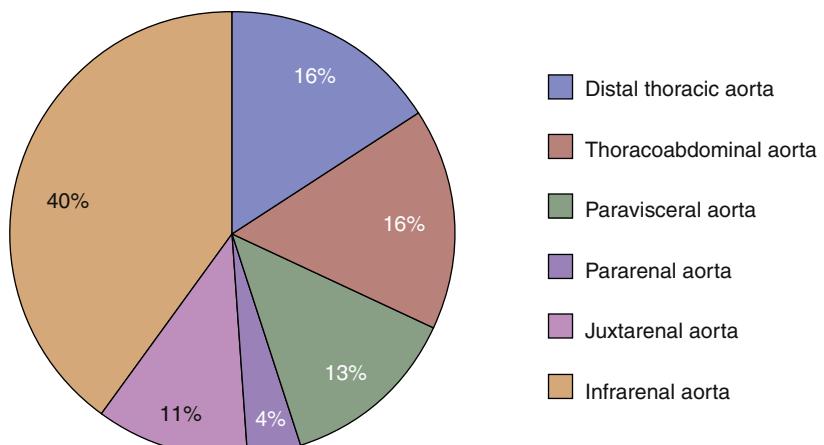
### Antibiotics

Antibiotic therapy has a critical role in the treatment of all infected aneurysms and should be initiated immediately and continued for at least 6 weeks after surgical treatment. Pre- and postoperative antibiotic therapy should be broad spectrum, until organism-specific therapy can be instituted. Because of the importance of organism-specific therapy, obtaining a set of blood cultures before initiating antibiotics and obtaining tissue and fluid cultures at the time of operation is paramount. The actual duration of antibiotic therapy varies from weeks to lifelong and is guided by organism virulence and antibiotic sensitivity profile as well as the arterial segment involved and type of reconstruction.<sup>84,85</sup> At a minimum, 6 weeks of intravenous antibiotic therapy should be employed.<sup>21,86</sup> Especially in locations where recurrent infection is often lethal, such as aortic infections, most surgeons lean toward longer, even lifelong, suppressive antibiotic treatment.

### Operative Treatment

While the nuances of the operative treatment depend on anatomic location, the following general principles apply to the treatment of all infected aneurysms.

1. To minimize excessive bleeding, proximal and distal arterial control should be obtained early in the course of the operation.
2. Intraoperative cultures should be obtained in all patients. Intraoperative Gram stain can be useful in certain patients to assist intraoperative decision-making regarding arterial conduit and method of revascularization. Importantly, a negative intraoperative Gram stain does not rule out infection.<sup>87</sup>
3. Infection control requires resection of the involved arterial segment and wide debridement of adjacent tissues, including all surrounding necrotic or infected tissues.
4. Either *in situ* or extra-anatomic reconstruction can be used. Graft conduits for *in situ* reconstruction include autogenous vein (saphenous, femoral), cryopreserved arterial allograft, or prosthetic graft that is either silver impregnated or soaked



**Figure 145.4** Distribution of infected aortic aneurysms in a report of 43 consecutive patients from the Mayo Clinic. (From Oderich GS, Panneton JM, Bower TC, et al. Infected aortic aneurysms: aggressive presentation, complicated early outcome, but durable results. *J Vasc Surg*. 2001;34:900–908.)

- in antibiotics such as rifampin. The type of reconstruction used is guided by multiple factors, including the surgeon's experience, the patient's surgical risk, the anatomic location of the aneurysm, and the availability of autogenous conduit.
- Following *in situ* reconstruction, the graft should be covered by well-vascularized tissue such as omentum or muscle flaps. The use of antibiotic beads placed into the infected bed and/or surrounding the arterial reconstruction has also been reported to potentially be of benefit.

## AORTA

Infected aneurysms have been described in all segments of the aorta from the aortic root to the aortic bifurcation. Oderich et al. reported the following distribution: infrarenal 40%, distal thoracic 16%, thoracoabdominal 16%, paravisceral 13%, and juxtarenal 11% and pararenal 4%, making surgical repair technically challenging in a large percentage of patients (Fig. 145.4).<sup>7</sup> The presence of a leukocytosis and positive blood culture have been reported in approximately 75% of patients.<sup>7</sup> CTA evidence of a peri-aortic mass or stranding is common and has been reported in 48% of patients.<sup>88,89</sup> Infected aortic aneurysms often involve parts of the aorta that are less frequently involved with atherosclerosis.<sup>89</sup> Despite the significant morbidity and mortality, outcomes have improved in the last 15 years, with the rupture status and expeditiousness of intervention impacting the outcome.<sup>90</sup>

### Thoracic Aorta

Infected thoracic aortic aneurysms are highly lethal with a reported mortality of 30%–50%. Gram-positive bacteria such as *Staphylococcal* species, *Enterococcal* species, and *Streptococcus pneumoniae* are the most common organisms.<sup>91</sup> *Salmonella* species infection does occur and is associated with a poor clinical outcome. Aneurysm formation can cause localized compressive symptoms such as dysphagia, dyspnea, hoarseness, cough, and superior vena cava compression, however the most common presentation is rupture.<sup>91</sup>

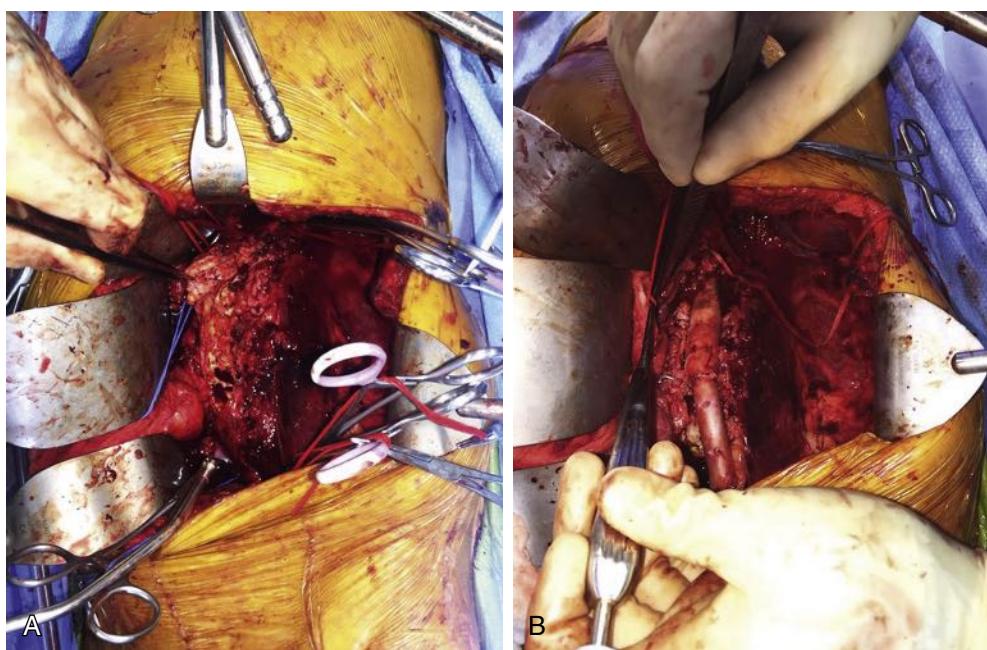
Surgical resection of the infected segment, wide debridement, and long-term intravenous antibiotics remain the

definitive treatment. Specific measures such as a spinal drain may be indicated to enhance spinal cord perfusion.<sup>92</sup> Depending on the aortic involvement, exposure may require a median sternotomy, left thoracotomy, or left thoracoabdominal incision. *In situ* reconstruction is the most common approach, usually with a cryopreserved arterial allograft or rifampin-soaked Dacron graft.

Another option for descending thoracic aorta infections is the ascending to infrarenal aortic reconstruction or “exclusion-bypass” first described by Kiefer.<sup>93</sup> A bypass from the ascending to infrarenal aorta is created through a median sternotomy and laparotomy. The ascending aorta is partially clamped, and an end-to-side proximal anastomosis is performed to a prosthetic graft, which is then tunneled through the right pleural cavity, across the diaphragm behind the left lobe of the liver, through the lesser sac, and behind the pancreas to reach the infrarenal aorta. The distal anastomosis is performed to the infrarenal aorta with the cross-clamp applied below the renal arteries. The operation is generally well tolerated, since aortic clamping does not result in visceral or renal ischemia. Upon completion of the bypass, the distal aortic arch and supraceliac aorta are stapled closed, excluding the descending thoracic aorta. Complete debridement of the infected descending thoracic aorta is performed usually as a staged procedure through a left posterior-lateral thoracotomy.

More recently, treatment using endovascular stent grafts combined with antibiotic therapy has been used as an alternative to conventional thoracotomy in managing infected aneurysms of the thoracic aorta. When combined with prolonged antibiotic therapy, this may be an especially attractive option in patients who are at high risk for open surgical repair.<sup>94</sup> Although published experience is limited, these grafts can serve as a bridge to definitive repair or as definitive palliation.<sup>95,96</sup>

Surgical complications are similar to those related to non-infected thoracic aneurysm repair. Infected Crawford extent II thoracoabdominal aneurysms, age greater than 65, and contained rupture are associated with a 20% 30-day mortality.<sup>97</sup> Mortality of 85% has been reported in patients who were managed with antibiotic therapy only, with in-hospital rupture occurring in two-thirds of patients.<sup>98</sup>



**Figure 145.5** Paravisceral abdominal aortic pseudoaneurysm, caused by *methicillin-resistant Staphylococcus aureus* aortitis. (A) Debridement of the infected aorta revealed rupture of the posterior aortic wall as well as thickened inflammatory phlegmon surrounding the paravisceral aorta. (B) *In situ* reconstruction using cryopreserved homograft. Celiac, superior mesenteric, and right renal arteries were incorporated with the beveled proximal anastomosis. The left renal artery was reimplanted.

## Abdominal Aorta

Surgical intervention is dependent on the location and extent of the infection and the patient's associated comorbidities. Infection of the aorta without a preexisting aneurysm tends to affect the posterior wall of the suprarenal or supraceliac segments. Infections of a preexisting aneurysm occur most commonly in the infrarenal location due to the frequency of aneurysms in this location.<sup>99</sup> Pararenal or paravisceral aortic infections are a greater surgical challenge, and the need to preserve the renal/visceral perfusion dictates that an *in situ* reconstruction is preferred rather than over-sewing of the aortic stump coupled with aortic-based bypasses to maintain visceral and renal perfusion.<sup>100–103</sup> Overall, surgical mortality due to infected abdominal aortic aneurysms varies between 15% to 38%.<sup>104</sup>

Currently, an *in situ* reconstruction is more commonly performed for infected abdominal aortic aneurysms.<sup>104</sup> Conduit options include cryopreserved arterial allografts, antibiotic treated Dacron grafts or creation of a “neo-aorto-iliac system” (NAIS) with autogenous femoral–popliteal vein.<sup>26,27,105–111</sup> When an *in situ* reconstruction is considered not possible or prudent, extra-anatomic reconstructions in a clean tissue plane with excision and debridement of the infected aneurysm and surrounding tissues may be employed. For all surgical reconstructions, liberal use of omental or muscle flaps is important. Recently, endovascular approaches have been utilized as either a bridge or definitive therapy in selected patients.<sup>49</sup>

### Cryopreserved Arterial Allografts

Arterial allografts for *in situ* aortic reconstruction have been shown to be quite resistant to reinfection by Gram-negative

organisms as well as other bacteria and microorganisms.<sup>112</sup> Allografts are procured from organ donors, processed using antimicrobial solutions, and then cryopreserved using liquid nitrogen. When requested, the allografts can be thawed in under 45 minutes. They are surgically easy to handle and can be used in most infected fields without concern for reinfection. The main limitation to the use of arterial allografts is expense and availability. Grafts need to be ordered usually 24 hours in advance and supply may be limited. Depending on the number and segments of allograft needed, the cost can be more than \$20,000. Nevertheless, cryopreserved arterial allografts are an excellent option and are our preferred option for *in situ* revascularization, especially for those infections involving the pararenal and paravisceral aorta (Fig. 145.5). A recent multicenter review demonstrates 75% 1-year survival and 51% at 5 years with freedom from graft explant of 99% at 1 year and 88% at 5 years.<sup>113</sup>

Complications associated with allograft reconstruction include peri-anastomotic hemorrhage, graft limb occlusion, and pseudoaneurysm. A higher rate of graft failure and hemorrhage has been associated with aorto-enteric fistulae, and this should be taken into consideration when planning repair.<sup>114</sup> In a recent series, allograft-related morbidity was 11.8% compared with 57.1% in patients who underwent extra-anatomic bypass or *in situ* reconstruction with a prosthetic graft.<sup>115</sup>

### Antibiotic-Soaked Dacron Grafts

*In situ* reconstruction with prosthetic grafts has reported reinfection rates as high as 20%.<sup>116</sup> For this reason, antibiotic, usually rifampin-soaked, Dacron grafts are used for infected aneurysms with paravisceral and thoracoabdominal extension and in patients

who present in extremis and require rapid surgical management for control of hemorrhage and sepsis. Antibiotic-soaked grafts maintain their bactericidal activity by being coated with collagen or gelatin to provide a bond between the graft and antibiotic.<sup>117</sup> Rifampin has been the agent of choice given that it has broad-spectrum activity against Gram-positive and Gram-negative organisms.<sup>118</sup>

A cumulative review of antibiotic-soaked grafts found perioperative morbidity to occur in 20% to 60% of patients with a reported graft reinfection rate of 4% to 22%.<sup>118</sup> A series from the Mayo Clinic in patients who were treated with *in situ* rifampin-soaked Dacron grafts had an operative mortality of 20%, but no patients had a late graft reinfection.<sup>119</sup> Another series from the same group focused on 54 patients in whom *in situ* rifampin-soaked Dacron graft reconstruction was performed for aortic graft enteric erosion or fistula. Their protocol was excision of the infected graft, intestinal repair, reconstruction with *in situ* rifampin-soaked Dacron graft with omental wrap and long-term antibiotics.<sup>120</sup> Patient survival at 1 year, 5 years, and 10 years were 85%, 59%, and 40%, respectively, with no patients dying from graft-related complications.<sup>120</sup> Late graft-related complications occurred in 16% with 4% developing graft reinfection.<sup>120</sup> Another recent single-center series reported a 30-day mortality of 18% and a 2-year survival of 73% with silver-coated Dacron grafts bathed in 5000 IU neomycin/250 IU bacitracin solution.<sup>121</sup>

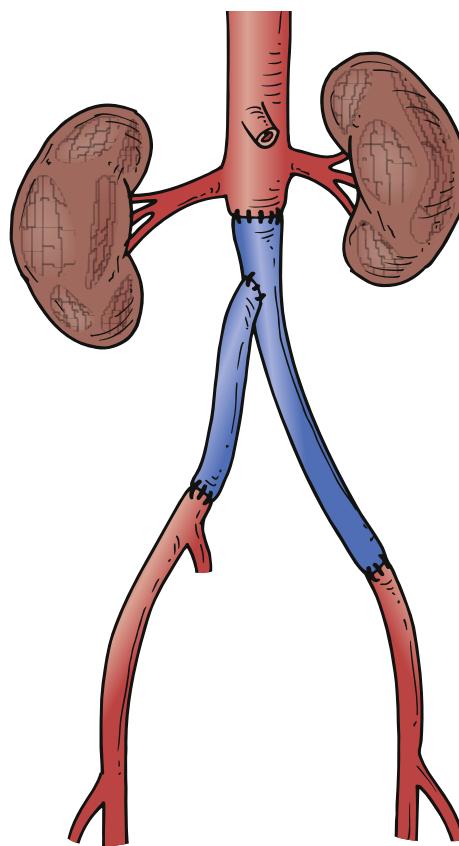
Small case series have reported high rates of graft reinfection in rifampin-soaked Dacron grafts when used in patients with active MRSA infection at the time of implantation.<sup>122</sup> *In vivo* canine experiments comparing resistance to MRSA growth with rifampin-soaked and silver-impregnated Dacron grafts have found in both graft configurations diminishing levels of bacterial growth suppression after 7 days.<sup>123</sup> Consequently, some authors advocate limiting antibiotic-soaked grafts to patients with low virulence organism infection.<sup>124</sup>

### **Neo-Aorto-Iliac System**

Described by Clagett, the NAIS procedure utilizes the deep femoral–popliteal vein to create a neo-aorto-iliac conduit.<sup>125</sup> The procedure has a prolonged operative time, averaging 10 hours, and because of that, it may be of limited use in patients with overt sepsis or the elderly with a multitude of comorbidities.<sup>126</sup>

The femoral–popliteal vein can be used in a number of different configurations to achieve *in situ* revascularization, depending on the extent of infection, the necessary reconstruction, and the availability of conduit. The most common configuration is demonstrated in Figure 145.6, and an intraoperative picture is demonstrated in Figure 145.7. Further details are provided in Chapter 49 (Graft Infection).

The femoral–popliteal veins provide a reasonably good size match for the aorta in most cases and are resistant to recurrent infection, with reinfection occurring in less than 2% of patients.<sup>127</sup> Primary patency rates are 87% and 82% at 2 and 5 years, respectively, along with primary-assisted patency rates of 96% and 94% at 2 and 5 years, respectively.<sup>128–130</sup>



**Figure 145.6** A common configuration of neo-aorto-iliac system reconstruction using an autogenous femoral vein. Various configurations can be used to accommodate more or less extensive infection or occlusive disease. (Courtesy G. Patrick Clagett, MD.)



**Figure 145.7** Neo-aorto-iliac system reconstruction with femoropopliteal vein in a patient with *Salmonella*-infected infrarenal aortic aneurysm. (Courtesy G. Patrick Clagett, MD.)

Despite the magnitude of the operation, the reported 30-day mortality rate is less than 10%, and the 5-year survival is 60% when used for an infrarenal aortic graft infection.<sup>130</sup> As evidenced by the excellent patency, graft stenosis after NAIS reconstruction is uncommon. The risk factors for stenosis include small graft size (<7 mm), history of coronary artery disease, and smoking.<sup>128</sup> Patients should be monitored by duplex ultrasonography to promptly detect and treat graft stenosis.

Specific morbidity associated with femoral–popliteal vein harvest includes the need for fasciotomy in 12% of patients, with a higher rate in patients with previous ipsilateral saphenous vein harvest. Compartment syndrome can be related to the compromised venous outflow following the vein harvest coupled with the large volume crystalloid resuscitation often required in these critically ill patients.<sup>127</sup> Late clinically significant chronic venous insufficiency develops in less than 15% of patients and is generally mild when it occurs.<sup>131</sup>

### Extra-Anatomic Abdominal Aortic Reconstruction

The primary extra-anatomic approach is an axillary–femoral bypass in a clean operative field followed by aneurysm resection, debridement of surrounding tissues, and aortic stump closure. In stable patients, the procedure can be staged with the extra-anatomic bypass being performed first, followed in a day or so by the definitive resection of the aneurysm. The axillary artery with the highest brachial pressure should be selected for inflow. Generally, an 8-mm ringed polytetrafluoroethylene graft is sufficient. Aortic stump closure can be difficult due to the limited and friable aorta available for closure. A two-layer closure is recommended buttressed with anterior spinal ligament and an omental pedicle when possible.

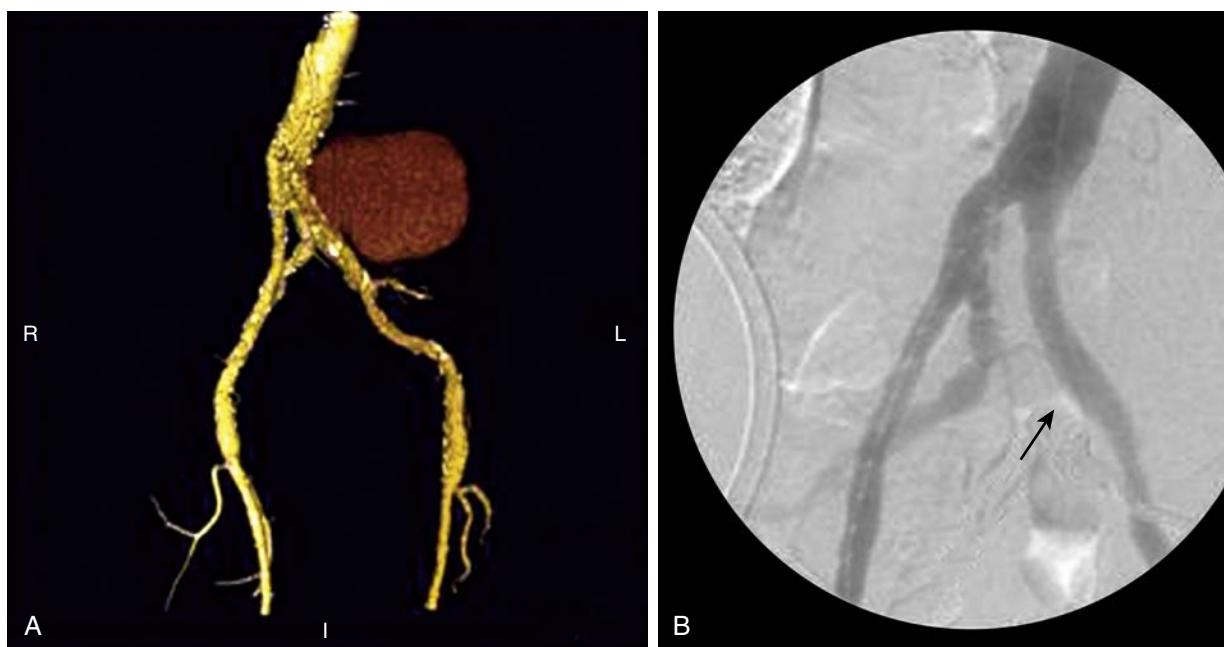
Although this method of reconstruction may seem like an attractive option in older, more debilitated patients, it is associated with significant perioperative morbidity and mortality. Because the infected aneurysm tissue must still be resected and the aorta closed, the added benefit of using an extra-anatomic bypass is less than would be expected. Furthermore, aortic stump disruption, which may occur late in the patient's course, has been reported in up to 12% of patients.<sup>132</sup> Five-year patency of the axillary–femoral graft is reasonably good at 70%.<sup>133</sup> However, infection of the extra-anatomic reconstruction can

occur in 6% to 20% of cases, often necessitating a very difficult *in situ* reconstruction.<sup>19,71,134–137</sup> Contemporary series have reported long-term survival to be equal to *in situ* reconstruction.<sup>104,138</sup>

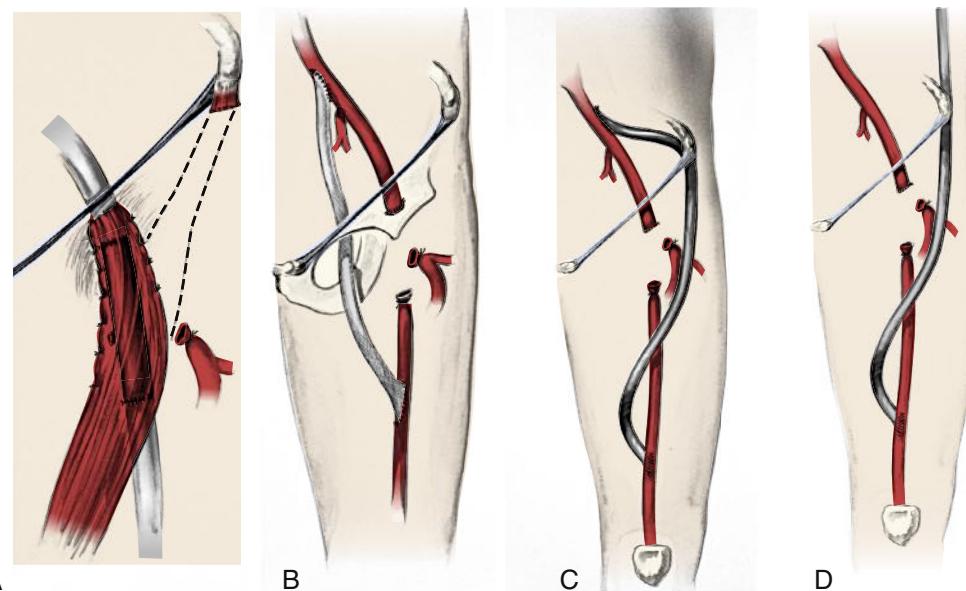
### Endovascular Aortic Repair

Endovascular aortic repair (EVAR) for infected abdominal aortic aneurysms has increased in recent years. A recent meta-analysis of 48 patients treated with EVAR found that a ruptured aneurysm and fever at time of operation were the two most significant predictors of persistent infection. Persistent infection after EVAR, in turn, had a poor outcome with 12-month survival of 39%. Persistent sepsis and re-bleeding were reported in 23% of the cases, but overall 30-day and 2-year survival were reasonable at  $89.6 \pm 4.4\%$  and  $82 \pm 5.8\%$ , respectively.<sup>139</sup> Another recent study found no significant difference between EVAR and open repair in the 24-month actuarial aneurysm-related event-free rate ( $78.3 \pm 9.7\%$  vs.  $80.1 \pm 8.9\%$ ).<sup>140</sup>

The virulence of the infectious organism is an important factor when contemplating EVAR. Some have found *Salmonella* to be associated with persistent and extended infection, while we have found that no patients treated with EVAR for MRSA infections survived at 1 year.<sup>49,141</sup> In addition, EVAR outcomes appear to be adversely impacted by the presence of aorta-aero-digestive fistulas with a reported 30-day mortality rate of 33% and overall mortality of 67%.<sup>142,143</sup> Finally, other authors have demonstrated that re-operation for these infected aneurysms, after being initially treated by EVAR, is more likely to be unsuccessful or more complicated, with higher operative mortality (Fig. 145.8A and B).<sup>139,141,144,145</sup> Consequently, if EVAR is chosen as the initial approach, it should be considered only a bridge to more definitive therapy in the patient who can tolerate an open reconstruction.<sup>143</sup>



**Figure 145.8** (A) Computed tomographic angiography findings in an 80-year-old debilitated woman demonstrating a large infected false aneurysm of the left common iliac artery. (B) Digital subtraction angiogram revealing exclusion of the pseudoaneurysm after emergency stent-graft (arrow) deployment for control of hemorrhage.



**Figure 145.9** Methods of femoral artery reconstruction. (A) Interposition vein autograft covered by rotated sartorius muscle. (B) Obturator bypass. (C) Lateral femoral bypass. (D) Axillary-to-distal femoral bypass. (A, B, and D, From Reddy DJ, Smith RF, Elliott JP Jr, et al. Infected femoral artery false aneurysms in drug addicts: evolution of selective vascular reconstruction. *J Vasc Surg*. 1986;3:718–724.)

## FEMORAL ARTERY

Infected femoral artery aneurysms are most commonly due to endovascular arterial access or illicit drug injection and often involve organisms that are highly resistant to conventional antibiotics. Clinically, these infections present with fevers, groin pain, cellulitis, and a pulsatile mass. Risk factors include obesity, diabetes mellitus, and groin hematomas after endovascular intervention. *S. aureus* and Gram-negative organisms are commonly cultured.

The reported rate of infectious complications related to femoral percutaneous procedures is less than 1%, but the innumerable procedures performed through femoral artery access on a daily basis means that it is not an infrequent clinical problem. Notably, some authors have described an association between the use of percutaneous closure devices with braided nonabsorbable suture and infected femoral artery aneurysms.<sup>31,146–150</sup>

The development of an infected femoral aneurysm in the setting of illicit drug abuse is a particularly challenging problem due to the presence of highly resistant organisms. These patients have a high rate of limb loss, and aggressive definitive treatment should be quickly undertaken. Because of organism virulence, the method of revascularization should be carefully considered, and wide debridement of the infected tissue with tissue culture should always be performed to guide antibiotic therapy.

Options for revascularization are described in Figure 145.9A and B and include an *in situ* interposition graft with autogenous vein or cryopreserved arterial allograft covered with a sartorius or other rotational muscle flap. Extra-anatomic reconstructions include obturator bypass, lateral femoral bypass, and axillary-femoral bypass with distal target either the superficial femoral or profunda femoris artery. With the exception of the infected aneurysms due to illicit drug injection, an interposition graft

using cryopreserved arterial allograft is in our practice the preferred option.<sup>151,152</sup> Due to the virulence of organisms associated with aneurysms due to illicit drug injection, ligation and an extra-anatomic method of revascularization or ligation alone is advisable.<sup>153</sup>

Ligation of the common femoral artery alone without reconstruction allows for limb preservation in cases in which the profunda–superficial femoral artery junction is maintained.<sup>154</sup> Collateral flow between the internal iliac artery and the distal extremity circulation, including the inferior gluteal artery, the obturator artery, and the inferior epigastric artery can provide sufficient perfusion for limb viability. However, the absence of a pedal artery Doppler signal during test occlusion of the distal iliac artery indicates inadequate collateral flow, thus precluding femoral artery ligation, as symptoms of ischemia can develop in up to 88% of patients, with disabling claudication the most common complaint (Fig. 145.10).<sup>155–158</sup> Finally, if ligation of the common femoral, superficial femoral, and profunda femoris arteries are required for control of the infectious process, the amputation rate has been reported to be as high as 33% in the absence of an extra-anatomic reconstruction; however, the University of Washington group recently reported that in their population ligation of the common femoral, superficial femoral, and profunda femoral arteries without reconstruction only required delayed reconstruction in 7% of patients (Table 145.2).<sup>5,14,16,154,159</sup>

## POPLITEAL ARTERY

Infected popliteal artery aneurysms are rare, and the available data comes mostly from case reports. This condition usually presents as a tender pulsatile mass with associated cellulitis, deep vein thrombosis from compression, lower extremity edema, and fever. Acute lower extremity ischemia may be present

due to thrombosis or rupture.<sup>160,161</sup> The most common etiology is septic embolization from endocarditis due to *Streptococcus* and *Staphylococcus* species.<sup>162</sup> *Salmonella* infections are associated with microbial arteritis and spontaneous rupture of a nonaneurysmal popliteal artery. Antibiotics against suspected organisms should be instituted early, and the duration of therapy should be guided by the treatment of the causative endocarditis. Arterial duplex and CTA are used to confirm the diagnosis, define the extension of the infection, and plan revascularization.<sup>163</sup>



**Figure 145.10** Arteriogram after ligation of the femoral artery bifurcation showing prompt reconstitution of the deep femoral artery by numerous collaterals (long arrow) with faint visualization of the slightly more distal superficial femoral artery (short arrow).

Surgical treatment includes wide debridement and excision of all infected segments. In many patients, the popliteal vein is also involved, and this should be excised as well. Reconstruction with an autogenous saphenous vein bypass is the preferred option performed through a medial approach. Other reports have described the use of *in situ* interposition cryopreserved arterial allografts with good results.<sup>115,162</sup>

## CAROTID ARTERY

Historically, most primary carotid infected aneurysms were the result of pharyngeal infections, but with the inception of antibiotics, carotid artery infections have become rare. Currently, as is the case with infected popliteal aneurysms, embolization due to endocarditis is the most common cause with *S. aureus* and *Streptococcus pyogenes* being the most common pathogens.<sup>164–166</sup>

Common clinical findings include fever, chills, and a pulsatile tender neck mass. The carotid mass is often medially deviated, leading to misdiagnosis as a pharyngeal mass. Patients can also present with dysphonia and dysphagia due to structural compression or with a neurologic deficit from cerebral embolism.<sup>166</sup> If left untreated, these aneurysms can shower septic emboli to the brain or rupture.<sup>167</sup> As in other arterial segments, diagnosis is confirmed by arterial duplex and CTA.

Because of the potential consequences of disruption and hemorrhage after *in situ* reconstruction, some authors recommend ligation and excision alone.<sup>168,169</sup> Ehrenfeld et al. demonstrated that ligation of the internal carotid artery is safe if the systolic carotid stump pressure exceeds 70 mm Hg and long-term anticoagulation is used.<sup>170</sup> However, some authors have reported late neurologic events after ligation in up to 20% to 60% of patients.<sup>171,172</sup> Extracranial–intracranial bypass has been utilized following ligation, as has *in situ* reconstruction of the carotid artery with an autogenous femoral or a saphenous vein.<sup>25,165,173</sup> Covered stents have been used to allow temporary exclusion of the aneurysm and control bleeding prior to definitive surgical management.<sup>174</sup> The rarity and complexity

**TABLE 145.2** Treatment Method and Results of Infected Femoral Artery False Aneurysms Secondary to Drug Addiction

Type of Aneurysm and Treatment	No. of Aneurysms	No. of Viable Limbs	Cases of Graft Sepsis (%)	No. of Amputations (%)
Common femoral artery: ligation–excision	14	14	–	0
Deep femoral artery: ligation–excision	11	11	–	0
Superficial femoral artery: ligation–excision	4	4	–	0
<b>Common Femoral Bifurcation</b>				
Ligation–excision	21	14	–	7 (33)
Reconstruction with autogenous vein	6	6	1	0
Reconstruction with synthetic prosthesis	3	3	3 (100)	0
Reconstruction by primary anastomosis	1	1	0	0
<b>Total</b>	<b>60</b>	<b>53</b>	<b>4</b>	<b>7 (12)</b>

From Reddy DJ, Smith RF, Elliott JP Jr, Haddad GK, Wanek EA. Infected femoral artery false aneurysms in drug addicts: evolution of selective vascular reconstruction. *J Vasc Surg*. 1986;3:718–724.

of these patients with an infected carotid artery aneurysm emphasizes the need for individualized and creative patient management.<sup>175–177</sup>

## UPPER EXTREMITY ARTERIES

Most infected aneurysms of the upper extremities are secondary to trauma and are occasionally the result of emboli from endocarditis. The use of percutaneous catheterizations and indwelling catheters for diagnostic procedures and arterial monitoring can lead to the development of infected brachial and radial artery aneurysms.<sup>178</sup> A tender mass with or without cellulitis is usually present, along with fever, chills, and leukocytosis. Infected radial artery aneurysms from indwelling catheters often have digital embolization as the first manifestation.<sup>179</sup> As with most pseudoaneurysms from direct arterial trauma, Gram-positive bacteria are the most frequently isolated organisms. Intravenous drug users are a frequently affected population, and as with femoral artery infections, the arterial involvement is often extensive, making management difficult. Additionally, autogenous vein conduit may be limited in this patient population, and distal arterial runoff may also be compromised from long-term use of illicit drugs.<sup>180</sup>

Ligation and excision of the infected arterial segment with debridement of surrounding tissue followed by revascularization is usually required if the infectious process involves the brachial artery. If the radial or ulnar artery alone is involved, ligation and debridement is generally well tolerated. When revascularization is needed, the use of the greater saphenous vein is the preferred choice; however, in the case of patients who use illicit drugs, an autogenous conduit may not be available. In these patients, prosthetic graft tunneled in a clean tissue plane may be required. Six weeks of culture-directed intravenous antibiotic therapy is recommended.

## VISCERAL ARTERIES

Visceral artery infected aneurysms are rare, with the superior mesenteric artery (SMA) being the most common site, followed by the celiac artery and its branches. These infected aneurysms usually result from an embolic event due to infectious endocarditis.<sup>181</sup> As reported in a recent series, intravenous drug abuse can also have an etiologic role.<sup>181,182</sup> When symptomatic, patients can have severe abdominal or back pain with a nonfixed tender pulsatile mass. Fever, nausea, gastrointestinal bleeding, and jaundice may also be present.<sup>182,183</sup> It is important to recognize that a significant percentage (19%) of patients have synchronous infected aneurysms at remote locations.<sup>182</sup> Diagnosis is confirmed by CTA, but in some patients, angiography may also be helpful. Location is usually within 5 cm of the SMA origin, and a single segment is affected. Rupture has been reported to occur in 38% to 50% of cases, and mortality after rupture approaches 30%.<sup>182,184</sup>

Surgical treatment includes ligation and excision of the affected segment; further revascularization is required in approximately 15% of patients and is dependent on visceral collateral flow and the location of the aneurysm. An autogenous conduit, usually the greater saphenous vein, is the preferred conduit.<sup>177,185,186</sup> After open repair and prior to closure, careful examination of bowel perfusion and viability is of utmost importance.<sup>182</sup>

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*Large series consisting of 54 patients with aortic graft enteric erosion or fistula who were treated with in situ rifampin-soaked grafts. No late graft-related deaths were noted, and in this cohort, 4% experienced graft reinfection.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Acute Deep Venous Thrombosis: Epidemiology and Natural History

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Based on a previous edition chapter by Andrea T. Obi, Jordan Knepper, and Thomas W. Wakefield

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Acute venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), are the most common preventable causes of hospital death<sup>1</sup> and a source of substantial long-term morbidity.<sup>2–4</sup> The impact on health is so great that the Surgeon General of the United States issued a “Call to Action” to combat VTE.<sup>5</sup> An understanding of the risk factors and natural history of VTE is essential in guiding prophylaxis, diagnosis, and treatment. In addition, recognizing underlying risk factors and the multifactorial nature of VTE may aid in the identification of situations likely to provoke thrombosis in both high-risk individuals and those with unexplained thromboembolism. Furthermore, understanding the natural history of VTE is important in defining the relative risks and benefits of anticoagulation, as well as the duration of treatment in individual patients.

1938

## EPIDEMIOLOGY

### Incidence

The incidence of recurrent, fatal, and nonfatal VTEs is estimated to exceed 900,000 cases annually in the United States alone.<sup>6</sup> A 35-year population-based study using the Rochester Epidemiology Project database of Olmsted County, MN demonstrated an overall average age- and sex-adjusted annual VTE incidence of 122 per 100,000 person-years (DVT, 56 per 100,000; PE, 66 per 100,000).<sup>7</sup> This study also demonstrated higher age-adjusted rates among men than women (134 vs. 115 per 100,000, respectively). First-time VTEs are approximated to occur in 250,000 US white individuals annually.<sup>8</sup> When compared with other racial populations,

Whites have a lower incidence of VTE than do African Americans (104 vs. 141 per 100,000) and a higher incidence of VTE than do Hispanics and Asian/Pacific Islanders combined (104 vs. 21 per 100,000).<sup>9</sup> However, the problem of VTE is not just isolated to the United States; it is a global issue. The estimates of VTE across the European Union were 684,019 cases of DVT, 434,723 cases of PE, with 543,454 VTE-related fatalities.<sup>10</sup>

## Populations Affected

The incidence of VTE varies with the population studied, use of thromboprophylaxis, the intensity of screening, and the accuracy of the diagnostic test employed. For example, individuals with acute spinal cord injury who were screened systematically with venography demonstrated DVT at a rate of 81%.<sup>11</sup> However, medical–surgical intensive care unit (ICU) patients who received thromboprophylaxis had a DVT rate reported at 10% to 18%,<sup>12</sup> compared with those who were not given DVT prophylaxis having a rate of 25% to 32%.<sup>12,13</sup> Interestingly, the risk of VTE in the critically ill patient population is not limited to the time actually spent in the ICU. A single-center study showed that of the VTEs diagnosed in the critically ill, 64% were diagnosed with a VTE after discharge from the ICU. It is suggested that prolonged immobility after discharge from the ICU may have contributed to the high rate of DVT.<sup>14</sup> Similarly, prolonged immobility contributes to increased rates of VTE in nursing home residents.<sup>15</sup> In summary, it appears that medical–surgical ICU patients are at lower risk for DVT compared with acute spinal cord injury, trauma, or neurosurgery patients, but at a comparable risk to patients who have had major orthopedic surgery, and at higher risk than medical–surgical ward patients.<sup>13,16</sup> Furthermore, a more recent study noted a high (15.2%) rate of DVT in critically ill trauma patients within the first week that did not vary regardless of whether or not prophylaxis was used.<sup>17</sup>

The importance of viral infection on VTE risk is also a timely and important topic. Patients who were critically ill with H1N1 influenza infections had a 23.3-fold higher incidence of PE and a 17.9-fold higher incidence of DVT than critically ill patients without H1N1 influenza. Additionally, moderate intensity infusion of systemic heparin anticoagulation provided significant protection from thrombotic events in the critically ill patients with H1N1 but not those without H1N1 influenza infection.<sup>18</sup> Early data suggests a similarly high risk of VTE in patients with COVID-19 and potential benefits of heparin prophylaxis.<sup>19–22</sup> However, the optimal dose of heparin prophylaxis or treatment for patients with COVID-19 remains unknown at this time, and whether it is better to use systemic heparin or low-molecular-weight heparin.

## Risk Factors

DVT occurring in the setting of a recognized risk factor is often defined as a secondary event, whereas those that occur in the absence of risk factors is termed primary or idiopathic.<sup>23</sup> Known risk factors for DVT are listed in Table 146.1.

**TABLE 146.1** Risk Factors for Acute Deep Venous Thrombosis and Pulmonary Embolism

Risk Factor for DVT or PE	Odds Ratio	95% Confidence Interval
<b>Hospitalization</b>		
With recent surgery	21.72	9.44–49.93
Without recent surgery	7.98	4.49–14.18
Trauma	12.69	4.06–39.66
<b>Malignant Neoplasm</b>		
With chemotherapy	6.53	2.11–20.23
Without chemotherapy	4.05	1.93–8.52
Prior central venous catheter or pacemaker	5.55	1.57–19.58
Prior superficial vein thrombosis	4.32	1.76–10.61
Neurologic disease with extremity paresis	3.04	1.25–7.38
<b>Varicose Veins</b>		
Age 45 years	4.19	1.56–11.30
Age 60 years	1.93	1.03–3.61
Age 75 years	0.88	0.55–1.43
<b>Congestive Heart Failure</b>		
Thromboembolism not categorized as a cause of death at postmortem	9.64	2.44–38.10
Thromboembolism categorized as a cause of death at postmortem	1.36	0.69–2.68

DVT, deep venous thrombosis; PE, pulmonary embolism.

Modified from Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160:809.

However, use of the terms “provoked,” “unprovoked,” and “idiopathic” may no longer be as relevant as they once were given changes in recommended treatments for patients with VTE. Rather, the emphasis has begun to shift towards identifying reversible risk factors whenever possible. The high incidence of acute DVT in hospitalized patients, the availability of objective diagnostic tests, and the existence of clinical trials evaluating prophylactic measures have helped to more readily identify high-risk groups in this population compared with the outpatient population. Malignancy, surgery, and trauma within the previous 3 months remain significant risk factors for outpatient thrombosis, whereas the prevalence of surgery and malignancy is higher among inpatients with DVT.<sup>24,25</sup> Approximately 47% of outpatients with a documented DVT have one or more recognized risk factors.<sup>24</sup> The incidence of VTE proportionally increases with the number of risk factors.<sup>26</sup> The 2005 Caprini score is currently the most widely utilized system in the country for surgical cases (Fig. 146.1)<sup>12,27</sup> while other scores are more common for medical patients. These include the Padua score<sup>28</sup> and the IMPROVE score,<sup>29</sup> both of which

Patient's name: \_\_\_\_\_ Age: \_\_\_\_\_ Sex: \_\_\_\_\_ Wgt: \_\_\_\_\_ lbs

**Choose all that apply**

**Each risk factor represents 1 point**

- Age 41–60 years
- Minor surgery planned
- History of prior major surgery
- Varicose veins
- History of inflammatory bowel disease
- Swollen legs (current)
- Obesity (BMI >30)
- Acute myocardial infarction (<1 month)
- Congestive heart failure (<1 month)
- Sepsis (<1 month)
- Serious lung disease incl. pneumonia (<1 month)
- Abnormal pulmonary function (COPD)
- Medical patient currently at bed rest
- Leg plaster cast or brace
- Other risk factors \_\_\_\_\_

**Each risk factor represents 3 points**

- Age over 75 years
- Major surgery lasting 2–3 hours
- BMI >50 (venous stasis syndrome)
- History of SVT, DVT/PE
- Family history of DVT/PE
- Present cancer or chemotherapy
- Positive factor V leiden
- Positive prothrombin 20210A
- Elevated serum homocysteine
- Positive lupus anticoagulant
- Elevated anticardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia

Type \_\_\_\_\_

**Each risk factor represents 2 points**

- Age 60–74 years
- Major surgery (>60 minutes)
- Arthroscopic surgery (>60 minutes)
- Laparoscopic surgery (>60 minutes)
- Previous malignancy
- Central venous access
- Morbid obesity (BMI >40)

**Each risk factor represents 5 points**

- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (<1 month)
- Stroke (<1 month)
- Multiple trauma (<1 month)
- Acute spinal cord injury (paralysis) (<1 month)
- Major surgery lasting over 3 hours

**For women only (each represents 1 point)**

- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion ( $\geq 3$ ), premature birth with toxemia or growth-restricted infant

**Total risk factor score**

Please see following page for prophylaxis safety considerations  
revised May 16, 2006

**Prophylaxis regimen**

Total risk factor score	Incidence of DVT	Risk level	Prophylaxis regimen	Legend
0–1	<10%	Low risk	No specific measures; early ambulation	
2	10–20%	Moderate risk	ES or IPC or LDUH, or LMWH	
3–4	20–40%	High risk	IPC or LDUH, or LMWH alone or in combination with ES or IPC	
5 or more	40–80% 1–5% mortality	Highest risk	Pharmacological: LDUH, LMWH, Warfarin, or Fac Xa alone or in combination with ES or IPC	<b>ES</b> — Elastic stockings <b>IPC</b> — Intermittent pneumatic compression <b>LDUH</b> — Low dose unfractionated heparin <b>LMWH</b> — Low molecular weight heparin <b>Fac Xa</b> — Factor X inhibitor

**Prophylaxis safety considerations:** Check box if answer is 'YES'

**Anticoagulants: Factors associated with increased bleeding**

- Is patient experiencing any active bleeding?
- Does patient have (or has had history of) heparin-induced thrombocytopenia?
- Is patient's platelet count  $<100,000/\text{mm}^3$ ?
- Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, clopidogrel, salicylates)?
- Is patient's creatinine clearance abnormal? If yes, please indicate value \_\_\_\_\_

If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures.

**Intermittent pneumatic compression (IPC)**

- Does patient have severe peripheral arterial disease?
- Does patient have congestive heart failure?
- Does patient have an acute superficial/deep vein thrombosis?

If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures.

**Figure 146.1** The Caprini risk factor tool to predict the risk of venous thromboembolism. *DVT*, deep venous thrombosis; *PE*, pulmonary embolism. (From Wakefield T, Henke P. *Complications in Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011:353.)

have been externally validated but with only moderate discriminatory ability (see Ch. 20, Clinical Evaluation of the Venous and Lymphatic Systems).<sup>30</sup>

### Age

VTE occurs at all ages, although a higher incidence has consistently been associated with advanced age. In a community-based study of phlebographically documented DVT, the yearly incidence of DVT was noted to increase progressively from almost 0 in childhood to 7.65 cases per 1000 in men and 8.22 cases per 1000 in women older than 80 years.<sup>31</sup> The incidence of DVT increased 30-fold from those age 30 years to those older than 80 years. Rosendaal<sup>32</sup> similarly noted an incidence of 0.006 per 1000 children younger than 14 years, which rose to 0.7 per 1000 among adults 40 to 54 years old. Furthermore, Hansson and colleagues<sup>33</sup> found the prevalence of objectively documented thromboembolic events among men increased from 0.5% at age 50 years to 3.8% at age 80 years.

The influence of age on the incidence of VTE is likely multifactorial. The number of thrombotic risk factors increases with age, with three or more risk factors being present in only 3% of hospitalized patients younger than 40 years but in 30% of those 40 years and older.<sup>26</sup> Interestingly, it also appears that the number of risk factors required to precipitate thrombosis decreases with age.<sup>32</sup> This may be related to an acquired prothrombotic state associated with aging as higher levels of thrombin activation markers are found among older people.<sup>34</sup> Advanced age also has been associated with anatomic changes in the soleal veins and more pronounced stasis in the venous valve pockets.<sup>35,36</sup>

Venous diseases, including VTE, are rare in young children,<sup>3</sup> with an incidence of 0.006 per 1000 children younger than 14 years.<sup>32</sup> The incidence of VTE in hospitalized children younger than 18 years has been estimated to be 0.05%.<sup>37</sup> Early mobilization and discharge may partially explain the lower incidence in children.<sup>37</sup> However, the diagnosis is often not considered in pediatric patients, and few studies have systematically evaluated children for DVT. Over time the number of recognized cases in hospitalized children has increased from 0.3 to 28.8 per 10,000 from 1992 to 2005.<sup>38</sup>

VTE in children is almost always associated with recognized thrombotic risk factors,<sup>32,39–41</sup> and multiple risk factors are often required to precipitate thrombosis.<sup>32</sup> DVT may occur in as many as 3.7% of pediatric patients immobilized in halo-femoral traction for preoperative treatment of scoliosis,<sup>42</sup> 4% of children hospitalized in the ICU,<sup>43</sup> and 10% of children with spinal cord injuries.<sup>44,45</sup> Symptomatic postoperative DVT is regarded as unusual in children, although there are few data from studies using routine surveillance,<sup>46</sup> and autopsy-identified PE is approximately four times more frequent in pediatric patients who have undergone surgery than in the general pediatric medical population.<sup>39</sup> Other thrombotic risk factors in hospitalized children are local infection and trauma, immobilization,<sup>41</sup> inherited hypercoagulable states,<sup>32</sup> oral contraceptive use,<sup>47</sup> lower limb paresis,<sup>42</sup> and the use of femoral venous catheters.<sup>43</sup> Outpatient DVT is often associated with a prior DVT and thrombophilia.<sup>38</sup>

### Immobilization

Immobilization is a risk factor for VTE. Stasis in the soleal veins and behind the valve cusps is worsened by inactivity of the calf muscle pump,<sup>36</sup> which is associated with an increased risk of DVT. The prevalence of lower extremity DVT in autopsy studies also parallels the duration of bed rest, with an increase during the first 3 days of confinement and a rapid rise to very high levels after 2 weeks. DVT was found in 15% of patients dying after 0 to 7 days of bed rest, in comparison with 79% to 94% of those dying after 2 to 12 weeks.<sup>35</sup> Preoperative immobilization is also associated with a twofold increase in risk of postoperative DVT,<sup>48</sup> and DVT among stroke patients is significantly more common in paralyzed or paretic extremities (53% of limbs) than in nonparalyzed limbs (7%).<sup>49</sup> Patients with neurologic disease and extremity paresis or plegia have a threefold higher risk for DVT and PE, which appears to be independent of hospital confinement.<sup>50</sup>

### Travel

Immobilization as a thrombotic risk factor extends to include prolonged travel, particularly the “economy class syndrome,” which occurs in people who have sat in a cramped position during extended aircraft flights.<sup>51</sup> Several case series have reported the occurrence of PE in relation to extended travel,<sup>51–56</sup> although none has rigorously examined the prevalence relative to that of the general population, and few have thoroughly reported the presence of other risk factors. A high prevalence of preexisting venous disease and other thrombotic risk factors in this group of patients has sometimes been noted.<sup>34,56</sup> The question of prolonged travel as a risk factor is moderated by observations that extreme duration of venous stasis alone may fail to produce thrombosis<sup>57</sup> and that no consistent rheologic or prothrombotic changes have been demonstrated during prolonged travel.<sup>34,58</sup> However, PE is the second leading cause of travel-related death, accounting for 18% of 61 deaths in one study, suggesting that a relationship cannot be excluded.<sup>55</sup>

More evidence of a possible relationship between travel and DVT and PE has accumulated. In a case-control study, Ferrari and associates<sup>59</sup> found that long distance travel increased the risk of DVT, with an odds ratio (OR) of 4.0, and Samama<sup>60</sup> made similar observations (OR, 2.3). Scurr and colleagues<sup>61</sup> found a 10% risk of calf DVT in patients who traveled without compression stockings. Lapostolle and coworkers<sup>62</sup> observed that over an 86-month period, 56 of 135.3 million airline passengers had severe PE. The frequency among those who traveled more than 5000 km (~3100 miles) was 150 times as high as those who traveled less than 5000 km. In another case-control study, Paganin and associates<sup>63</sup> observed a high incidence of VTE in patients with risk factors for DVT who traveled long distances: in particular, a history of previous VTE (OR, 63.3), recent trauma (OR, 13.6), presence of varicose veins (OR, 10), obesity (OR, 9.6), immobility during flight (OR, 9.3), and cardiac disease (OR, 8.9) increased the risk of DVT. These investigators concluded that low mobility during flight was a modifiable risk factor for development of PE and that travelers with risk factors should increase their mobility.

After a consensus meeting, the World Health Organization published the following conclusions: (1) an association probably exists between air travel and DVT; (2) such an association is likely to be small and mainly affects passengers with additional risk factors for VTE; and (3) similar links may exist for other forms of travel.<sup>64</sup> The available evidence does not permit an estimation of actual risk. Even space flight has now been associated with the development of venous thrombosis, with an obstructive jugular vein thrombosis developing 2 months into a 6-month space mission on the space station.<sup>65</sup>

### History of Venous Thromboembolism

Approximately 23% to 26% of patients presenting with acute DVT have a previous history of thrombosis,<sup>31,66</sup> and histologic studies confirm that acute thrombi are often associated with fibrous remnants of previous thrombi in the same or nearby veins.<sup>67</sup> Depending on sex and age, population-based studies have demonstrated that recurrent VTE occurs in 2% to 9% of cases.<sup>3</sup>

The risk of recurrent VTE is higher among patients without identifiable risk factors for DVT.<sup>68</sup> In addition, primary hypercoagulability appears to have a significant role in many recurrences. Heterozygous factor V Leiden mutation, which is found in up to 5% of Caucasians and 1%–2% of African and Hispanic Americans, is associated with a four-time greater risk of initial VTE event than the general population. This is even greater in patients with homozygous mutations; however, this is quite rare.<sup>69</sup> Interestingly, factor V Leiden does not seem to have a clinically significant association with VTE recurrence risk, limiting its utility for testing in patients after an initial VTE event.<sup>70</sup> Other identified thrombophilias include inherited conditions (e.g., prothrombin gene mutation, protein C or S deficiency, and antithrombin deficiency) and acquired thrombophilias (e.g., anti-phospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, malignancy). Of the inherited thrombophilias, those with the greatest VTE risk are also the least prevalent, including protein C or S deficiency and antithrombin deficiency, each of which is found in <0.5% of the population.<sup>71,72</sup> The presence of antiphospholipid antibodies alone, which can be found in up to 5% of the general population, do not necessarily qualify for the diagnosis of the antiphospholipid antibody syndrome. This diagnosis requires confirmation of persistently elevated laboratory markers in the clinical setting of a VTE or other related thrombotic events.<sup>73</sup>

### Malignancy

Approximately 20% of all first-time VTE events are associated with malignancy.<sup>74</sup> An estimated 1 in 200 individuals with malignancy will develop either DVT or PE, a fourfold higher risk than those without malignancy.<sup>50</sup> Considering all-cause mortality of in-hospital death for cancer patients, one in seven will die of PE.<sup>75</sup> Strikingly, the discovery of an occult malignancy associated with an otherwise first-time idiopathic VTE is as high as 12% to 17% in some series.<sup>76,77</sup> In another 5% to 11% of patients, malignancy appears within 1 to 2 years of presentation for DVT.<sup>76–78</sup> Several series have documented a significantly higher risk of malignancy in patients with presumed

idiopathic DVT.<sup>76,79</sup> Among such patients, 7.6% have been noted to have a malignancy during follow-up, with an OR of 2.3 in comparison with those with secondary thrombosis.<sup>77</sup> The incidence of occult malignancy diagnosed within 6 to 12 months of an idiopathic DVT is 2.2 to 5.3 times higher than that expected from general population estimates.<sup>80,81</sup> The highest rates of VTE are associated with pancreatic malignancies, followed by kidney, ovary, lung, and stomach.<sup>82</sup>

The underlying mechanisms contributing to the hypercoagulable state in malignancy have been well studied and are multifactorial. ① Venous compression secondary to tumor growth, cancer-associated thrombocytosis, immobility, indwelling central lines, and chemotherapy or radiation therapy are all risk factors that increase the possibility of VTE.<sup>83</sup> However, the systemic prothrombotic response seen in malignancy is mediated by cytokines, inhibitors of fibrinolysis, and procoagulants.<sup>84</sup> ② Tumor cells can directly initiate hemostasis through constitutive expression of TF. TF is not normally expressed on resting vascular endothelium but rather induced by chemical mediators during times of inflammation or vessel damage to bind factors VII and VIIa. This complex of TF and factor VII activates factors X and XI through proteolysis, leading to the generation of thrombin.<sup>85</sup> Another mediator in malignancy-associated VTE is ③ cancer procoagulant (CP). The role of CP in coagulation is limited to its association with malignancy because it has not been identified in normal healthy tissue. CP serves as a direct activator of factor X, independent of the presence of factor VIIa. ④ platelet adhesion molecules glycoprotein Ib and glycoprotein IIb/IIIa (GPIIb/IIIa) have also been identified on tumor cells, allowing for platelet activation and aggregation.<sup>86</sup>

The prothrombotic contribution of ④ cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-1 (IL-1) mediate their actions through induction of TF on vascular endothelium, monocytes, and leukocytes.<sup>85,87</sup> In addition, IL-1 and TNF- $\alpha$  downregulate the expression of thrombomodulin, the receptor for thrombin, on the endothelial surface. This results in a decrease in thrombin–thrombomodulin complexes, the activating complex of protein C, a natural anticoagulant.<sup>85,87</sup> Furthermore, IL-1 and TNF- $\alpha$  stimulate the production of plasminogen activator inhibitor 1 (PAI-1), the main physiologic inhibitor of fibrinolysis.<sup>88</sup>

As many as 90% of patients with cancer have abnormal coagulation parameters, including increased levels of coagulation factors, elevated fibrinogen or fibrin degradation products, and thrombocytosis.<sup>89</sup> Elevated fibrinogen and thrombocytosis are the most common abnormalities, perhaps reflecting an overcompensated form of intravascular coagulation.<sup>89</sup> Levels of the coagulation inhibitors antithrombin, protein C, and protein S also may be reduced in malignancy.<sup>90</sup>

Markers of activated coagulation are elevated in the majority of patients with solid tumors and leukemia.<sup>89</sup> Fibrinopeptide A levels reflect tumor activity, decreasing or increasing in response to treatment or progression of disease, suggesting that tumor growth and thrombin generation are intimately related.<sup>89</sup> Furthermore, these levels may fail to normalize after

administration of heparin to patients with cancer and DVT, perhaps explaining why these DVTs may be refractory to anticoagulants.<sup>89</sup>

VTE is also associated with the treatment of some cancers. DVT complicates 29% of general surgical procedures for malignancy.<sup>90</sup> Preoperative activation of the coagulation system, as reflected by elevated thrombin–antithrombin complex values, is associated with a 7.5-fold increased risk of postoperative DVT.<sup>89</sup> Some chemotherapeutic regimens also predispose to DVT, and thrombotic complications may be as common as the more widely recognized infectious complications.<sup>91</sup> VTE has been reported in up to 6% of patients undergoing treatment for non-Hodgkin lymphoma, and in 17.5% of those receiving therapy for breast cancer.<sup>92</sup> Among patients with stage II breast cancer, thrombosis was significantly more common in those randomly assigned to 36 weeks of chemotherapy (8.8%) than in those receiving only 12 weeks of treatment (4.9%).<sup>91</sup> Potential thrombogenic mechanisms associated with chemotherapy include direct endothelial toxicity,<sup>①</sup> induction of a hypercoagulable state,<sup>②</sup> reduced fibrinolytic activity,<sup>③</sup> tumor cell lysis, and<sup>④</sup> use of central venous catheters.<sup>92,93</sup> Some intravenous chemotherapeutic agents are associated with activation of coagulation and increased markers of thrombin generation, a response that is blocked by pretreatment with heparin.<sup>94</sup> An additional risk factor in some cancer patients is an elevated soluble P-selectin.<sup>95</sup>

## Surgery

The high incidence of postoperative DVT, as well as the availability of easily repeatable, noninvasive diagnostic tests, has allowed a greater understanding of the risk factors associated with surgery than in other conditions. Surgery constitutes a spectrum of risk that is influenced by patient age, coexistent thrombotic risk factors, type of procedure, extent of surgical trauma, length of procedure, and duration of postoperative immobilization.<sup>96</sup> The type of surgical procedure is particularly important.<sup>48</sup> Historically, the overall incidence of DVT is approximately 19% in patients undergoing general surgical operations, 24% in those having elective neurosurgical procedures; and 48%, 51%, and 61% among those undergoing surgery for hip fracture, hip arthroplasty, and knee arthroplasty, respectively.<sup>96</sup> On the basis of these data, patients can be classified as being at low, moderate, or high risk for thromboembolic complications. Approximately half of postoperative lower extremity thrombi develop in the operating room, with the remainder occurring over the next 3 to 5 days.<sup>97</sup> However, the risk for development of DVT does not end uniformly at hospital discharge. In one study, 51% of the thromboembolic events occurred after discharge from gynecologic surgical procedures.<sup>50</sup> Similarly, up to 25% of patients undergoing abdominal surgery have DVT within 6 weeks of discharge.<sup>61</sup> Heit and associates found a nearly 22-fold higher risk of DVT and PE among patients who were hospitalized following previous surgery.<sup>50</sup>

All components of the Virchow triad may be present in the surgical patient – perioperative immobilization, transient changes in coagulation and fibrinolysis, and the potential for gross venous injury. Immobilization is associated with a

reduction in venous outflow and capacitance during the early postoperative period.<sup>98</sup> Surgery is also accompanied by a transient, low-level hypercoagulable state, presumably mediated by the release of TF, which is marked by a rise in thrombin activation markers shortly after the procedure begins.<sup>98</sup> The thrombogenic potential of different surgical procedures appears to differ, with greater rises in thrombin activation markers during hip arthroplasty than after laparotomy.<sup>99</sup> Increased levels of PAI-1 are also associated with a decrease in fibrinolytic activity on the first postoperative day, the “postoperative fibrinolytic shutdown.”<sup>100</sup> This relationship between impaired fibrinolysis and postoperative DVT may be particularly important,<sup>101</sup> with preoperative and early postoperative elevations in PAI-1 correlating with the development of thrombosis in orthopedic patients.<sup>100</sup> Complications are also an important trigger: in a large VA study involving more than 76,000 patients, the strongest predictors of postoperative VTE included myocardial infarction, blood transfusion (>4 units), and urinary tract infection.<sup>102</sup>

## Trauma

The prevalence of DVT among autopsied trauma casualties has been reported to be as high as 65%, comparable to the 58% incidence among injured patients in modern venographic series.<sup>11</sup> Substantially lower DVT rates, ranging from 4% to 20%,<sup>103</sup> have been noted in series using duplex ultrasonography, although many patients studied were receiving prophylaxis and the limitations of ultrasound in screening asymptomatic patients are well recognized. Recent trauma was associated with nearly a 13-fold increase in risk.<sup>50</sup>

Although the risk of DVT may be less than 20% in some injured patients,<sup>11</sup> certain subgroups are at particularly high risk. Age (OR, 1.05 for each 1-year increment), blood transfusion (OR, 1.74), surgery (OR, 2.30), fracture of the femur or tibia (OR, 4.82), and spinal cord injury (OR, 8.59) have been significantly associated with the development of DVT in this population.<sup>11</sup> Other reported risk factors are a hospital stay longer than 7 days,<sup>104</sup> increased Injury Severity Score (ISS),<sup>104–106</sup> pelvic fractures,<sup>107</sup> major venous injury,<sup>108</sup> presence of femoral venous lines,<sup>109</sup> the duration of immobilization,<sup>104</sup> and prolongation of the partial thromboplastin time.<sup>103</sup>

As with postoperative DVT, many of the same pathophysiologic elements may be responsible for the high incidence of DVT in trauma patients. Less well appreciated is the hypercoagulable state after depletion of coagulation inhibitors and components of the fibrinolytic system. Fibrinopeptide A levels rise after injury,<sup>110</sup> consistent with activation of coagulation, whereas fibrinolytic activity has been found to increase initially and then decrease.<sup>111,112</sup>

## Pregnancy

The incidence of VTE in the pregnant population is 6 to 10 times greater than matched controls<sup>113</sup> and causes approximately 10% of all maternal deaths.<sup>114</sup> Using clinical evaluation, VTE has been reported at a rate of 1.3% to 7% during pregnancy and 6.1% to 23% in the postpartum period.<sup>115</sup>

However, studies that used venography, Doppler ultrasonography, or ventilation–perfusion scans for evaluation of clinically suspected thromboembolism have suggested an incidence of 0.029% to 0.055% in this population.<sup>116</sup> The risk of thrombosis appears to be two to three times greater during the puerperium, with the highest incidence found after cesarean section.<sup>117</sup> Interestingly, when VTE has been objectively documented, the occurrence of thrombosis is equally distributed throughout all three trimesters.<sup>118</sup>

DVT in pregnancy has been attributed to impaired venous outflow due to uterine compression because 97% of reported thromboses have been isolated to the left leg.<sup>118</sup> Furthermore, pregnancy is associated with transient hypercoagulable state due to increases in the levels of fibrinogen, von Willebrand factor, and factors II, VII, VIII, and X. Compounding this acquired functional resistance to activated protein C is also seen during pregnancy.<sup>119</sup> Similar protein S levels are decreased by 50% to 60% early during pregnancy, with free protein S levels comparable with hereditary heterozygous protein S deficiency.<sup>120,121</sup> The fibrinolytic system is also altered in pregnancy: levels of tissue plasminogen activator (tPA) are decreased and PAI-1 and PAI-2 increased.<sup>122</sup>

Both retrospective and prospective studies have demonstrated that between 30% and 50% of women with a pregnancy-associated VTE also have an inherited thrombophilia. This high incidence has led to the recommendation of screening for thrombophilia in those pregnant patients with a personal or family history of VTE.<sup>123,124</sup> The risk of puerperal DVT also increases with maternal age, suppression of lactation, hypertension, and assisted delivery but not with the number of pregnancies.<sup>125</sup>

## Oral Contraceptives and Hormonal Therapy

As suggested by case reports in the early 1960s, further studies have now established the use of oral contraceptives as an independent risk factor for the development of DVT. These studies noted ORs of 3.8 to 11.0 for thrombosis,<sup>126</sup> and an unweighted summary relative risk among 18 controlled studies was 2.9.<sup>127</sup> Approximately one-quarter of apparently idiopathic thromboembolic events among women of childbearing age have been attributed to oral contraceptives. Early studies also suggested that thromboembolism is responsible for approximately 2% of deaths in young women, with contraceptive-associated mortality rates of 1.3 and 3.4 per 100,000 among women aged 20 to 34 and 35 to 44 years, respectively.<sup>128</sup> The increased risk of thromboembolism appears to diminish soon after oral contraceptives are discontinued and is independent of the duration of use.<sup>129</sup>

Risk is correspondingly higher when oral contraceptive use is combined with other factors, such as surgery<sup>130</sup> and inherited inhibitor deficiencies (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).<sup>131</sup> The factor V Leiden mutation may be particularly important in this regard. Resistance to activated protein C, which occurs in the setting of the factor V Leiden mutation, has been reported in up to 30% of patients with contraceptive-associated thromboembolism.<sup>132</sup> The use

of third-generation oral contraceptives may act synergistically with the factor V Leiden mutation, raising thromboembolic risk 30- to 50-fold.<sup>133–135</sup>

Estrogenic compounds also increase the risk of VTE when used for lactation suppression<sup>125</sup> in treatment of carcinoma of the prostate and as postmenopausal replacement therapy.<sup>136</sup> Although estrogen doses used for postmenopausal replacement therapy are approximately one-sixth those in oral contraceptives, some data support an increased thromboembolic risk at these doses as well. Several studies show a twofold to fourfold higher risk of VTE among women taking hormone replacement therapy.<sup>136–140</sup> This increased risk is greatest during the first year of treatment.<sup>137–140</sup> However, given the relative infrequency of thromboembolism, this risk represents only one or two additional cases of thromboembolism per year in every 10,000 women in this age group.

Estrogen in pharmacologic doses is associated with alterations in the coagulation system that may contribute to this thrombotic tendency. Such alterations include decreases in PAI-1<sup>141</sup> and increases in blood viscosity, fibrinogen, plasma levels of factors VII and X, and platelet adhesion and aggregation.<sup>142,143</sup> An associated prothrombotic state is implied by rises in markers of activated coagulation occurring in conjunction with elevations of circulating factor VIIa and decreases in antithrombin and protein S inhibitor activity.<sup>142,144</sup> The extent to which antithrombin and protein S are depressed is significantly less with lower-estrogen preparations.<sup>145</sup>

## Blood Group

There also appears to be a relationship between VTE risk and the ABO blood groups, with a higher prevalence of blood type A and correspondingly lower prevalence of blood type O groups.<sup>31,146</sup> In reviewing the literature, Mourant and colleagues<sup>147</sup> found the relative incidence of type A to be 1.41 times higher among patients with VTE than among controls. The effect of blood type was greater in young women who were taking oral contraceptives or were pregnant; the relative incidence of type A among patients with VTE was 3.12 in those taking oral contraceptives and 1.85 in those who were pregnant. A relationship between soluble endothelial cell markers and ABO blood group is known to exist, with significantly lower levels of von Willebrand factor among those with type O blood.<sup>145</sup>

## Geography and Ethnicity

There are also geographic differences in the frequency of VTE, as the incidence of postoperative DVT in Europe has been noted to be nearly twice that of North America.<sup>90,96</sup> Higher rates of thromboembolism have also been noted in the central United States compared with either coast.<sup>148</sup> Autopsy series suggest that although the prevalence of thromboembolism is identical among American Black and White patients, it is significantly higher than in a matched Ugandan Black population.<sup>149</sup> A similar autopsy series noted the prevalence of thromboembolism to be 40.6% in Boston and 13.9% in Kyushu, Japan.<sup>150</sup>

Unfortunately, regional variations in underlying medical and surgical conditions, as well as in prophylactic measures and diagnostic methods, may confound any apparent differences in the incidence of thromboembolism among different ethnic and geographic groups. Nevertheless, it is certainly conceivable that differences between ethnic groups might arise from either genetic and/or environmental factors. Such differences seem likely based on recognized geographic differences in the spectrum of mutations leading to congenital anticoagulant deficiencies.<sup>151</sup> Such theoretical concerns are also supported by geographic variability in the incidence of the factor V Leiden mutation. The factor V Leiden allele has a prevalence of 4.4% in Europeans, corresponding to a carrier rate of 8.8%, but the allele has not been identified in Southeast Asian or African populations.<sup>129</sup>

## Inflammatory Bowel Disease

Clinical series have reported VTE to complicate inflammatory bowel disease (IBD) in 1.2% to 7.1% of cases.<sup>152,153</sup> Crohn disease has incidence rates of 31.4/10,000 person-years and 10.3/10,000 person-years for DVT and PE, respectively. Ulcerative colitis also has a high incident rate of 30.0/10,000 and 19.8/10,000 person-years for DVT and PE, respectively. Such thromboses frequently occur among young patients, are more common with active disease, and may affect unusual sites, such as the cerebral veins.<sup>152,153</sup> Greater extent of colonic disease in ulcerative colitis portends a higher risk of VTE. Most cases are not associated with inherited hypercoagulable states. However, fibrinopeptide A elevations in IBD suggest that active inflammation is associated with activation of coagulation, possibly mediated by endotoxin-induced monocyte activation.<sup>152–154</sup>

## Systemic Lupus Erythematosis

A syndrome of arterial and venous thrombosis, recurrent abortion, thrombocytopenia, and neurologic disease may complicate systemic lupus erythematosus (SLE) when accompanied by the presence of antiphospholipid antibodies.<sup>155</sup> Lupus anticoagulant and anticardiolipin antibodies may be seen in association with SLE; with other autoimmune disorders; with nonautoimmune disorders, such as syphilis and acute infection, with drugs, including chlorpromazine, procainamide, and hydralazine; and with older age.<sup>156</sup>

Lupus anticoagulant is present in 34% of patients with SLE and anticardiolipin antibodies in 44%, in comparison with 2% and 0% to 7.5%, respectively, of the general population.<sup>156</sup> Among patients with SLE, those with lupus anticoagulant are at a sixfold higher risk for VTE, whereas those with anticardiolipin antibodies are at a twofold greater risk.<sup>157</sup> The incidence of arterial or venous thrombosis is 25% in patients with lupus anticoagulant and 28% in patients with anticardiolipin antibodies.<sup>156</sup>

## Varicose Veins

Varicose veins are also included as a risk factor for acute DVT, although frequently only as a marker of previous venous disease.<sup>158</sup> Most studies evaluating thrombotic risk have been

performed in inpatients with other major risk factors for DVT. Such studies have inconsistently supported varicose veins as a risk factor in postoperative, post-stroke, or postmyocardial infarction cases.<sup>49,158,159</sup> The importance of varicose veins in otherwise healthy outpatients with DVT has been questioned by some researchers<sup>160</sup> because varicose veins were not identified as independent risk factor in young women,<sup>161</sup> although some studies of postmenopausal women have reported varicose veins or superficial thrombophlebitis to be associated with ORs of 3.6 to 6.9 for the development of thromboembolism.<sup>137,140</sup>

However, Heit<sup>8</sup> found that varicose veins were independent predictors of DVT. They also reported that age is an important factor in these patients, reporting a higher correlation between DVT and varicosity in young patients. For example, 45-year-old patients with varicose veins had a fourfold higher risk of VTE, 60-year-old patients had a twofold greater risk, and 75-year-old patients had no increase in risk. This group also found that patients with previous superficial vein thrombosis were more than four times more likely to have DVT or PE.<sup>8</sup> Interestingly, a recent study of over 200,000 patients with varicose veins revealed a significantly increased risk of DVT (HR 5.3) but not as high a risk for PE (HR 1.73).<sup>162</sup>

## Iliac Vein Compression

The association of VTE and anatomic anomalies or syndromes represents a congenital risk factor responsible for DVT in both the upper and lower extremities. Left iliac vein compression by the right iliac artery and fifth lumbar artery was first described in cadavers by May and Thurner, who hypothesized that chronic pulsation of the right iliac artery and mechanical obstruction led to intimal hypertrophy of the vein wall and subsequent venous obstruction.<sup>163</sup> In actuality, it was Virchow who had initially observed that iliofemoral vein thrombosis was five times more likely to occur in the left leg than in the right leg over a century earlier.<sup>164</sup> Although left lower extremity venous hypertension associated with or without left iliofemoral DVT has come to be known as May–Thurner syndrome, it is important to recognize, if only for historical nomenclature, that a similar syndrome was described by Cockett in 1965 (*Cockett syndrome*) and took popularity over the term *May–Thurner syndrome* in Europe. However, it was Cockett who associated the acute phase of iliofemoral DVT secondary to compression of the iliac vein with the long-term consequence of chronic venous insufficiency (CVI). In addition, it was Cockett who noted that surgical intervention for the purpose of alleviating the skin ulcers and varicosities associated with iliac vein compression was ineffective unless the underlying disease process was identified.<sup>165</sup>

May–Thurner syndrome is more common in young to middle-aged women, especially after multiple pregnancies. The presenting symptom is often acute onset of left leg pain and swelling secondary to thrombosis (see Ch. 20, Clinical Evaluation of the Venous and Lymphatic Systems). Atypically, patients may present with symptoms of CVI that are unresponsive to compression stockings, leg elevation, and a calf exercise program.<sup>166</sup> Early 20th century postmortem dissections

revealed a 22% to 32% incidence of left iliac vein compression.<sup>167</sup> Modern computed tomography imaging has revealed that in an asymptomatic population, the average amount of compression on the left iliac vein was 35%, and 24% of this population demonstrated greater than 50% compression.<sup>167</sup> Although individuals in such series were asymptomatic, the incidence of symptomatic left common iliac vein compression presenting with either edema or DVT is estimated to be between 37% and 61%.<sup>168,169</sup> Interestingly, the presence of an abdominal aortic aneurysm was associated with a significantly less amount of compression on the left common iliac vein by the right common iliac artery secondary to a higher prevalence of tortuosity in that artery.<sup>170</sup>

## Popliteal Vein Entrapment

Although arterial entrapment syndrome is well described in the literature, popliteal vein entrapment has been reported to occur either alone or with the artery in 10% of cases.<sup>171</sup> Anatomic anomalies of the medial head of the gastrocnemius have been associated with popliteal vascular entrapment. However, when venous entrapment occurs in a setting without arterial entrapment, both the medial or the lateral head of the gastrocnemius have been shown to contribute.<sup>172</sup> Bony tumors and hypertrophied fibrous fascia have also been associated with isolated venous involvement.<sup>173,174</sup> Traditionally, popliteal artery entrapment has been more associated with the male gender; venous entrapment has been reported to occur 70% of the time in females.<sup>175</sup> The presentation is often that of a young adult with signs of CVI, including leg swelling varicosities, skin changes, and DVT. Another group with a high incidence of both DVT and PE are patients presenting with popliteal venous aneurysms, where the rate of PE at presentation may be as high as 30%; thus, the recommendation that all popliteal venous aneurysms be repaired.<sup>176</sup>

## Other Risk Factors

Traditional risk factors for VTE have also included obesity and cardiac disease; however, the evidence supporting these risk factors remains equivocal. Among postmenopausal women, a body mass index of greater than 25 to 30 kg/m<sup>2</sup> has been associated with a significantly increased risk of VTE.<sup>138,140</sup> Some investigators have reported obesity to be associated with a two-fold greater risk for postoperative DVT, although multivariate analyses by others has not demonstrated obesity to constitute an independent risk.<sup>158</sup> Obesity (and past tobacco smoking) was not an independent risk factor of DVT in the Olmsted County study<sup>177</sup> and has not been proven to be a risk factor for the development of DVT after stroke.<sup>49</sup> However, obesity is a risk factor for recurrent DVT.<sup>178</sup>

Systemic hypercoagulability, congestive heart failure, and enforced bed rest may predispose patients who are hospitalized with acute myocardial infarction to DVT. The incidence of DVT in this population has been reported to be 20% to 40%.<sup>96,159,179</sup> Some investigators have noted the incidence of DVT to be higher among patients in whom myocardial

infarction was confirmed (34%) than in those in whom the diagnosis was excluded (7%). The prevalence of PE among autopsied patients has also not differed substantially from that in other inpatients.<sup>148,149</sup>

Although MI as a risk factor may be in question, those older than 60 years with congestive heart failure have a DVT rate of 54%.<sup>180</sup> However, the evidence supporting congestive heart failure as an independent risk factor for DVT is also conflicting. A variety of thromboembolic complications account for nearly half the deaths among patients who did not undergo anticoagulation after hospitalization for congestive heart failure, but congestive heart failure has not been identified as an independent risk factor for postoperative DVT. The balance of evidence suggests that severely ill medical patients are at significant risk for VTE,<sup>181</sup> although it is difficult to define the additional risk associated with cardiac disease.

## NATURAL HISTORY

The relative balance between organization, thrombolysis, propagation, and rethrombosis determines outcomes after acute venous thrombosis. From a clinical perspective, the most important events after thrombosis are recanalization and recurrent thrombosis.

### Recanalization

Impedance plethysmography was the first widely available noninvasive test permitting serial evaluations of outflow obstruction due to an acute DVT. Although this test could not distinguish between recanalization and the development of collateral venous outflow, results of such studies were found to normalize in 67% of patients by 3 months and in 92% of patients by 9 months.<sup>182</sup> Venous duplex ultrasonography allows individual venous segments to be observed over time and has further documented that recanalization does occur in most patients after acute DVT. In 21 patients monitored prospectively with duplex scanning, recanalization occurred in 44% of patients at 7 days and in 100% of patients by 90 days after the acute event.<sup>183</sup> Several additional studies<sup>184,185</sup> confirm the histologic findings that recanalization begins early after an acute DVT, with the greatest reduction in thrombus load occurring within 3 months of the event. Complete thrombus resolution has been reported in 56% of patients monitored for 9 months.<sup>183,186</sup> However, recanalization may continue for months to years after the acute event.<sup>185</sup>

### Recurrent Venous Thrombosis

Nearly 30% of patients will develop a recurrence within a 10-year time span.<sup>187</sup> Recurrences are more likely with the same event type as the incident event; for example, those who initially developed a PE are more likely to develop another PE instead of a DVT.<sup>188</sup> Independent predictors for recurrent DVT include increasing age, obesity, malignant neoplasm, and extremity paresis. In a series of older landmark trials, among patients with proximal DVT, recurrent VTE events were found in 5.2%

of patients treated with standard anticoagulation for 3 months, compared with 47% of patients treated with a 3-month course of low-dose subcutaneous heparin.<sup>189,190</sup>

Despite the significance of these observations, reports of serial noninvasive follow-up examinations suggest that these studies may underestimate the incidence of new thrombotic events. In a series of 177 patients, most of whom were treated with standard anticoagulation measures, recurrent thrombotic events were observed in 52% of patients.<sup>191</sup> New thrombi were observed in 6% of uninvolving contralateral extremities, whereas propagation of thrombi to new segments occurred in 30% of involved limbs and rethrombosis of a partially occluded or recanalized segment in 31% of extremities. Propagation in the ipsilateral limb tended to occur as an early event at a median of less than 40 days after presentation, whereas rethrombosis and extension to the contralateral limb tended to occur sporadically as late events.

## Mortality

The severity of PE is shown in 30-year autopsy studies, which demonstrated a 26% incidence of PE in hospitalized patients, of which 9% was fatal. This translates to a 1% incidence of PE and a 0.36% incidence of death from PE in all hospitalized patients per year (see Ch. 152, Pulmonary Embolism: Presentation, Natural History, and Treatment).<sup>192</sup>

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Venous Thromboembolic Disease: Mechanical and Pharmacologic Prophylaxis

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## CHALLENGES IN CLINICAL PRACTICE 1954

Between 350,000 and 600,000 people in the United States (US) develop venous thromboembolism (VTE) each year, with at least 100,000 deaths from VTE annually.<sup>1</sup> The incidence of VTE is higher among currently or recently hospitalized patients,<sup>2</sup> the annual cost of treatment of VTE in the US as high as \$10 billion.<sup>3</sup> The US Surgeon General recognized deep vein thrombosis (DVT) and pulmonary embolism (PE) as major health problems in 2008 in a call to action for prophylaxis,<sup>1</sup> and the Agency for Healthcare Research and Quality updated a guide for quality improvement in preventing VTE in 2016, which identified VTE among the most common preventable causes of hospital death.<sup>4</sup> This chapter provides an overview of risk factors, risk stratification models, methods of VTE prophylaxis, a discussion of specific surgical populations, and recommendations regarding VTE prophylaxis.

## RATIONALE FOR RISK STRATIFICATION AND PROPHYLAXIS

A number of patient-specific and procedural risk factors for VTE have been identified,<sup>5</sup> allowing for individualized risk assessment.<sup>6</sup> Risk factors are categorized as strong, moderate, and weak in *Box 147.1*<sup>15</sup> and further discussed below. There has not been much change in the specific risk factors for VTE in hospitalized patients over the past two decades, until the COVID-19 pandemic, as COVID infection is one of the diseases with highest risk for VTE.

**Strong risk factors** include hip or leg fracture, hip or knee replacement, major general surgery, major trauma, and spinal cord injury. An early trial on VTE prophylaxis from 1959 compared 150 patients with hip fracture who were given a vitamin K antagonist to 150 who were given no prophylaxis,

**BOX 147.1****Risk Factors for VTE****Strong risk factors (odds ratio >10)**

Fracture (hip or leg)  
Hip or knee replacement  
Major general surgery  
Major trauma  
Spinal cord injury

**Moderate risk factors (odds ratio 2–9)**

Arthroscopic knee surgery  
Central venous lines  
Chemotherapy  
Congestive heart or respiratory failure  
Hormone replacement therapy  
Malignancy

Oral contraceptive therapy

Paralytic stroke  
Pregnancy/post-partum  
Previous venous thromboembolism  
Thrombophilia

**Weak risk factors (odds ratio <2)**

Bed rest >3 days  
Immobility due to sitting (e.g., prolonged car or air travel)  
Increasing age  
Laparoscopic surgery  
Obesity  
Pregnancy/antepartum  
Varicose veins

(From Anderson Jr FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I-9.<sup>5</sup>)

and found VTE in 29% of control participants compared to 3% of the treated participants.<sup>7</sup> In patients undergoing surgery, there is a linear relationship between length of surgery and incidence of VTE.<sup>8</sup> In trauma patients, proximal DVT was seen in 12% of patients within the first 2 weeks and 35%–40% of patients with spinal cord injury during the first 3 months.<sup>9</sup>

**Moderate risk factors** include cancer and chemotherapy, prior VTE, thrombophilia, congestive heart failure, respiratory failure, and hormone replacement, oral contraceptives, and postpartum status. In a study of over 2000 patients undergoing surgery for an abdominal cancer, the incidence of VTE was 2%, and 46% of deaths in the study were due to VTE.<sup>10</sup> Chemotherapy also increases the risk of VTE: women undergoing chemotherapy and surgery for breast cancer had three times higher risk of VTE compared to those undergoing surgery alone.<sup>11</sup> A case-control study found that patients with a history of VTE were eight times more likely to develop a new VTE during a high-risk period such as perioperatively, during an illness, or during immobilization, compared with those without a prior history.<sup>12</sup> Thrombophilia naturally increases the risk of VTE. The most common inherited thrombophilias in the US are factor V Leiden (with a lifetime risk of VTE of 10%), the prothrombin gene mutation, protein C and S deficiencies, and antithrombin deficiency.<sup>13</sup> Antiphospholipid antibodies are the most common acquired thrombophilia. In congestive heart failure, there is a higher incidence of VTE with a decreasing ejection fraction.<sup>5</sup> Alterations in hormones, whether hormone replacement therapy, oral contraceptive use, or pregnancy and postpartum state, increase risk of VTE. It is important to note this is also a varying exposure: oral contraceptives with less than 35 µg of ethinyl estradiol are associated with a lower incidence of VTE in the community compared with those containing more than 50 µg.<sup>14</sup>

**Weak risk factors** include bed rest, immobility, increasing age, obesity, and varicose veins. Bed rest and immobility contribute to venous stasis. The incidence of DVT is also higher

among patients with leg plaster casts, leading to a recommendation they receive prophylaxis for the duration of their immobilization.<sup>15</sup> Patients over 40 years of age are at higher risk of VTE with the risk approximately doubling for each decade of age.<sup>16</sup> While obesity was noted as a risk factor for DVT in an early study,<sup>17</sup> Heit et al. did not find an association between BMI and DVT in their study of 627 community-dwelling residents.<sup>18</sup> In a study of cancer patients, presence of superficial phlebitis or varicose veins was associated with higher risk of VTE.<sup>19</sup>

**Risk Assessment Models**

While a number of risk-assessment models have been developed to guide decision making and balance the risk of a VTE event with risk of bleeding, some of the most commonly used are the “3 bucket” model, the Caprini, Padua, Rogers, and Improve scores.<sup>20</sup> In the “3 bucket” model (Table 147.1),<sup>21</sup> patient and procedural factors are used to categorize risk of VTE as low, moderate, or high risk, with recommended prophylaxis for each category.

The Caprini score was first described in 1991 and similarly categorizes patients at low, moderate, or high risk for VTE (Fig. 147.1).<sup>22</sup> A score of 0–1 is associated with <10% incidence of DVT and is considered low risk, with no specific prophylaxis indicated. A score of 2 is considered moderate risk and a score of 3–4 is considered high risk; those at moderate or high risk of DVT should receive mechanical and/or pharmacologic prophylaxis. A score of 5 or more is considered highest risk with a 40%–80% incidence of DVT without prophylaxis, and these patients may benefit from extended prophylaxis up to a month following surgery. However, these are historically derived rates which are from nonprophylaxed patients, and overestimate the actual VTE incidence. A meta-analysis published in 2017 pooled 13 studies including 7590 patients and found patients with higher Caprini scores were significantly more likely to have VTE events. There was no association between Caprini score and postoperative bleeding.<sup>23</sup>

**TABLE 147.1** “3 Bucket” Model<sup>[21]</sup>

<b>Low Risk:</b> Observation status, expected length of stay <48 hours. Minor ambulatory surgery unless multiple strong risk factors. Medical patients ambulatory in hall and not moderate or high risk. Ambulatory cancer patients admitted for short chemotherapy infusion.	No prophylaxis; reassess periodically, ambulate.
<b>Moderate Risk (most general medical/surgical patients):</b> Most general, thoracic, open gynecologic, or urologic surgery patients. Active cancer or past VTE/known thrombophilia in medical patient with length of stay >48 hours. Medical patients with decrease in usual ambulation and VTE risk factors (myocardial infarction, stroke, congestive heart failure, pneumonia, active inflammation/infection, dehydration, age >65).	Unfractionated heparin or low-molecular-weight heparin prophylaxis.
<b>High Risk:</b> Hip or knee arthroplasty, hip fracture surgery, multiple major trauma, spinal cord injury or major neurosurgery, abdominal–pelvic surgery for cancer.	Mechanical and pharmacologic prophylaxis.

### Thrombosis risk factor assessment

Patient's name: \_\_\_\_\_ Age: \_\_\_ Sex: \_\_\_ Wgt: \_\_\_ lbs

Choose all that apply

<b>Each risk factor represents 1 point</b>	<b>Each risk factor represents 2 points</b>
<input type="checkbox"/> Age 41–60 years <input type="checkbox"/> Minor surgery planned <input type="checkbox"/> History of prior major surgery (<1 month) <input type="checkbox"/> Varicose veins <input type="checkbox"/> History of inflammatory bowel disease <input type="checkbox"/> Swollen legs (current) <input type="checkbox"/> Obesity (BMI >25) <input type="checkbox"/> Acute myocardial infarction <input type="checkbox"/> Congestive heart failure(<1 month) <input type="checkbox"/> Sepsis (<1 month) <input type="checkbox"/> Serious lung disease incl. pneumonia (<1 month) <input type="checkbox"/> Abnormal pulmonary function (COPD) <input type="checkbox"/> Medical patient currently at bed rest <input type="checkbox"/> Other risk factors _____	<input type="checkbox"/> Age 60–74 years <input type="checkbox"/> Arthroscopic surgery <input type="checkbox"/> Malignancy (present or previous) <input type="checkbox"/> Major surgery (>45 minutes) <input type="checkbox"/> Laparoscopic surgery (>45 minutes) <input type="checkbox"/> Patient confined to bed (>72 hours) <input type="checkbox"/> Immobilizing plaster cast (<1 month) <input type="checkbox"/> Central venous access
<b>Each risk factor represents 5 points</b>	
<input type="checkbox"/> Elective major lower extremity arthroplasty <input type="checkbox"/> Hip, pelvis or leg fracture (<1 month) <input type="checkbox"/> Stroke (<1 month) <input type="checkbox"/> Multiple trauma (<1 month) <input type="checkbox"/> Acute spinal cord injury (paralysis)(<1 month )	
<b>For women only (each represents 1 point)</b>	
<input type="checkbox"/> Oral contraceptives or hormone replacement therapy <input type="checkbox"/> Pregnancy or postpartum (<1 month) <input type="checkbox"/> History of unexplained stillborn infant, recurrent spontaneous abortion ( $\geq 3$ ), premature birth with toxemia or growth-restricted infant	
<b>Total risk factor score</b> <input type="text"/>	

*Caprini incidence*  
 ↗ 0 - 1  
 Low = < 10%.  
 High = 40 - 80%.  
 ↗ 5

## METHODS OF PROPHYLAXIS

Risk stratification of all hospitalized patients will help determine who are considered moderate or high risk for VTE and should be treated with mechanical and/or pharmacologic prophylaxis to decrease VTE incidence.<sup>[24]</sup>

### Mechanical Methods of Prophylaxis

Mechanical methods of VTE prophylaxis include graduated elastic compression stockings,<sup>①</sup> intermittent pneumatic compression of the legs,<sup>②</sup> foot compression devices,<sup>③</sup> and inferior vena cava filters.<sup>④</sup>

## Elastic Compression Stockings

Graduated elastic compression stockings reduce the cross-sectional area of the veins and increase the velocity of venous blood flow. While compression stockings are made with a variety of levels of compression, those used for DVT prophylaxis have optimal flow augmentation with a pressure of 18 mm Hg at the ankle decreasing to 8 mm Hg at the thigh.<sup>25</sup>

A Cochrane review of randomized controlled trials of compression stockings for DVT prophylaxis following surgery first published in 2000<sup>26</sup> and updated in 2010 included 18 trials.<sup>27</sup> They found that while compression stockings alone decreased the incidence of DVT (13% of those with stockings developed DVT compared to 26% without stockings), compression stockings used with another method of DVT prophylaxis were more effective than stockings alone (4% of those with stockings and another prophylaxis developed DVT compared to 16% with the other method alone). Two other meta-analyses studying compression stockings in patients undergoing surgery found a 68% reduction in the incidence of DVT with compression stockings<sup>28</sup> and the combination of pharmacologic prophylaxis with compression stockings is more effective than stockings alone.<sup>29</sup>

Studies of compression stockings in hospitalized patients who have ~~not~~ undergone surgery are more inconclusive. A study of patients with stroke who were treated with compression stockings identified no decreased risk of VTE, but a higher risk of skin complications associated with stockings (5.1% vs. 1.3%).<sup>30</sup> Another study of patients with stroke compared thigh-high compression stockings to knee-high compression stockings and did find a lower incidence of VTE with thigh-high stockings, however this group also had skin complications in 3.9% of patients.<sup>31</sup> In a study of orthopedic patients, 56% of patients with thigh-high compression stockings developed constriction bands from folding or rolling of stockings.<sup>32</sup> Given that patients report more discomfort with thigh-high compression stockings<sup>33</sup> with a relatively high rate of skin complications, including pressure bands, tears, and skin necrosis, enthusiasm for compression stockings as DVT prophylaxis has waned. Approximately 2% of patients in a surgical intensive care unit were noted to have pressure injury related to compression stockings.<sup>34</sup> Notably, compression stockings should not be used for patients with severe leg edema, dermatitis, or those with peripheral arterial disease.

## Intermittent Pneumatic Compression of the Legs

Intermittent pneumatic compression (IPC) devices consist of inflatable boots or sleeves wrapped around the legs and secured by Velcro, that are connected to an electrical compressor that intermittently insufflates air to a preselected pressure. The sleeves can be applied to the calf alone, calf and thigh, foot and calf, or whole limb. Some types of IPC devices inflate the sleeves sequentially from distal to proximal to increase venous flow and are called sequential compression devices (SCDs). In addition to flow augmentation, IPC stimulates fibrinolytic activity through the release of endothelial tissue-type plasminogen activator (t-PA), prostacyclin, von Willebrand factor, and tissue factor pathway inhibitor.<sup>35–37</sup>

IPC devices are generally considered the most effective mechanical prophylaxis method in preventing postoperative DVT. In nonorthopedic surgery, the American College of Chest Physicians (ACCP) estimates a reduction in symptomatic VTE from 60 to 30 per 1000 as a result of using IPC in high-risk patients, and recommends use of IPC alongside pharmacologic prophylaxis or alone, in case of contraindication for pharmacologic methods.<sup>6</sup> In orthopedic surgery patients who are generally at higher risk of VTE postoperatively, ACCP guidelines recommend IPC in addition to pharmacologic prophylaxis.<sup>38</sup> A systematic review of the literature that analyzed 19 trials including 2225 patients concluded that IPC as monotherapy reduced DVT from 23% in patients without IPC to 10% in those receiving IPC ( $P < 0.0001$ ).<sup>39</sup> Similarly, a meta-analysis of 15 studies with 2270 patients who underwent different types of surgery showed that, in comparison with no prophylaxis, IPC reduced the risk of DVT by 60% ( $P < 0.001$ ).<sup>40</sup>

For patients with contraindications to pharmacologic prophylaxis including active bleeding or high risk of bleeding, IPC can be used alone. The ENDORSE study revealed that 9% of surgical patients considered at high VTE risk had some contraindication to receive pharmacologic prophylaxis.<sup>41</sup> However, IPC may not decrease PE incidence: a meta-analysis of nine studies including 3347 neurosurgery and orthopedic surgery patients found lower incidence of DVT with IPC devices, however no difference in PE.<sup>42</sup> Similarly, in the CLOTS 3 trial of patients immobilized following acute stroke, while IPC reduced the risk of DVT at 30 days after randomization, there was no difference in the secondary outcome of imaging- or autopsy-confirmed PE at 30 days after randomization.<sup>43</sup>

Risks of IPC are similar to compression stockings with a small risk of skin injury,<sup>43</sup> and thus use of IPC should be avoided in patients with dermatitis, severe edema, or peripheral arterial disease. While presence of DVT is a theoretical contraindication for IPC due to the concept that thrombus could be pushed to embolize, evidence for this is lacking. Patient discomfort and lack of reapplication after ambulation are common reasons for noncompliance.<sup>33</sup>

## Foot Compression Devices

Foot compression devices or foot pumps are inelastic slippers or boots with an air bladder in the area of the sole of the foot which rapidly inflates to a pressure up to 200 mm Hg over 3 seconds every 20 seconds. This plantar compression increases venous outflow and reduces stasis in the legs, similar to IPC. Although there is evidence that foot pumps reduce DVT compared to no prophylaxis,<sup>39</sup> pharmacologic prophylaxis has better results.<sup>44,45</sup> Foot pumps could represent an alternative in trauma patients in whom anticoagulants are contraindicated and leg IPC cannot be used because of the presence of casts, wounds, or external fixators.

## Ambulation

While early ambulation has been suggested by many as a strategy to reduce VTE, no objective data have proven this hypothesis to be true.<sup>46</sup> We do not recommend against ambulation, but the common myth that hospitalized patients are protected

from VTE by ambulation alone might put patients at higher risk if patient, physicians, and nurses choose ambulation rather than other proven approaches such as pharmacologic agents and/or compression devices.

### Inferior Vena Cava Filters

While inferior vena cava (IVC) filters do not prevent DVT, they can be used for PE prophylaxis in selected patients who cannot be pharmacologically anticoagulated and are extremely high risk for DVT (see Ch. 153, Vena Cava Interruption). The patient population in which that has been studied the most is the severely injured trauma patient. A meta-analysis examining the effectiveness of IVC filters in trauma patients found that while there was no difference in incidence of DVT, there was reduction in PE and fatal PE with IVC filter placement.<sup>47</sup> However, this practice has been less prevalent in recent years as the more aggressive use of early pharmacologic prevention has been shown to be safe, even in patients with traumatic brain injury, spinal cord injury, or solid organ injury. The use of IVC filters for prophylaxis in bariatric surgery patients has been shown to be ineffective, may be associated with higher rates of DVT, and should not be used.<sup>48</sup> The ACCP guidelines for both nonorthopedic and orthopedic surgery patients recommend against the use of IVC filter for primary prevention in patients with contraindications for both pharmacologic and other mechanical prophylaxis,<sup>6,38</sup> given potential complications associated with placement and the risk of an IVC filter serving as a nidus for thrombus.

## Pharmacologic Methods of Prophylaxis

### Aspirin

Aspirin, an irreversible cyclooxygenase inhibitor, blocks formation of thromboxane A2 thereby decreasing platelet aggregation and vasoconstriction (see Ch. 42, Antiplatelet Agents). Aspirin for VTE prophylaxis has mainly been studied in the context of extended prophylaxis following orthopedic surgery. In a multicenter trial of 778 patients who underwent total hip arthroplasty, after receiving 10 days of low-molecular-weight heparin (LMWH), patients were randomized to continue LMWH or to take 81 mg aspirin for a total duration of 28 days postoperatively. Aspirin was found to be noninferior to LMWH with 1.3% of the LMWH group and 0.3% of the aspirin group developing VTE.<sup>49</sup> In a subsequent trial published in 2018 by the same researchers, 3424 patients undergoing total hip arthroplasty or total knee arthroplasty received 5 days of oral rivaroxaban postoperatively then were randomized to receive extended prophylaxis either continuing rivaroxaban or switching to aspirin 81 mg. The study found no difference in VTE or bleeding events between aspirin and rivaroxaban.<sup>50</sup> A meta-analysis including studies comparing aspirin to anticoagulation in orthopedic patients included 1408 patients and found that although there was no difference in VTE, there was a lower risk of bleeding events with aspirin.<sup>51</sup> Due to its cost and accessibility, aspirin is an appealing option for extended outpatient prophylaxis. However, the data remain controversial and further trials will need to settle the debate about its use.<sup>52</sup>

### Warfarin

Although warfarin, a vitamin K antagonist, has generally been used for therapeutic anticoagulation and prevention of recurrent thromboembolism, numerous studies have been published over the past few decades examining warfarin for prophylaxis in orthopedic patients (see Ch. 41, Anticoagulant Therapy). In a trial including 670 patients undergoing knee arthroplasty, patients were randomized to receive LMWH or warfarin postoperatively. Warfarin was dosed to an international normalized ratio (INR) of 2.0–3.0. DVT was examined using venograms, and with 51.7% of the warfarin group developing DVT compared to 36.9% of the LMWH group.<sup>53</sup> In another study of 860 patients randomized to LMWH or warfarin after knee replacement, patients on fixed-dose LMWH had a lower incidence of DVT by venogram (27%) compared to patients treated with adjusted-dose warfarin (38%).<sup>54</sup> While the ACCP guidelines include warfarin as an option for VTE prophylaxis following orthopedic surgery,<sup>38</sup> the literature suggests alternative pharmacologic methods are more effective.

### Heparins

Unfractionated heparin (UFH) is a sulfated polysaccharide with a molecular weight of 15,000 Da which acts as an anticoagulant through inactivation of activated factor Xa and activation of antithrombin (see Ch. 41, Anticoagulant Therapy). LMWH is derived from UFH to fragments of ~5000 Da and its anticoagulation effect is through factor Xa inhibition. Because LMWH has lower protein binding than UFH, it has more predictable pharmacodynamic behavior. LMWH is renally excreted, thus should be avoided, or have its dose adjusted in patients with renal dysfunction.

ACCP guidelines for VTE prophylaxis recommend UFH or LMWH for patients undergoing orthopedic or nonorthopedic surgery who are at moderate or high risk for VTE.<sup>6,38</sup> A study of 1351 patients undergoing abdominal surgery compared LMWH to 5000 units UFH twice daily and found no difference in VTE, with 4.7% of patients in the LMWH group developing VTE compared to 4.3% of patients in the UFH group, but a significantly higher risk of bleeding in the UFH group (11.8% vs. 8.3%).<sup>55</sup> Another study of patients undergoing surgery for abdominal or pelvic cancer included 631 patients randomized to LMWH or UFH who were evaluated by venogram. They found 18.2% of the UFH group developed VTE compared to 14.7% of the LMWH group, with no difference in bleeding complications.<sup>56</sup> A study of patients undergoing total knee arthroplasty randomized patients to LMWH or 5000 units UFH three times a day and found no difference in the incidence of VTE or major bleeding events.<sup>57</sup> In a meta-analysis including 24 orthopedic and 34 general surgery studies comparing LMWH to UFH, the risk of VTE was lower for LMWH,<sup>58</sup> leading to a general preference for LMWH over UFH in many surgical specialties.

UFH and LMWH are effective pharmacologic prophylaxis in medical patients as well. In a study that evaluated 451 patients with heart failure or severe respiratory disease randomized to LMWH or 5000 units UFH three times a day, 8.4% of the LMWH group compared to 10.4% of the UFH group

had VTE events, with fewer deaths and bleeding events in the LMWH group.<sup>59</sup> A meta-analysis of trials studying prophylaxis after acute stroke included 2028 patients randomized to LMWH or UFH and found that LMWH was associated with fewer proximal DVTs, fewer PEs, and had no significant difference in bleeding or intracranial hemorrhage compared to UFH.<sup>60</sup>

### Fondaparinux = Arrixtra

Fondaparinux is a synthetic selective factor Xa inhibitor with a linear pharmacokinetic profile that allows it to serve as an alternative to LMWH. In a study of 1711 orthopedic surgery patients randomized to LMWH or fondaparinux, there was a lower risk of VTE and no difference in bleeding events.<sup>61</sup> In a meta-analysis of 7344 orthopedic surgery patients randomized to LMWH or fondaparinux, there was a lower risk of VTE with fondaparinux but a higher risk of major bleeding (2.7% vs. 1.7%).<sup>62</sup> The ACCP recommends fondaparinux as an alternative to LMWH or UFH for orthopedic surgery prophylaxis.<sup>38</sup> It can also safely be used in patients with a history of heparin-induced thrombocytopenia (HIT).

### Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) include dabigatran, a direct thrombin inhibitor, and the factor X inhibitors including edoxaban, apixaban, rivaroxaban, and betrixaban. While these agents are mostly used for therapeutic anticoagulation, there have been many studies of their effectiveness for VTE prophylaxis, primarily in the postoperative orthopedic surgery patient. In a randomized trial of 3494 patients undergoing total hip replacement, dabigatran 220 mg daily was compared to dabigatran 180 mg daily and LMWH. Both dabigatran dose groups were found to be noninferior to LMWH in VTE incidence and had no difference in bleeding events.<sup>63</sup> In a meta-analysis of 9581 patients undergoing hip or knee replacement, rivaroxaban 10 mg daily was more effective than LMWH in preventing symptomatic VTE with a similar bleeding risk.<sup>64</sup> Apixaban has also been shown to have similar effectiveness in VTE prevention compared to LMWH for orthopedic surgery patients, and may have lower risk of bleeding.<sup>65</sup> In a phase 3 trial, edoxaban 30 mg once daily was superior to enoxaparin 20 mg twice daily in patients undergoing knee replacement, with 6.9% of patients receiving enoxaparin developing VTE compared to 2.4% of patients receiving edoxaban.<sup>66</sup> There is also support for use of DOACs over heparin for extended prophylaxis in a meta-analysis of 15,977 orthopedic patients.<sup>67</sup> Rivaroxaban is also indicated for VTE prevention in the hospitalized medically ill patient, based on the MAGELLAN trial.<sup>68</sup>

### Missed Doses of Pharmacologic Prophylaxis

While it may seem intuitive, data show that missed doses of VTE prophylaxis in hospitalized patients is associated with higher rates of DVT events. In a study of trauma and general surgery patients, 58.9% of patients missed at least one dose of prophylactic enoxaparin. The incidence of DVT was 23.5% in the group that missed at least one dose of enoxaparin compared

to 4.8% of the group who did not miss any doses.<sup>69</sup> It is important to note that intermittent interruption of pharmacologic prophylaxis is common with well over 10% of doses not being administered, most often due to patient refusal.<sup>70</sup> Targeted quality improvement measures focused on educating both nurses and patients have been shown to dramatically impact these missed doses.<sup>71,72</sup>

## Combination of Mechanical and Pharmacologic Methods

The combination of mechanical and pharmacologic methods for VTE prevention should be considered complementary rather than competitive. The ACCP guidelines recommend IPC or compression stockings in addition to pharmacologic prophylaxis for patients who are high risk for VTE.<sup>6</sup> In a Cochrane review, the combination of heparin and compression stockings was better than heparin alone in the prevention of VTE in patients who underwent colorectal surgery.<sup>73</sup> In a study of 2551 cardiac surgery patients randomized to receive either heparin alone or in combination with IPC, the incidence of PE was 62% lower in patients who received combination therapy (4% vs. 1.5%).<sup>74</sup> In a meta-analysis of surgical patients, the addition of compression stockings or IPC to pharmacologic prophylaxis decreased the risk of DVT by 49% compared with anticoagulants alone.<sup>75</sup>

## SPECIFIC SURGICAL POPULATIONS

### Vascular Surgery

In a study of patients who underwent elective vascular surgery, VTE was more frequent in patients who underwent chest or abdominal surgery for aortic repair, and 40% of VTE events occurred after discharge.<sup>76</sup> Importantly, in this patient population, often vascular disease indicates the use of antiplatelet and anticoagulant agents that may also serve to prevent VTE events.

### Cancer Surgery

In patients undergoing cancer surgery, VTE is the most common cause of death at 30 days after surgery.<sup>10</sup> Therefore, several investigators studied the impact of extended prophylaxis for 4 weeks after surgery. In a study of 44,656 patients undergoing surgery for nine cancers, a third of VTE events occurred post-discharge.<sup>77</sup> In patients who underwent laparoscopic colorectal cancer operations, those treated with four weeks of prophylaxis had 0.9% incidence of VTE compared to 9.7% in the group treated with one week of prophylaxis.<sup>78</sup> Brown et al. recently reviewed the use of VTE prophylaxis in cancer surgery patients.<sup>79</sup>

### Cardiac Surgery

The ACCP guidelines recommend that cardiac surgery patients who have had an uncomplicated course receive IPC prophylaxis over pharmacologic prophylaxis due to the relatively high

risk of bleeding events.<sup>6</sup> In a large cohort of 92,699 patients undergoing coronary artery bypass grafting, the incidence of VTE with mechanical versus pharmacologic prophylaxis or combined therapy was not statistically different, nor was there a difference in risk of major bleeding.<sup>80</sup>

## Bariatric Surgery

The bariatric surgical population is at very high risk for developing VTE due to the presence of obesity and associated comorbid disease.<sup>81</sup> Adjusted dosing is required for these obese patients: in a study of 481 patients who underwent bariatric surgery, those treated with enoxaparin 40 mg twice daily had lower DVT rates than those treated with enoxaparin 30 mg twice daily, without a difference in bleeding events.<sup>82</sup> Others have confirmed the improved effectiveness of higher LMWH dosing.<sup>83,84</sup> In a study of 73,921 patients who underwent bariatric surgery, 73% of VTE events within 90 days of surgery occurred after discharge, leading to extended post-discharge prophylaxis for many patients.<sup>85</sup>

## Neurosurgery

Patients undergoing craniotomy or spinal surgery are at high risk for VTE given additional risk factors including benign and malignant tumors, immobility, prolonged hospitalizations, and prolonged courses of corticosteroids, but also could have highly morbid sequelae from bleeding events. The ACCP guidelines suggest that craniotomy and spinal surgery patients receive IPC over pharmacologic prophylaxis, although recommend pharmacologic prophylaxis be added for high-risk patients, such as those with cancer, once the bleeding risk decreases.<sup>6</sup> In a study of 40,663 patients enrolled in a multicenter study of VTE, within those who had undergone neurosurgery, 2.6% died of PE while none died of bleeding events following diagnosis of DVT.<sup>86</sup> Importantly, however, subtherapeutic doses of anticoagulation were given in one-third of these patients.

## Trauma

Major trauma patients are at high risk both for bleeding and for VTE. In trauma patients, data support the use of LMWH over unfractionated heparin for VTE prevention. In a study of 344 trauma patients without intracranial bleeding who were randomized to UFH or LMWH, 31% of patients treated with LMWH vs. 44% of patients treated with UFH developed DVT on venogram.<sup>87</sup> In patients who cannot be pharmacologically anticoagulated, there may be a role for temporary IVC filter placement to reduce the risk of PE during the acute phase of hospitalization.<sup>47</sup>

## Orthopedic Surgery

Orthopedic surgery patients are at high risk for VTE due to procedural factors including immobilization, local swelling, and potential vascular injury, in addition to patient-specific factors that may be present. The ACCP recommends that patients

undergoing total hip or knee arthroplasty or hip fracture surgery receive a minimum of 10–14 days of pharmacologic prophylaxis with LMWH in preference to other recommended agents.<sup>38</sup> Other guidelines can be found that suggest alternative medications (warfarin, aspirin, DOACs) rather than LMWH. The addition of IPC mechanical prophylaxis is also recommended.

## CHALLENGES IN CLINICAL PRACTICE

VTE prophylaxis will not prevent all PE and DVT.<sup>88</sup> Yet, even with the abundance of evidence showing that VTE prophylaxis is effective, historically less than half of hospitalized patients have been prescribed optimal prophylaxis.<sup>89</sup> Education alone is ineffective to move the needle; active strategies are required and recommended. Within the US, addressing the morbidity and mortality of VTE is a major goal of the Agency for Healthcare Research and Quality and they provide examples of quality improvement processes and resources to implement at the hospital level.<sup>4,90</sup> For example, computerized clinical decision support tools built into electronic health record systems have been shown to improve prescription.<sup>91,92</sup>

Thus, patient risk stratification, prescription of appropriate VTE prophylaxis based on the score, and audited receipt of the prophylaxis represent the best practices to prevent VTE in hospitalized patients.

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# Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment

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Based on a previous edition chapter by Fedor Lurie, David Paolini, and John Fish

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## INTRODUCTION

Acute thrombosis of the lower extremity deep veins is a significant public health problem affecting more than 350,000 people in the United States each year. **Lower extremity deep vein thrombosis (DVT)** is associated with a 6% mortality at 30 days and responsible for 100,000 to 300,000 deaths annually.<sup>1,2</sup> Its economic impact is substantial; in the United States, the annual cost of DVT was estimated to be 7.5 to 39 billion U.S. dollars in 2010.<sup>3</sup>

Advances in risk prediction scores, diagnostic imaging, and medical therapy, specifically direct oral anticoagulants, have

increased the safety and convenience of management of acute DVT, recurrent thrombosis, and DVT prophylaxis. Therapeutic anticoagulation remains the foundation of medical management of DVT and should be started in patients with high pre-test probability of acute DVT before confirmation or in patients with confirmed DVT, who do not have an absolute contraindication to anticoagulation. This chapter will present the diagnosis and management of DVT including optimal diagnostic and therapeutic approach to isolated distal DVT, duration of therapy for DVT, and appropriate indications for invasive treatment for acute DVT.<sup>4</sup>

## CLINICAL ASSESSMENT

The clinical manifestations of acute DVT are nonspecific and presentations vary from asymptomatic to dramatic including phlegmasia cerulea dolens or venous gangrene. Common signs and symptoms of DVT include a dull ache or pain in the leg, tenderness, swelling, erythema, cyanosis of the leg, and fever. These symptoms cannot reliably distinguish DVT from hematoma, cellulitis, congestive heart failure or superficial thrombophlebitis. Concurrent edema, cyanosis, and pain are features of phlegmasia cerulea dolens. Venous gangrene, a rare complication of DVT characterized by thrombotic occlusion of superficial collateral veins and sometimes associated with phlegmasia, can result in limb loss with palpable arterial pulses. It most often occurs in patients treated acutely with warfarin for cancer-associated thrombosis, or heparin-induced thrombocytopenia with thrombosis. Venous gangrene is associated with warfarin-mediated protein C depletion in the setting of ongoing thrombin generation.<sup>5,6</sup>

The diagnostic value of signs and symptoms of DVT and their combinations have been extensively studied.<sup>7–11</sup> The most common symptom, calf pain, has a sensitivity between 75% and 91% and specificity between 3% and 87%. The sensitivity of calf swelling for DVT diagnosis ranges from 35% to 97%, and its specificity ranges from 8% to 88%. In part, such variability is due to the high prevalence of the same signs and symptoms in patients without DVT.<sup>11</sup> In patients at high risk for DVT, the diagnostic value of clinical signs and symptoms is substantially higher. For example, in patients with cancer, the negative predictive value of the absence of swelling is as high as 97% for outpatients and 92% for inpatients.<sup>12</sup> A valid alternative diagnosis, such as cellulitis or a musculoskeletal disorder that explains the presence of signs and symptoms, also improves the negative predictive value of the clinical examination.<sup>13</sup>

High variability and lack of specificity limit the role of clinical examination in patients with suspected DVT. A meta-analysis of studies evaluating individual clinical features of DVT showed only past history of DVT and malignant disease are useful for diagnosis, and no individual clinical feature is useful for ruling out DVT.<sup>14</sup> The delay in clinical presentation makes the clinical diagnosis of DVT even more challenging. On average, patients are seen by a medical professional more than 4 days after onset of symptoms, and in more than 20% of patients, more than 10 days after onset.<sup>15,16</sup> Withholding treatment until clinical evaluation in primary care settings leads to inadequate management of more than 10% of patients with DVT.<sup>17</sup>

## DIAGNOSTIC TESTS

### D-Dimer

The concentration of D-dimer (DD) in plasma is a biomarker that is widely used for the diagnosis of DVT. DD is produced by degradation of cross-linked fibrin by plasmin. Elevated levels signify ongoing fibrin formation and degradation, which

occurs as part of the physiologic response to injury in patients undergoing surgical procedures or trauma, the normal changes during pregnancy, and the pathophysiologic processes in patients with cancer, infection, inflammation or thrombotic disorders. The degree of DD elevation in patients with DVT varies with the size and extent of the thrombus, the time from DVT onset, and the use of anticoagulation.

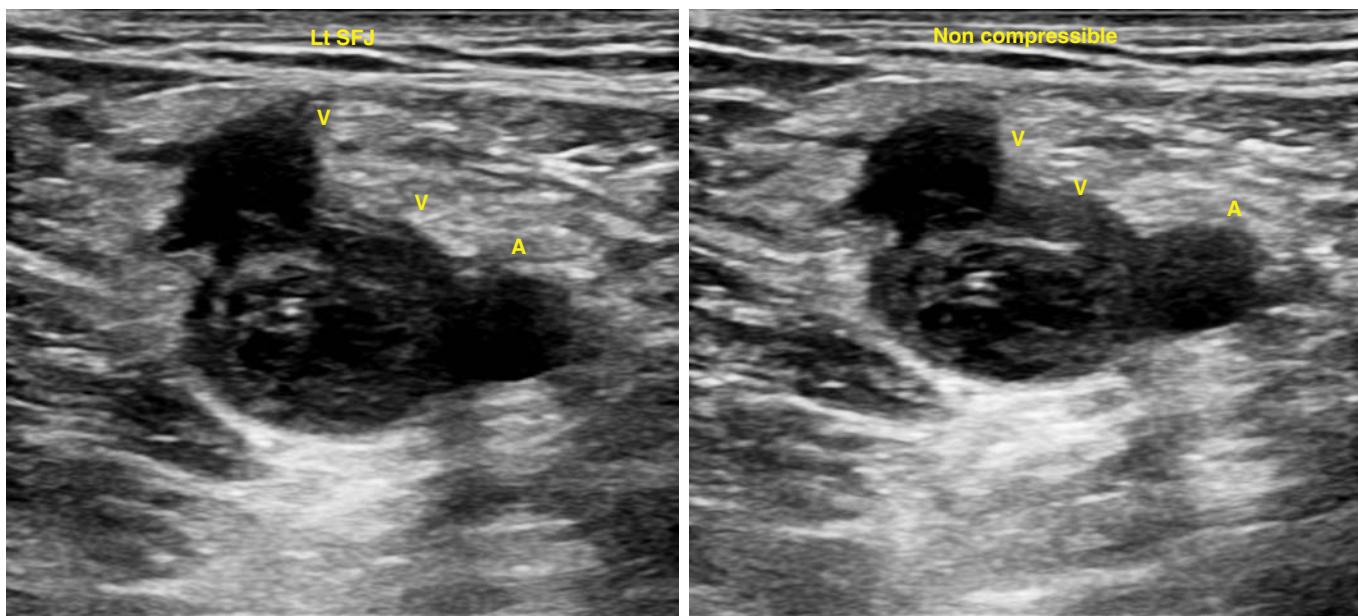
Currently used DD assays differ in result type (qualitative versus quantitative), the specificity of antibody to various binding sites on the DD molecule, units of measurements, reference values, speed and cost of testing. Quantitative point-of-care tests are more sensitive and may be superior to exclude DVT in these patients.<sup>18</sup> In general, use of point-of-care DD testing remains limited.

For the aforementioned reasons, DD assays are difficult to standardize and results are not comparable across laboratories.<sup>19</sup> In addition, assay sensitivity for DVT diagnosis ranges from 60% to 96%.<sup>20,21</sup> Enzyme-linked immunosorbent or immunofluorescent assays (ELISA or ELFA) and latex agglutination assays are the most sensitive assays.<sup>20,22–24</sup>

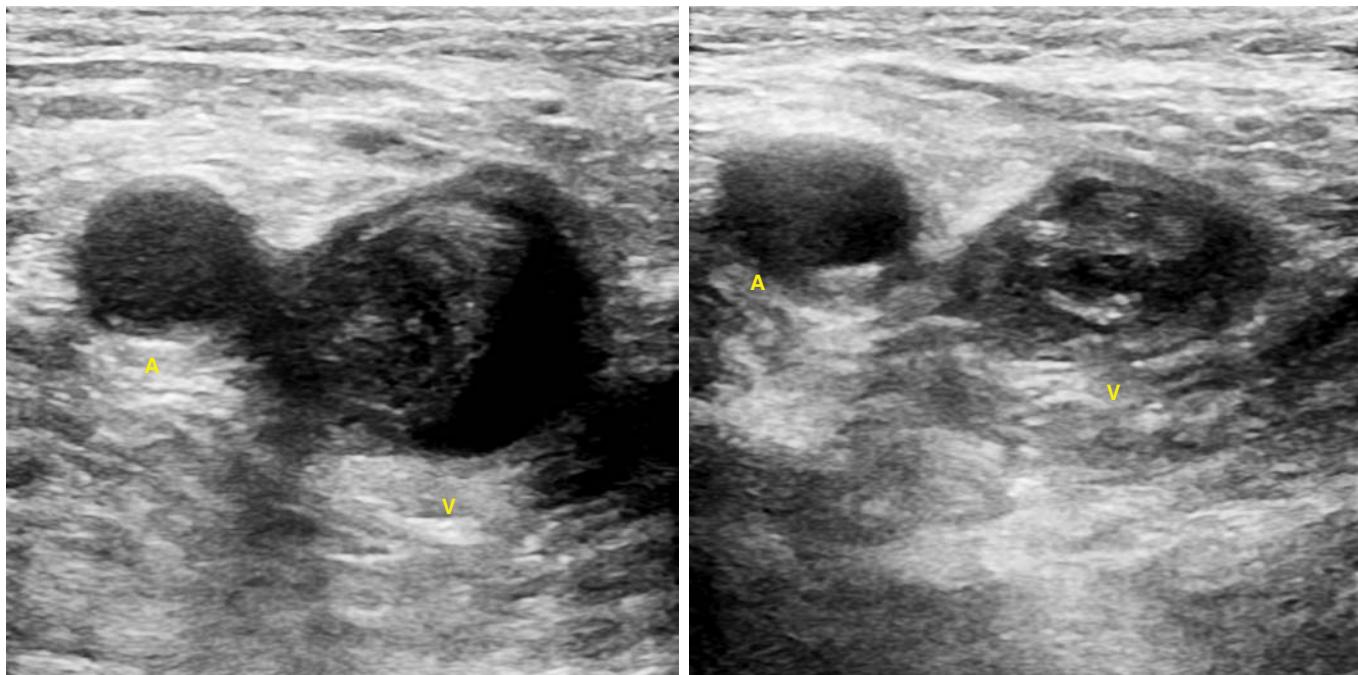
Low specificity limits the use of DD in a subset of patients with suspected DVT, including those who have a high pre-test probability of DVT, who are pregnant, have cancer, have had recent surgery or trauma, or who are hospitalized. However, concentration of DD below a cutoff value in low or intermediate pre-test probability cases indicates a very low probability of DVT. Recent adjustments of negative DD values based on age or pre-test clinical probability have increased the diagnostic value of DD testing in these patients.<sup>19</sup> The value of DD testing for evaluation of DVT is further population specific as it does not exclude DVT with sufficient accuracy in cases of distal thrombi, with use of anticoagulation, or of long duration between the initiation of thrombosis and testing.<sup>21,23,25</sup> Similar to clinical evaluation, the use of DD as a single diagnostic tool may result in inadequate management of more than 15% of patients with suspected DVT.<sup>21</sup> DD is best integrated with a clinical risk assessment of the patient (see below) and when used as a diagnostic test in the correct clinical context.

### Duplex Ultrasonography

Duplex ultrasonography is the first-line imaging modality for evaluation of DVT and has almost completely replaced venography because of its accuracy, lack of radiation, portability, noninvasiveness, and relative cost-effectiveness (see Ch. 25, Vascular Laboratory: Venous Duplex Scanning). In addition, ultrasound can distinguish among nonvascular pathologic processes such as inguinal adenopathy, Baker cyst, abscess, and hematoma. The primary diagnostic criteria of duplex ultrasound for DVT is non-compressibility of the vein under moderate pressure from the transducer with secondary criteria including increased intraluminal echogenicity, increased venous diameter, absence of spontaneous blood flow, and absence of flow augmentation with distal compression (Figs. 148.1–148.5).<sup>26</sup> Noncompressibility has excellent test characteristics for the detection of proximal DVT, with sensitivity and specificity of 97% and 94%, respectively.<sup>27</sup>



**Figure 148.1** Totally Occluding, Acute Common Femoral Vein (CFV) Thrombosis. Size of the CFV is increased, intraluminal echogenicity is increased, and the vein does not collapse under pressure from the transducer. *A*, artery; *V*, vein; *SFJ*, saphenofemoral junction.

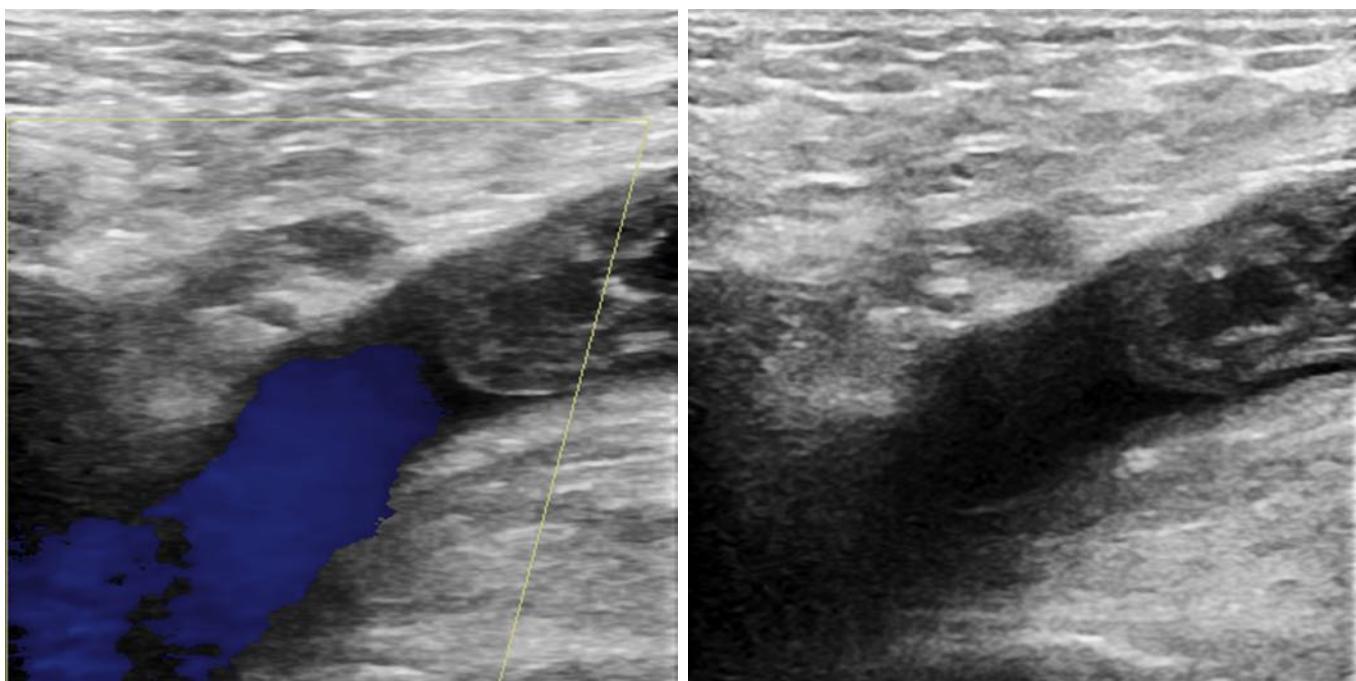


**Figure 148.2** Age-Indeterminate Thrombus in the Femoral Vein. The size of the vein is normal, intraluminal echogenicity is increased and uneven suggesting chronicity. The lumen is partially occluded suggesting either recanalization, or nonocclusive thrombosis. The vein partially collapses under pressure from transducer. *A*, artery; *V*, vein.

Limitations of compression ultrasound are its decreased accuracy in the evaluation of calf veins, fresh thrombi, and small segmental thrombi as well as limited use in patients with obesity,<sup>28</sup> significant edema,<sup>29</sup> overlying bandages or casts, and recent DVT with recrudescent symptoms. Additional pitfalls in venous duplex imaging include misidentification of veins, missing or duplicate venous systems, systemic illness, or hypovolemia resulting in decreased venous distention, and areas not

amenable to compression such as the iliac veins, the femoral vein at the adductor canal, and the subclavian veins. As with most ultrasound-based imaging studies, the quality of the examination depends on the skill of the individual performing the study.

There are a number of ultrasound strategies used for detection of DVT including single limited (popliteal veins and proximal vessels), serial limited, and whole-leg ultrasonography.<sup>30</sup>



**Figure 148.3 Thrombus in the Common Femoral Vein Extending into the External Iliac Vein.** The most proximal part of the thrombus appears free-floating. The flow from tributaries is present proximal to the thrombus.

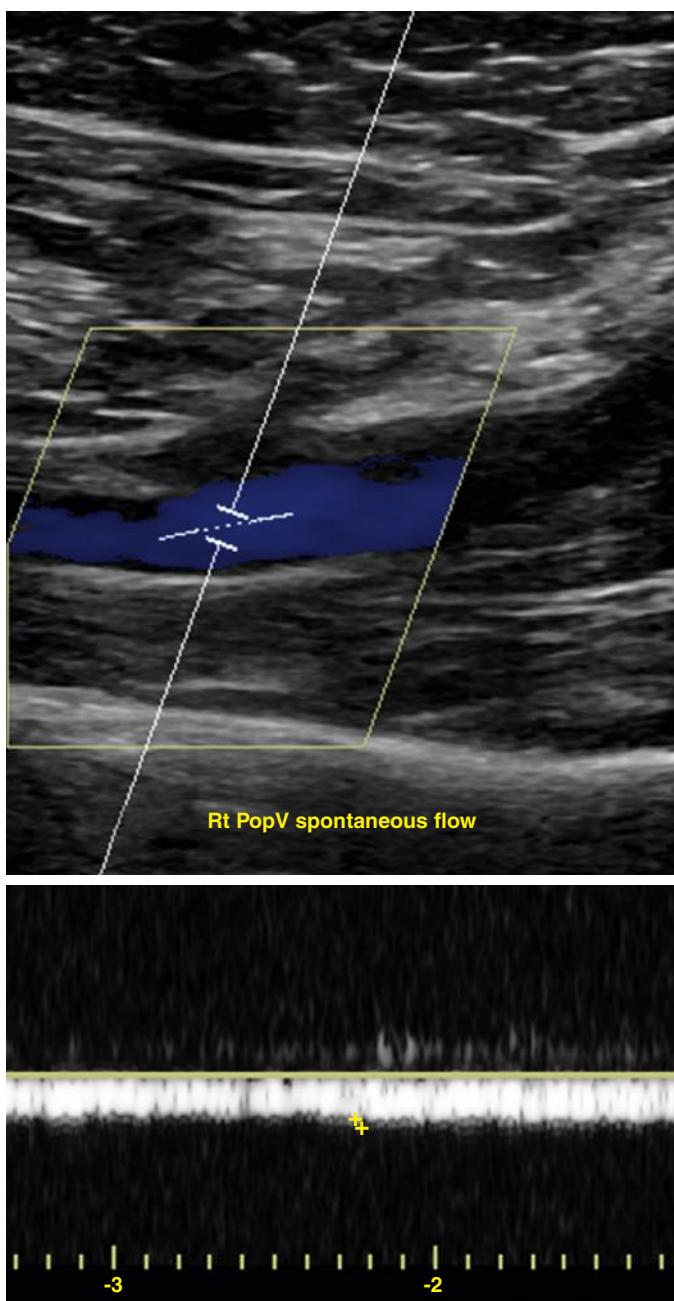
The serial limited strategy includes a repeat ultrasound approximately one week after an initial negative study if no alternative diagnosis is identified and assesses for proximal extension of distal DVT. Whole leg ultrasonography images both distal and proximal veins, eliminating the need for repeat imaging; however, it may identify distal DVTs that do not require anticoagulation. The risk of venous thromboembolism (VTE) with negative studies using either the whole-leg or serial limited strategy is less than 1%.<sup>31,32</sup> There is some controversy regarding the most appropriate diagnostic algorithm and the clinical importance of identifying and treating distal DVTs (isolated calf vein thrombi). The American College of Chest Physicians (ACCP) Guidelines for diagnosis of VTE are equivocal regarding use of serial proximal leg or whole-leg ultrasound in patients with moderate or high pre-test probability of DVT. However, the ACCP guidelines suggest whole-leg imaging for patients who are unable to return for serial imaging or with severe symptoms consistent with calf DVT.<sup>4</sup> Guidelines from other professional societies are similarly equivocal regarding the optimal initial ultrasound technique or favor whole-leg ultrasonography.<sup>33–35</sup> Studies to date have not found differences in the test performance characteristics of limited versus whole-leg strategies, although many institutions favor whole-leg imaging for comprehensive venous assessment.<sup>30,36</sup>

Ultrasound is not sufficiently accurate in all patients and test characteristics are affected by pre-test probability and location of thrombus. In contrast to the 94% sensitivity of ultrasound for detection of proximal DVT, the sensitivity is only 63% for distal DVT. This results in overall sensitivity of 90% and specificity 94% for detection of both proximal and distal DVT.<sup>14</sup> The diagnostic properties of ultrasonography

are also substantially different among subpopulations of symptomatic outpatients. In patients with a high Wells score (Table 148.1), sensitivity of proximal ultrasound is 91% for proximal and distal DVT and specificity approaches 100%; whereas sensitivity and specificity are 61% and 99%, respectively, in patients with an intermediate Wells score; and 67% and 98% in patients with a low Wells score.<sup>37</sup> In asymptomatic patients, sensitivities of ultrasound for detection of proximal and distal DVT are 66.7% and 39.0%, respectively, with an overall specificity of 96.5%.<sup>14</sup> These data indicate that the use of ultrasound alone for evaluation of DVT in low pre-test probability or asymptomatic patients may result in a significant number of false positives and is not recommended. However, in symptomatic patients or patients with intermediate or high pre-test probability, ultrasound can reliably rule out proximal DVT.

## Venography

Contrast venography for the sole purpose of diagnosing DVT is largely of historical interest. Diagnostic use of contrast venography has declined dramatically due to its expense and inconvenience, the potential for patient discomfort, and in light of the utility, accuracy, and safety of ultrasonography.<sup>38,39</sup> Venography may be helpful in cases when ultrasound suggests the presence of proximal obstruction by demonstrating a loss of the flow phasicity but fails to visualize the thrombus in iliac veins. Several historical studies found contrast venography was more accurate in the diagnosis of acute calf DVT, although ultrasound techniques have since improved and the clinical significance of this is uncertain.<sup>40,41</sup> Because of its high sensitivity and specificity, contrast venography can be used as the “golden

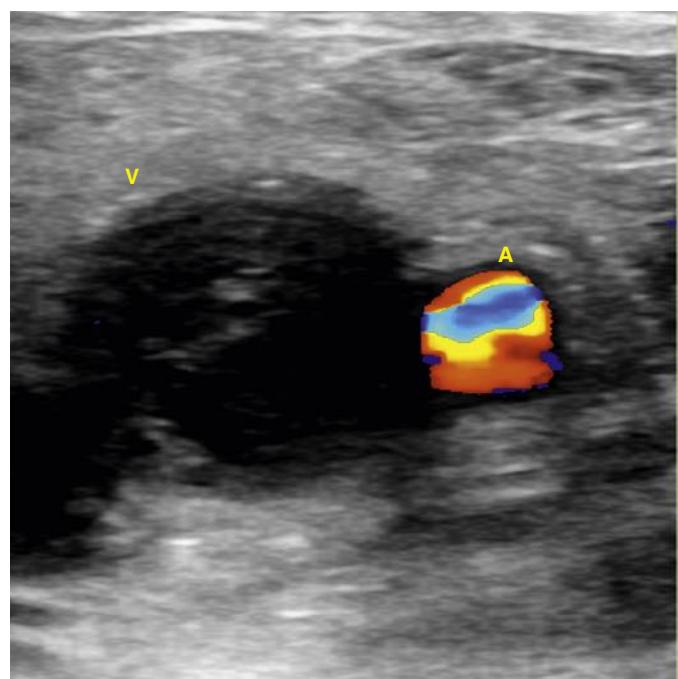


**Figure 148.4** Duplex ultrasound image of popliteal vein in extremity with acute femoral-popliteal venous thrombosis during spontaneous flow. Color Doppler indicates the presence of the flow in the popliteal vein. The spectral Doppler demonstrates low-velocity continuous flow with lost phasicity (respiratory and cardiac) indicating more proximal obstruction.

“backup” when the diagnosis of acute DVT remains in question after an ultrasound or in patients with previous DVT and non-diagnostic ultrasonography.<sup>42</sup>

## Computed Tomography Venography

While computed tomographic arteriography is an excellent technique for the diagnosis of PE, its venous counterpart, computed tomographic venography (CTV) has yet to gain traction in the diagnosis of acute DVT in the lower or upper extremities.



**Figure 148.5** Duplex Ultrasound Image of Acute Thrombosis of the Common Femoral Vein (CFV). Size of the CFV is increased, intraluminal echogenicity is increased, and the color Doppler demonstrates the absence of venous flow. *A*, artery; *V*, vein.

**TABLE 148.1 Modified Wells’ Criteria for DVT<sup>80</sup>**

Clinical Characteristic	Points
Active cancer (treatment within last 6 months or palliative)	+1
Paralysis, paresis, or plaster immobilization of lower extremity	+1
Bedridden 3 days or major surgery within past 12 weeks requiring general or local anesthesia	+1
Localized tenderness along deep venous system	+1
Entire leg swollen	+1
Calf swelling 3 cm compared to asymptomatic side	+1
Pitting edema isolated to symptomatic leg	+1
Collateral superficial veins (nonvaricose)	+1
Previous DVT	+1
Alternative diagnosis at least as likely as DVT	-2

Low-risk: Score 0 (prevalence of DVT 5%). Negative moderate or high-sensitivity D-dimer testing can rule out DVT.

Moderate-risk: Score 1–2 (prevalence of DVT 17%). Negative high-sensitivity D-dimer testing can rule out DVT.

High-risk: Score 3. Patients with a high-risk score should proceed directly to diagnostic imaging (ultrasound). *47%*

CTV is as accurate as ultrasound in the diagnosis of proximal DVT with a sensitivity and specificity of 98% and 100% in the thigh and 94% and 100% in the pelvis, respectively,<sup>43–45</sup> and an overall positive predictive and negative predictive values of 92% and 100%, respectively.<sup>46–49</sup> Use of CTV has the benefit of evaluating pelvic veins and the inferior vena cava

(IVC), the assessment of which are limited with ultrasound, as well as of detecting other etiologies of lower extremity swelling such as malignancies in the pelvis or extrinsic compression by other vascular structures such as iliac vein compression syndrome (also called May–Thurner syndrome).<sup>50,51</sup> When CTV is used in conjunction with evaluation of PE, it adds only 3 to 5 minutes to the examination, making it an attractive option as the sole diagnostic modality for acute lower extremity DVT and PE.<sup>52</sup> Limitations of CTV include artifacts from orthopedic implants, poor venous enhancement, interpretation errors due to inexperience or nearby pathology, and the requirement for contrast administration which is a concern for patients with renal dysfunction. It is worth noting not all studies found CTV sufficiently accurate in the diagnosis of acute DVT with CTV. Peterson et al.<sup>53</sup> demonstrated that although the sensitivity is high at 93%, producing a 97% negative predictive value, the ability of CTV to accurately diagnose DVT has a specificity of 71%, giving a positive predictive value of only 53%; and others have shown a 50% false-positive rate for CTV for pelvic DVT.<sup>54</sup>

## Magnetic Resonance Venography

This technology is based on the detection of moving versus stationary tissues. MRV can be used with or without contrast enhancement. Non-contrast-enhanced techniques include time-of-flight (TOF) imaging, spin echo, steady-state free procession, flow-independent, and phase-contrast imaging.<sup>55</sup> However, contrast-enhanced MRV is less susceptible to artifacts, acquired faster, has better signal-to-noise ratio and is more accurate in slow flow vessels<sup>56</sup> (Fig. 148.6).

A meta-analysis of the accuracy of MRI for the diagnosis of acute DVT<sup>50</sup> found a pooled sensitivity of 92% (range 0%–100%), and specificity of 95% (range 43%–100%).<sup>50</sup> The sensitivity and specificity were higher for proximal DVT than for below-knee thrombus. Studies comparing MRV to contrast venography, found the sensitivity and specificity of MRV up to 100% for the diagnosis of femoro-popliteal DVT, however accuracy was lower for distal thrombi.<sup>57–61</sup> Overall, in the evaluation of proximal DVT, MRV has similar accuracy as ultrasound and contrast venography, with the benefit of high rates of detection of the proximal extent of the thrombus and isolated pelvic thrombi.<sup>57</sup> For example, one small study showed MRV identified a thrombus in 27% of patients who sustained a PE with no detectable source of thrombus by ultrasound.<sup>62</sup> Moreover, vessel wall enhancement associated with acute thrombus can be visualized with MRV, allowing the examiner a crude detection of thrombus age.<sup>57,63</sup>

Although MRV technology demonstrates excellent accuracy for the detection of acute DVT, it has several disadvantages. The examination requires a nonmoving patient for long imaging times and cannot be used in patients with MRI incompatible devices or clips. Gadolinium can be toxic in patients with renal dysfunction and the need for frequent examinations can produce problematic utilization issues in larger institutions. Finally, the quality of MRV depends on experience with contrast timing and interpretation and therefore is institution dependent. MRV has been recommended as the imaging modality of choice by the American College of Radiology (ACR)



**Figure 148.6** Time-resolved magnetic resonance imaging after intravenous administration of a long-acting contrast agent in a female patient with symptoms consistent with pelvic congestion syndrome. The image shows early reflux through the left ovarian vein into pelvic varices. The patient also has compression of the left renal vein between the superior mesenteric artery and aorta, consistent with the “nutcracker syndrome.”

appropriateness criteria for evaluation of pelvic or thigh DVT when ultrasound is nondiagnostic or for initial investigation in case of suspect central vein or pelvic vein thrombus.<sup>64</sup>

## <sup>18</sup>F-Labeled Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

<sup>18</sup>F-labeled fluorodeoxyglucose (<sup>18</sup>F-FDG) is a glucose analogue that is actively and avidly absorbed by tissues and cells with rapid metabolism. Among these are tumor cells, endothelial cells, macrophages, and lymphocytes. <sup>18</sup>F-FDG is frequently used in positive emission tomography/computer tomography (PET/CT) for the detection of primary and metastatic cancer; however, it has shown value in the diagnosis of acute DVT. <sup>18</sup>F-FDG PET/CT can detect acute DVT, determine thrombus age, and differentiate acute thrombus from tumor thrombus.<sup>51</sup> Several studies have characterized the ability of <sup>18</sup>F-FDG PET/CT to detect acute DVT,<sup>65–68</sup> but few studies have examined its utility for the direct diagnosis of acute DVT. Rondina et al.<sup>69</sup> evaluated 12 patients with ultrasound-proven proximal acute DVT with <sup>18</sup>F-FDG PET/CT (median time from symptoms to PET/CT scan was 26 days). They demonstrated that metabolic activity was significantly higher in thrombosed vein compared to non-thrombosed veins and that <sup>18</sup>F-FDG PET/CT had excellent test

characteristics for the diagnosis of acute symptomatic proximal DVT. Limitations of the technique include cost, radiation exposure, availability, false positives due to active inflammation or infection, and limited clinical data.

## DIAGNOSTIC STRATEGIES

### Risk Assessment and Assessment of Pre-Test Probability

Because there is no single reliable, accurate, and inexpensive diagnostic test, nor sensitive nor specific symptoms, stratification of patients based on their risk of DVT using gestalt or clinical decision rules enables differential accurate cost-effective testing without sacrificing clinical outcomes. This approach to management of patients with suspected DVT requires identification of risk factors for development of DVT and stratification of patients based on predicted probability of a thrombotic event (see Chapter Algorithm).

Acquired risk factors for venous thrombosis include age, malignant disease, immobility, exposure to surgery or trauma, estrogen therapy, obesity, pregnancy, chronic inflammation, infections, nephrotic syndrome, antiphospholipid syndrome or other autoimmune disease, and history of VTE (Table 148.2). The relative role of each individual risk factor in estimation of DVT probability varies. For example, in the absence of prophylaxis, the risk of proximal DVT postoperatively is as high as 25% after hip arthroplasty and ranges between 5% and 25% for other surgeries; and rates of total DVT (proximal and distal) without prophylaxis after hip fracture surgery are as high as 50%–60%.<sup>70</sup> This risk continues after discharge from the hospital.<sup>61</sup>

A novel coronavirus infection associated with a hypercoagulable state was identified in late 2019. Severe acute respiratory coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which results in a hypercoagulable state in some patients.<sup>71,72</sup> Treatment guidelines for confirmed DVT or PE are unchanged from other causes of DVT or PE, and appropriate VTE prophylaxis trials for the hospitalized, outpatient, and post-discharge populations are ongoing.<sup>73–75</sup>

Hereditary thrombophilias, including protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin gene mutation, and factor V Leiden mutation, also increase the risk of DVT. The relatively low prevalence of inherited causes of DVT combined with the high cost of testing, questionable clinical value of their detection, variable accuracy of testing during an acute thrombotic event, and long turnaround time make testing for thrombophilias impractical for assessment of DVT risk in an individual patient. However, the known presence of such coagulation abnormalities is valuable clinical information (see Ch. 40, Disorders of Coagulation: Hypercoagulable States). Patients with heterozygous antithrombin deficiency, protein C deficiency, and protein S deficiency have a 5- to 50-fold, 3-fold, and 10-fold respective increase in risk of DVT.<sup>76–78</sup> The lifetime probability of symptomatic DVT in patients with heterozygous factor V Leiden mutation is about 10%, but concurrent thrombophilic conditions increase this risk significantly.<sup>79</sup> Other conditions associated with elevated

**TABLE 148.2 Major and Minor Risk Factors of VTE**

Major Transient	Minor Transient
<ul style="list-style-type: none"> <li>surgery with general anesthesia &gt;30 minutes</li> <li>confined to bed in hospital ≥3 days with an acute illness</li> <li>caesarean section</li> </ul>	<ul style="list-style-type: none"> <li>surgery with general anesthesia &lt;30 minutes</li> <li>admission to hospital &lt;3 days with an acute illness</li> <li>estrogen therapy</li> <li>pregnancy or 6 weeks postpartum</li> <li>confined to bed out of hospital for ≥3 days with an acute illness</li> <li>leg injury with reduced mobility</li> </ul>
Major Persistent	
<ul style="list-style-type: none"> <li>active cancer</li> <li>chronic inflammation, chronic infections or other nonmalignant conditions associated with 2-fold risk of recurrent VTE after cessation of anticoagulation</li> </ul>	

Classified by Scientific and Standardization Committee of ISTH.<sup>191</sup> Risk factor classified as major if associated with greater than 10-fold increased risk of first VTE or half risk of recurrence after stopping therapeutic anticoagulation as compared to risk of recurrence if no risk factor within 3 months before VTE. Minor is defined as 3- to 10-fold increase in risk of first VTE or half the risk of recurrence compared to risk of recurrence if no minor risk factor within 2 months before VTE.

thrombosis risk, such as elevated factor VIII, hyperhomocysteinemia, dysfibrinogenemia, and hypofibrinolysis, increase the risk of DVT twofold or less.

The most widely used scoring tool for symptomatic outpatients with suspected DVT is the Wells criteria for DVT (distinct from the Wells criteria for PE), which assigns one point to each of the nine clinical characteristics and subtracts two points if an alternative diagnosis is at least as likely as DVT (Table 148.1).<sup>80</sup> The Wells score has been shown to be a consistent, reproducible instrument to stratify outpatients into high, moderate, and low risk of proximal DVT. It has been validated in a variety of patient populations including patients presenting to primary care office or the hospital, both men and women, and trauma patients.<sup>80,81,82</sup> A meta-analysis of 24 studies that used the Wells score showed that in a population with 15% prevalence of DVT, the Wells score alone will classify 18% of the patients as high risk with a DVT prevalence of 47% in this group, 40% as intermediate risk with a DVT prevalence of 12%, and 42% as low risk with a DVT prevalence of 4%.<sup>14</sup> However, the Wells score cannot be used to rule out DVT in all populations, including in pregnant patients.<sup>81</sup> It also has been variably accurate in hospitalized patients who benefit from imaging to evaluate for DVT.<sup>83,84</sup>

### Diagnostic Strategies for Symptomatic Deep Venous Thrombosis

There is increasing consensus that the optimal approach to DVT diagnosis includes risk stratification based on simple low-cost methods, such as the Wells score, with DD testing in low- and intermediate-risk patients and diagnostic imaging in high-risk patients, and lower-risk patients with elevated DD levels (Fig. 148.1). In low-risk patients, determined by Wells score, a negative DD result has a negative predictive value approaching 100%.<sup>85,86</sup> Because most of the studies of low-risk patients were done in outpatient settings and excluded patients with a

clinical suspicion of PE or on anticoagulation,<sup>37,87</sup> these factors should be considered in addition to the Wells score.

Similar results were shown in intermediate-risk patients when a combination of Wells score and DD assay was used for DVT diagnosis.<sup>22,88,89</sup> Without treatment, the 3-month incidence of DVT in patients who are classified as intermediate risk by a Wells score and have a negative DD result is 0.6%,<sup>90</sup> indicating no additional testing is necessary in these groups, as it is unlikely to improve clinical outcomes.

Evaluation of patients with a high probability of DVT, assessed by clinical gestalt or a validated scoring method, almost universally involves diagnostic imaging. Negative DD results in these patients are associated with PE rates of up to 15%.<sup>91</sup> This unexpectedly high rate of VTE indicates that treatment should be started in patients with a high pre-test probability before additional testing is completed. When anticoagulation is initiated, delay in definitive diagnostic studies has been shown to be safe.<sup>492</sup> The majority of inpatients fall into the high-risk category and the Wells score has not been consistently accurate in hospitalized patients, limiting its utility. In hospitalized patients classified as low risk based on a Wells score, the incidence of DVT has been as high as 10%.<sup>93</sup> In addition, both sensitivity and specificity of DD testing are substantially lower in inpatients than in outpatients. Unlike outpatients, most hospitalized patients with a clinical suspicion of DVT need confirmatory diagnostic imaging.

In summary, in outpatients or patients presenting to the emergency room, a combination of a low or intermediate Wells score and a negative high sensitivity DD result is sufficient to rule out DVT. In these patients, it is reasonable to withhold empiric anticoagulation if test results are available within 24 hours. High-risk patients and patients in whom risk scores have not been validated should proceed to imaging without DD testing. These patients should be started on therapeutic anticoagulation while awaiting diagnostic imaging unless they are considered high risk for bleeding.<sup>4</sup>

### Adjusted D-Dimer Thresholds

Initial studies using DD values to exclude DVT in low and intermediate risk patients defined a negative DD value as less than 500 µg/L FEU or 230–250 µg/L DDU. Two modifications to negative values, based on age or pre-test clinical probability, have been studied and increase the diagnostic yield of DD testing. Using the age-adjusted modification, for patients 50 years of age the negative value threshold remains ≤500 µg/L FEU; however, for patients >50 years old the negative DD value is defined at 10 times the patient's age (µg/L FEU or 5× patient's age in DDU). For example, for a 75-year-old patient with a low or intermediate risk of DVT, a negative DD value would be less than 750 µg/L FEU. Age-adjusted thresholds increased the specificity without compromising the sensitivity for DVT.<sup>94–98</sup> The second modification involves adjusting the cutoff of a negative DD value based on pre-test probability. For patients with low pre-test probability, a DD value less than 1000 µg/L FEU is considered negative and sufficient to exonerate DVT. For patients with intermediate pre-test probability, the threshold remains at 500 µg/L FEU. The second approach has been validated prospectively in patients with possible DVT<sup>99</sup> and a recent meta-analysis found no difference between the two strategies, which both have high negative predictive value.<sup>95</sup>

### Diagnosis of DVT During Pregnancy

The diagnosis and management of DVT in pregnant patients have unique challenges and diagnostic algorithms for DVT in non-pregnant patients should not be applied. The Wells score has not been assessed in a pregnant population and therefore is of uncertain utility. DD testing is less likely to rule out DVT as levels increase during the course of a normal pregnancy.<sup>100</sup> An alternative clinical prediction rule, the "LEFT rule" has been developed specifically for assessment of DVT in pregnant patients. This rule assigns one point for symptoms in the left leg, calf circumference difference of 2 cm or more, and presentation during first trimester of pregnancy.<sup>101</sup> Patients with no risk factors were found to be at very low risk for DVT<sup>102,103</sup>; however, this rule has not been prospectively validated and therefore should not be used alone to rule out DVT in these patients.

The anatomic distribution of DVTs differs between pregnant and non-pregnant patients with an increase in proximal iliac vein and left-sided thrombosis in pregnant patients.<sup>104</sup> Ultrasound with iliac vein imaging remains the preferred diagnostic test for detection of DVT in pregnancy. In pregnant patients thought to have DVT, repeat ultrasound or MRV is recommended if the initial examination findings are normal.<sup>105</sup> Upon confirmation of DVT, LMWH is the most appropriate anticoagulant.

### Thrombus Age and Diagnosis of Recurrent DVT

Venous thrombosis initiates a sequence of biologic processes within the thrombus and the venous wall. Organization of the thrombus and vein wall remodeling occur at a variable pace. Within 7 to 10 days, the thrombus becomes adherent to the vein wall, making treatment modalities such as systemic thrombolysis and thrombectomy less effective and impossible in 30% of patients.<sup>106–109</sup> It is desirable to simultaneously diagnose an acute DVT and determine the age of the thrombus as this can inform therapeutic decisions.

The onset of the clinical manifestations of DVT is an unreliable indicator of the start of thrombosis and conventional imaging techniques are rarely helpful in determining the age of the thrombus.<sup>7</sup> Initial results with ultrasound elastography to estimate thrombus age were promising,<sup>110,111</sup> but have been inconsistent.<sup>112</sup> Most of the studies of ultrasound elastography were done in animal models or *ex vivo*,<sup>113</sup> but a small clinical study found a mean elasticity index of >4 to be both sensitive and specific for distinguishing acute versus chronic thrombosis.<sup>114</sup>

Radiolabeled markers, such as recombinant tissue plasminogen activator, can be used to determine if the thrombus is more than 30 days old,<sup>115</sup> and MRI may show that the time from onset of thrombosis exceeds 6 months.<sup>116</sup> These tests, however, are more suitable in the diagnosis of recurrent thrombosis than in determining the age of the initial thrombus. There remains a need for diagnostic tools to determine the age of acute thrombus.

Diagnosis of recurrent ipsilateral DVT is also a challenging task. Clinical presentation of recurrent thrombosis is frequently identical to manifestations of post-thrombotic syndrome (PTS) and diagnostic imaging is unable to reliably detect acute thrombus when post-thrombotic changes are present in the venous wall and vessel lumen. Residual thrombus after treatment for initial DVT predisposes patients to both PTS and recurrent

thrombosis.<sup>117</sup> A negative DD in a patient with a history of DVT and low pre-test probability is sufficient to exclude a recurrent event, however the proportion of patients with a negative result is overall lower, reducing the clinical usefulness of DD in assessment of recurrent DVT.<sup>118,119</sup> MRI may be able to differentiate thrombi from fibrotic changes in the vein 6 months after acute DVT,<sup>116</sup> but neither MRI nor CTV has been tested in patients with suspected recurrence. Since there is minimal evidence suggesting that any test to determine the age of thrombus may be clinically useful, and no evidence showing that the diagnostic approach to recurrences should be different from what is used for initial DVT, clinical practice remains dependent on conventional testing and good clinical judgment.

## MEDICAL TREATMENT OF ACUTE LOWER EXTREMITY DEEP VENOUS THROMBOSIS

Treatment for DVT aims to stabilize the developing thrombus within the deep veins, prevent thrombus extension and embolization, permit the body's natural fibrinolytic system to dissolve fibrin, and reduce morbidity and mortality. These objectives can be divided into two major categories: (1) immediate reduction of morbidity and mortality and (2) reduction of late post-thrombotic morbidity (see Ch. 156, Postthrombotic Syndrome: Natural History, Pathophysiology, and Etiology). Since the landmark paper in 1961 by Barritt and Jordan,<sup>120</sup> anticoagulation therapy, in both enteral and parenteral forms, has been the cornerstone of VTE treatment.

The introduction of direct oral anticoagulants (see Ch. 41, Anticoagulant Therapy) has increased the safety of outpatient treatment for lower extremity DVT. Many patients can begin treatment in the outpatient clinic or emergency department and be sent home, even if diagnostic imaging is delayed. However, patients with active bleeding, at high-risk for bleeding, severe symptomatic venous obstruction, thrombocytopenia, poor hepatic function, unstable renal function, noncompliance, and a poor support environment at home cannot be managed as outpatients.

Beyond anticoagulation, nonpharmacologic measures include early ambulation, compression therapy and leg elevation. However, results of studies evaluating compression therapy and leg elevation have been mixed.

### Anatomic Considerations of Medical Treatment for Lower Extremity DVT

Therapeutic anticoagulation, for at least three months, is the cornerstone of therapy for patients with proximal lower extremity DVT. Thrombolysis or surgical thrombectomy may have a role in a subset of patients with severe symptoms such as phlegmasia cerulea dolens or with extensive iliofemoral DVT with symptoms for less than 14 days and low risk of bleeding; however, consistent benefit has not been found and overall randomized data is lacking (see Ch. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment).<sup>4,121</sup> Briefly, trial data includes the CaVenT trial, which found decreased rates of PTS at both 2 and 5 years in patients

with iliofemoral DVT treated with catheter-directed thrombolysis (CDT). There was no difference in rate of recurrent thrombus or mortality and there was an increased likelihood of bleeding in the CDT group.<sup>122,123</sup> A second larger randomized trial of pharmacomechanical catheter-directed thrombolysis (PCDT) in addition to standard of care versus standard of care in patients with proximal DVT found no difference in rates of PTS at 6 and 24 months, recurrent VTE, nor quality of life and PCDT was associated with an increased risk of bleeding at 10 days.<sup>124</sup> The ACCP guidelines recommend anticoagulation therapy alone over CDT for management of acute proximal lower extremity DVT, but highlight the role of CDT in patients with impending venous gangrene. It also mentions that other patients most likely to benefit from CDT are patients with iliofemoral DVT, symptoms <14 days, good function status, life expectancy 1 year, and a low risk of bleeding.

Management of distal lower extremity DVT, isolated to the deep calf veins, is controversial. Complications of distal DVT, including PE, are less common than with proximal DVT and only approximately 15% of patients with isolated DVT have progression to a proximal vein (usually within two weeks).<sup>125–127</sup> The CACTUS trial, the most recent study designed to determine optimal management, was terminated early due to slow recruitment with only half of planned enrollment. Notably underpowered, it found no difference in the composite endpoint of proximal vein DVT, contralateral DVT or PE in patients with distal DVT (without cancer or history of VTE) randomized to 6 weeks of placebo or LMWH, but found a nonsignificant increase in bleeding in the LMWH arm.<sup>128</sup> Guidelines for the treatment of isolated distal DVT have been conflicting. The 2016 ACCP guidelines for antithrombotic therapy for VTE gives a grade 2C recommendation for serial imaging of the deep veins for 2 weeks over anticoagulation in patients with acute isolated distal DVT without severe symptoms or risk factors for extension, and recommends 3 months of anticoagulation for patients with severe symptoms or risk factors for extension, including positive DD, extensive thrombosis (>5 cm in length, involving multiple veins, >7 mm in diameter), thrombosis close to proximal veins, no reversible provoking factor, active cancer, history of DVT, and inpatient status). Additional considerations include the patient's bleeding risk and preference. In patients who are monitored with repeat ultrasound, ACCP guidelines recommend against anticoagulation if the thrombus does not extend (grade 1B) and suggests anticoagulation if the thrombus extends either in the distal vein (grade 2C) or into the proximal veins (grade 1B).<sup>4</sup> Others have found only inpatient status and age 60 years old as risk factors for proximal DVT or PE in patients with isolated distal DVT.<sup>125</sup> A different contemporary guideline published by Streiff et al. recommends anticoagulation for 3 months over ultrasound surveillance,<sup>33</sup> although the latter approach is preferred over IVC filter placement for individuals who are thought to be at too high risk for bleeding.

### Anticoagulation

Anticoagulation therapy reduces thrombus extension, mortality, recurrence, and rate of PTS. Therapy can be divided into three phases: acute (5–10 days), intermediate (first 3 months) and

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extended (beyond 3 months). Anticoagulation should be initiated when there is a high suspicion for or confirmed DVT and should not be delayed while awaiting diagnostic imaging in high-risk patients. Historically, patients were managed with unfractionated heparin (UFH) followed by vitamin K antagonist (VKA) therapy. Fortunately, there are now several options for the initial anticoagulant treatment of VTE including subcutaneous low-molecular-weight heparin (LMWH), subcutaneous pentasaccharide (fondaparinux), and direct-acting oral anticoagulants (DOACs), and many patients can be managed as outpatients (Table 148.3).

When initiating or deciding to continue anticoagulation, the patient's risk factors for bleeding should be reviewed with a risk–benefit analysis of therapeutic anticoagulation. Risk factors for bleeding include age >65 years old, history of bleeding, cancer, metastatic cancer, lower functional status, renal or liver disease, thrombocytopenia, anemia, recent surgery, frequent falls, alcohol use disorder, concomitant use of anti-platelet or nonsteroidal anti-inflammatory therapy, and prior stroke.<sup>4</sup> Severe life-threatening bleeding or active intracranial bleeding are contraindications to initiating therapeutic anticoagulation. Relative contraindications include severe thrombocytopenia, recent bleeding (gastrointestinal within 2 weeks, intracranial within 3 months), recent trauma, known bleeding disorder, endocarditis, and uncontrolled hypertension.<sup>129</sup> A number of clinical risk prediction scores for major bleeding have been developed for patients with acute VTE on anticoagulation including Kuijer, VTE-BLEED, and RIETE or have been validated in patients with VTE including HAS-BLED and OBRI.<sup>130–134</sup> However, it is worth noting that many of these tools were developed before the routine of DOACs in VTE, many have not had reproducible accuracy, and none are routinely used in clinical care.<sup>135,136</sup> After the initial and intermediate treatment phase of anticoagulation (3 months), the benefit of continued anticoagulation – a reduction in risk of recurrence by 80%–90% – needs to be balanced with the patient's preference and individual risk of bleeding on extended treatment as the case fatality for a bleeding event is higher than for a recurrent VTE.<sup>137,138</sup> Management for patients who are not candidates for anticoagulation is case-specific and may include placement of retrievable IVC filter, platelet transfusion, or initiation of prophylactic dose anticoagulation. Rates of major bleeding, a feared complication of anticoagulation, depend on phase of treatment and anticoagulant used. Major bleeding in the first 3 months of therapy occurs in 1%–3% of patients, <1% with apixaban or rivaroxaban, with case fatality rates of 5%–20%.<sup>139–142</sup>

### Unfractionated Heparin (UFH)

Intravenous UFH is an indirect anticoagulant whose primary anticoagulant effect is through formation of heparin–antithrombin complexes, which inhibit thrombin and factors Xa, IXa, XIa, and XIIa. Although rare, some individuals can have congenital or acquired antithrombin, which can decrease or eliminate the efficacy of heparin if not identified. Laboratory monitoring of UFH is necessary because of nonspecific binding of heparin to plasma proteins, endothelial cells, platelet factor 4, and macrophages,

which leads to unpredictable pharmacodynamics.<sup>143</sup> The therapeutic range is 1.5 to 2.5 times the upper limit of the control aPTT or an anti-Xa range correlating to a plasma heparin concentration of 0.3 to 0.7 IU/mL. Studies have not consistently found one monitoring strategy to be superior to another<sup>144</sup>; however, high incidence of recurrent VTE has been reported in individuals who failed to promptly reach a therapeutic aPTT.<sup>145</sup>

Given the ease of alternative therapy, UFH is now most commonly used for the treatment in inpatients with planned invasive procedures or recent bleeding, as initial therapy in patients with high bleeding risk,<sup>①</sup> significant renal dysfunction,<sup>②</sup> or extremes of body weight,<sup>③</sup> for the initial 5 to 10 days as a bridge to oral anticoagulation with warfarin,<sup>④</sup> or for the acute phase of treatment (5 days) in patients to be managed with dabigatran or edoxaban.<sup>⑤</sup> Major drawbacks to the use of UFH include the need for hospitalization and continuous intravenous infusion, frequent blood draws, variable response, difficulties in promptly achieving the target therapeutic range, and the risk of the life-threatening complication of heparin-induced thrombocytopenia (HIT).<sup>⑥</sup>

### Low-Molecular-Weight Heparin

Since its discovery in 1976, a number of LMWH fractions with different pharmacokinetic profiles have been developed, including the current fractions marketed in the United States: enoxaparin and dalteparin. LMWHs have improved bioavailability, more consistent response, and more predictable pharmacokinetics and pharmacodynamics compared to UFH. They contain heparin fragments approximately one third the size of UFH and LMWHs primarily inhibit factor Xa. They are uniformly absorbed from subcutaneous depots with a half-life in the range of 3 to 5 hours. LMWHs have undergone rigorous testing in clinical trials showing less major bleeding and reduced mortality compared to UFH.<sup>146,147</sup> LMWHs do not require routine monitoring. Some patients with renal insufficiency or significant obesity may require dose adjustments and these patients can be monitored by LMWH–anti factor Xa activity (0.5–1.0 IU/mL). The optimal management of these patients is under investigation.

Malignancy poses a particularly high risk for VTE<sup>148</sup> and, until recently, LMWH was the only recommended agent to treat cancer-associated thrombosis (CAT), as treatment with LMWH for CAT was superior to VKAs and data for DOACs was limited.<sup>149–151</sup> However, recent randomized studies of DOACs in the treatment of cancer-associated thrombosis have changed this paradigm (see below).

### Parenteral Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) bind directly to thrombin and inhibit both free and fibrin-bound thrombin, reducing thrombus formation and platelet activation. DTIs are used for the treatment of VTE as well as HIT and HITT. With a suspicion of HIT, heparin or LMWH (and in rare cases fondaparinux) should be discontinued and an appropriate alternative anticoagulant, such as a DTI, should be started while awaiting serologic test results. As of 2020, parenteral DTIs are the only class of anticoagulants that carry a specific Food and Drug Administration (FDA) package label to treat HIT. Although three intravenous DTIs have been licensed in North America, lepirudin,

**TABLE 148.3** Comparison of Anticoagulant Drugs for the Treatment of Deep Venous Thrombosis

	Mechanism	Venous Indications	Efficacy vs. LMWH/ VKA (for VTE Treatment)	Bleeding Risks (vs. LMWH/VKA) in VTE Treatment	Other Risks	Reference
<b>UFH</b>	Factor II and X inhibition via AT	VTE treatment VTE prophylaxis	Equivalent	<b>Major:</b> 2.0%	HIT 0.5%–2%	Mismetti et al. <sup>209</sup>
<b>LMWH</b> Enoxaparin, Dalteparin, Tinzaparin	More selective factor X inhibition via AT	VTE treatment VTE prophylaxis	n/a	<b>Major:</b> 2.0%	HIT <1%	Mismetti et al. <sup>209</sup>
Fondaparinux	Selective factor X inhibition via AT	VTE treatment VTE prophylaxis	Equivalent	<b>Major:</b> 1.2% vs. 1.2%	Thrombocytopenia 0.5%	Büller et al. <sup>210</sup>
<b>Parenteral DTI</b> Argatroban	Direct factor II inhibition	VTE treatment HIT treatment (initial)	n/a	<b>Major:</b> 1.3% <sup>a</sup>	Hypotension tachycardia	Koster et al. <sup>211</sup>
Bivalirudin	Direct factor II inhibition	VTE treatment	n/a	<b>Major:</b> 3.5%; (vs. UFH): OR 0.49 (0.36–0.67) <sup>a</sup>	Hypotension bradycardia	Farag et al. <sup>212</sup>
<b>VKA/warfarin</b>	Vitamin K- dependent factor inhibition (II, VII, IX, X)	VTE treatment VTE prophylaxis HIT treatment (long-term)	n/a	<b>Major:</b> 1.2%–1.9% (see below)	Multiple drug– drug, drug–food interactions	See below
<b>DOACs</b> Apixaban	Oral direct inhibitor of factor Xa	VTE treatment, reduce risk of recurrent VTE, VTE prophylaxis after hip and knee replacement	Noninferior	<b>Major:</b> 0.6% vs. 1.8%; HR 0.31 (0.17–0.55) <b>Major+CRNM:</b> 4.3% vs. 9.7%; HR 0.44 (0.36–0.55)	CrCl <30: 44% increased exposure	Amplify <sup>b</sup> Amplify-Ext <sup>158</sup>
Rivaroxaban		VTE treatment, reduce risk of recurrent VTE, VTE prophylaxis after hip and knee replacement	Noninferior	<b>Major:</b> 0.8% vs. 1.2%; HR 0.65 (0.33–1.30) <b>Major+CRNM:</b> 8.1% vs. 8.1%; HR 0.97 (0.76–1.22)	CrCl <30: 64% increased exposure Child-Pugh B: 2.3- fold increased exposure	EINSTEIN–DVT <sup>141</sup> EINSTEIN- CHOICE <sup>204</sup>
Edoxaban		VTE treatment after 5–10 days parenteral therapy	Noninferior	<b>Major:</b> 1.4% vs. 1.6%; HR 0.84 (0.59–1.21) <b>Major+CRNM:</b> 8.5% vs. 10.3%; HR 0.81 (0.71–0.94)	CrCl <30: 72% increased exposure Abnormal LFT (7.8%)	Hokusai-VTE <sup>b</sup>
Dabigatran	Oral direct factor IIa inhibitor	VTE treatment after 5–10 days parenteral therapy, reduce risk of recurrent VTE, VTE prophylaxis after hip replacement	Noninferior	<b>Major:</b> 1.6% vs. 1.9%; HR 0.82 (0.45–1.48) <b>Major+CRNM:</b> 5.6% vs. 8.8%; HR 0.63 (0.47–0.84)	CrCl < 30: 6.3- fold increased exposure	Re-cover <sup>b,161</sup> Re-medy <sup>213</sup> Re-novate <sup>214</sup>

<sup>a</sup>Bleeding data is based on patients with acute coronary syndrome.

<sup>b</sup>Pulmonary embolism patients were analyzed in these trials alongside deep venous thrombosis patients; bleeding data therefore includes a pooled analysis.

CRNM, clinically relevant nonmajor; DOACs, direct-acting oral anticoagulants; DTI, direct thrombin inhibitor; DVT, deep venous thrombosis; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; n/a, not available, not applicable; VKA, vitamin K antagonist; VTE, venous thromboembolism; UFH, unfractionated heparin.

Major bleeding generally defined as including fatal bleed, intracranial bleed, bleeding into a critical site.

argatroban, and bivalirudin, only the latter two have been commercially available in the United States since 2012.

### Vitamin K Antagonists (VKAs)

Oral anticoagulation with VKAs such as warfarin anticoagulant by inhibiting the production of vitamin K-dependent

coagulation factors, factors II, VII, IX, X, as well as production of the anticoagulants protein C and protein S. Because VKAs have no effect on circulating coagulation factors, the anticoagulant effect depends on depletion of the factors, a function of their half-lives. Protein C has a shorter half-life than the procoagulant factors, which is why VKAs, irrespective of the INR, produce a

paradoxical procoagulant state in the first few days of their administration. Warfarin compounds must therefore be administered alongside parenteral anticoagulation for at least the initial 5 days to achieve therapeutic anticoagulation (and until INR >2.0 on two occasions more than 24 hours apart). Unopposed VKA therapy in the setting of acute thrombosis can lead to thrombus propagation, early recurrence, and devastating thrombotic complications, including warfarin-induced skin necrosis, because of the rapid depletion of protein C and S. Effective reduction in the concentration of factors II and X (below 30% activity) usually requires at least a 5-day overlap with heparin.

VKAs have a narrow therapeutic window, variability in dose-response among individuals, interaction with dietary vitamin K and other dietary substances, and many drug-to-drug interactions (notably antibiotics) and therefore ongoing monitoring with the prothrombin time/international normalized ratio (PT/INR), typically for a goal INR range of 2.0–3.0 for VTE treatment, is necessary. In patients with prolongation of their baseline PT from antiphospholipid antibodies or concomitant administration of DTIs, PT/INR monitoring may be inaccurate. VKAs can instead be monitored with chromogenic factor X, which is a non-clot-based assay that measures amount of residual factor X activity (level 20%–40% is equivalent to goal INR 2–3).

### Direct-Acting Oral Anticoagulants (DOACs)

DOACs are oral medications that selectively target either factor Xa (rivaroxaban, apixaban, edoxaban, betrixaban) or thrombin (dabigatran). They have predictable pharmacokinetics and high bioavailability with relatively few drug-to-drug and no significant food interactions compared to VKA therapy. Additionally, they do not require routine monitoring or frequent dose adjustments. For these reasons, DOACs have generated justifiable enthusiasm since 2011 when rivaroxaban was first approved by the FDA for the treatment of VTE. Efficacy of these drugs is equivalent to warfarin in the both large industry-sponsored (Table 148.3) and in subsequent real-world trials.<sup>152–156</sup> Safety in the industry trials was equivalent, although intracranial bleeding and fatal bleeding were significantly lower with all three of the Xa inhibitors compared to VKA. Additionally, unlike during the initial trials, there are now FDA-approved reversal agents available for both direct anti-Xa and direct thrombin inhibitors (andexanet alfa and idarucizumab, respectively), which are approved for use in life-threatening or uncontrolled bleeding or before emergency surgeries or procedures (idarucizumab only). Admittedly, use of these antidotes is limited by cost and availability. The EINSTEIN trials evaluated rivaroxaban in the treatment of symptomatic acute DVT (acute DVT study) and PE (acute PE study). EINSTEIN acute DVT reported recurrent VTE in 2.1% of patients receiving rivaroxaban versus 3% in the standard group ( $P < 0.001$  for noninferiority,  $P = 0.08$  for superiority).<sup>141,157</sup> There were no differences in rates of major bleeding (0.8% in patients receiving rivaroxaban versus 1.2% in patients receiving LMWH–VKA) or combined major bleeding and clinically relevant nonmajor bleeding (8.1% in both groups) between the two groups. The extended treatment study showed superiority for rivaroxaban versus placebo with an 82% relative risk reduction for recurrent VTE and no difference in major bleeding events.

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Apixaban was investigated in a double-blinded noninferiority study for treatment of acute VTE.<sup>158</sup> Recurrent VTE occurred in 2.3% of the apixaban group and 2.7% receiving conventional therapy ( $P = 0.001$  for noninferiority). Major bleeding occurred significantly less in the apixaban group versus conventional therapy (0.6% vs. 1.8%;  $P < 0.001$  for superiority). Notably, apixaban has less renal clearance (27%) than the other factor Xa inhibitors and, for its VTE indication, does not require dose adjustment for renal dysfunction. The clinical efficacy and safety studies did not enroll patients with end-stage renal disease on dialysis or with creatinine clearance <15 mL/min and the dosing recommendation for these patients is based on pharmacokinetics and pharmacodynamic data of patients with ESRD. In a randomized, double-blind, noninferiority study, edoxaban<sup>159</sup> was noninferior in efficacy (recurrent VTE) and superior in safety (clinically relevant bleeding) compared to warfarin for the treatment of acute VTE.

In 2018, andexanet alfa, a modified recombinant inactive human factor Xa protein, was approved for management of life-threatening or uncontrolled bleeding in patients treated with rivaroxaban or apixaban.<sup>160</sup> Andexanet alfa is given intravenously as a bolus and followed by continuous infusion for up to 2 hours. The dose is based on the specific Xa inhibitor, dose of Xa inhibitor and timing of last dose. Availability and cost have limited widespread use of andexanet alfa. Dabigatran is the only oral DTI approved for the treatment of VTE.<sup>161,162</sup> Two trials showed noninferiority of dabigatran to warfarin. The safety analysis showed significantly less major or clinically relevant nonmajor bleeding (HR 0.62; 95% CI: 0.45–0.84) and lower rates of any bleeding (HR 0.67; 95% CI: 0.56–0.81). Similar to edoxaban, dabigatran was studied after at least 5 days of parenteral anticoagulation and therefore is approved for treatment of VTE after initial heparin therapy. In 2016, the humanized monoclonal antibody fragment, idarucizumab, was approved as a specific reversal agent for dabigatran for emergency surgery or for life-threatening bleeding in patients on dabigatran.<sup>104,163</sup> Idarucizumab is generally administered as a single 5-g IV dose with immediate reversal of anticoagulation effect, which persists for more than 24 hours. DOAC therapy is not recommended for treatment of DVT in patients who are pregnant, have triple-positive antiphospholipid syndrome, or are taking inhibitors of GYP3A4 (interactions with apixaban and rivaroxaban) or P-glycoprotein (interactions with apixaban, rivaroxaban, edoxaban, dabigatran).

### Cancer-Associated Thrombosis (CAT)

Patients with active malignancy are at significantly higher risk for VTE than patients without malignancy (4- to 7-fold) with annual VTE rates between 0.5%–20%.<sup>164,165</sup> Risk of VTE is dependent on site, histology and stage of cancer, treatment received, and patient-related factors among other things and a number of scores can be used to stratify risk of VTE in patients with cancer including the Khorana Risk Score and CATS score.<sup>166,167</sup> Numerous direct and indirect mechanisms of hypercoagulability are implicated in different cancers including tumor expression of TF, podoplanin, and plasminogen activation inhibitor-1 (PAI-1), tumor secretion of platelet agonists

(thrombin, ADP) and cytokines, expression of phosphatidylserine on tumor microparticles, and tumor stimulation of neutrophils to release neutrophil extracellular traps.<sup>168,169</sup> Many of these mechanisms are not specific to cancer and play roles in other acquired hypercoagulable states such as autoimmune diseases or acute viral infections such as COVID-19.<sup>170,171</sup>

Cancer-associated VTE (CAT) treatment is complex as these patients are at higher risk for both bleeding and recurrent VTE while on anticoagulation compared to patients with VTE without cancer. CAT treatment can be further complicated by nausea and vomiting, drug–drug interactions, thrombocytopenia, and invasive procedures.<sup>172,173</sup> Patients with cancer and VTE have poorer survival than those with cancer alone.<sup>174</sup> Although LMWH has been first-line therapy for patients with cancer and DVT for two decades, recent randomized trial data have demonstrated the safety and efficacy of edoxaban, rivaroxaban, and apixaban compared to LMWH in the treatment of most cancer-associated thrombosis.<sup>175–178</sup> Given these findings, recent guidelines, including by the National Comprehensive Cancer Network and American Society of Clinical Oncology, have included oral anti-Xa inhibitors as options for initial and extended treatment of VTE in patients with cancer.<sup>179–182</sup> The ACCP guidelines, last updated prior to the publication of these cancer-specific trials, recommend LMWH over VKA and DOACs in CAT. In general, guidelines recommend careful review of patients' bleeding risk and caution in patients with GI or GU malignancies. Additional considerations in the selection of therapy for VTE in patients with cancer are drug–drug interactions, management of anticoagulation if severe thrombocytopenia is expected, and the effect of nausea and vomiting on efficacy.

## Adjunctive Measures for Acute Deep Venous Thrombosis Management

While therapeutic anticoagulation is the foundation of DVT management, adjuvant therapies aimed at reducing short- and long-term morbidity have been studied. Elevation of the legs above the heart reduces edema acutely and pain; however, bed rest is no longer recommended for patients with VTE. The benefit of compression with ambulation was observed in two small randomized trials that compared initiation of gradient elastic compression and early ambulation at time of acute treatment of lower extremity DVT diagnosis to bed rest with elevation.<sup>183,184</sup> Reductions in the progression of thrombus length and volume along with reduced pain and edema were observed in those randomized to compression and ambulation. There was no increase in the incidence of PE with early ambulation, which has been further supported by large registry data.<sup>185</sup>

The value of graduated compression alone for DVT treatment has been debated and studies have yielded conflicting results. Available evidence suggests early use of elastic compression stockings (within 24 hours of diagnosis) reduces residual vein occlusion and may reduce rate of PTS. Early studies found 30 to 40 mm Hg thigh-length gradient compression stockings (GCS) reduced pain and the incidence of PTS when used consistently for 2 years.<sup>186,187</sup> These data have been scrutinized due to inadequate blinding and in light of results from the SOX

trial, a large, placebo-controlled trial that found routine use of GCS neither reduced the incidence of PTS at two years nor improved quality of life, rate of venous ulcers or venous valvular reflux at 12 months after DVT diagnosis.<sup>87,112</sup> However, the IDEAL DVT study found that personalized duration of compression stockings based on Villalta score, worn for at least 6 months, was noninferior to compression for a fixed duration of 2 years in preventing PTS.<sup>188</sup> Additionally, in a pre-specified substudy, initiation of compression within 24 hours was associated with a decrease in PTS and residual vein obstruction compared with patients receiving no compression.<sup>189</sup> The most recent ACCP guidelines suggest against routine use of compression stockings for PTS prevention (grade 2B) but notes that this recommendation focuses on the chronic complication of PTS and is not a statement on the use of GCS to treat symptoms, for which a trial of GCS is often justified. Additionally, new trials are underway that aim to avoid the pitfalls of the SOX trial (inadequate compliance) and definitively define the value of GCS in the short- and long-term management of DVT.

## Duration of Treatment for Deep Venous Thrombosis

The duration of anticoagulation treatment beyond 3 months is determined by relative risk of VTE recurrence and bleeding. The risk of recurrence can be challenging to estimate but is primarily a function of whether the initial event was provoked, by a transient or persistent factor, or unprovoked. For example, after 3–6 months of anticoagulation, the one-year risk of recurrence of anticoagulation for patients with a provoked DVT due to a major transient risk factor (see Table 148.2) is 1%–3% compared to 10% if the initial event was unprovoked.<sup>190</sup> Risk of recurrence in patients with active cancer is even higher than 10%.<sup>191</sup> Notably, the risk of recurrence after stopping anticoagulation is not affected by the duration of initial treatment.<sup>192</sup> Based on estimates of risks associated with bleeding versus recurrent VTE, ACCP recommends extended anticoagulation in patients with ① unprovoked VTE who have a low or moderate risk of bleeding, in patients with ② second unprovoked VTE, and in patients with ③ active cancer without a high bleeding risk. These guidelines suggest use of risk stratification with patient sex and D-dimer levels and recommend annual reassessment of continued treatment. The ISTH recommends cessation of anticoagulation when the risk of recurrent VTE is less than 5% in the first year and 15% in the first 5 years after stopping anticoagulation.<sup>193</sup>

There has been significant effort to stratify risk of recurrence in patients with unprovoked VTE. In regard to hereditary thrombophilia, FVL and prothrombin gene mutations are weak predictors of recurrence and presence should not determine duration of anticoagulation. Patients with deficiencies of protein C, protein S, or antithrombin have high rates of recurrence and some guidelines recommend extended therapy in patients with these deficiencies.<sup>194</sup> Additional predictors of recurrence include gender, elevated DD level measured after cessation of anticoagulation for 1–2 months following an initial 3-month period of therapy, residual thrombus burden, and site of index DVT.<sup>195–199</sup> While a single factor cannot reliably

identify a low-risk group, clinical prediction scores, including the Vienna Prediction Model, DASH score, and HERDOO2 rule,<sup>200–203</sup> incorporate a number of factors and can be used in the appropriate clinical context to further stratify recurrence risk in patients with an initial unprovoked event. However, there are likely underlying risk factors including transient and permanent inflammatory conditions that are not adequately characterized in these risk scores.

Three months of anticoagulation is recommended for treatment of proximal DVT provoked by major risk factor,<sup>②</sup> isolated distal DVT (if anticoagulation is used), or for patients with ③ unprovoked DVT with high risk of bleeding. Extended anticoagulation beyond 3 months is recommended for patients with ① persistent provoking factors, such as cancer, or ② unprovoked DVT and without high bleeding risk. The risk–benefit of extended anticoagulation should be revisited at least annually.

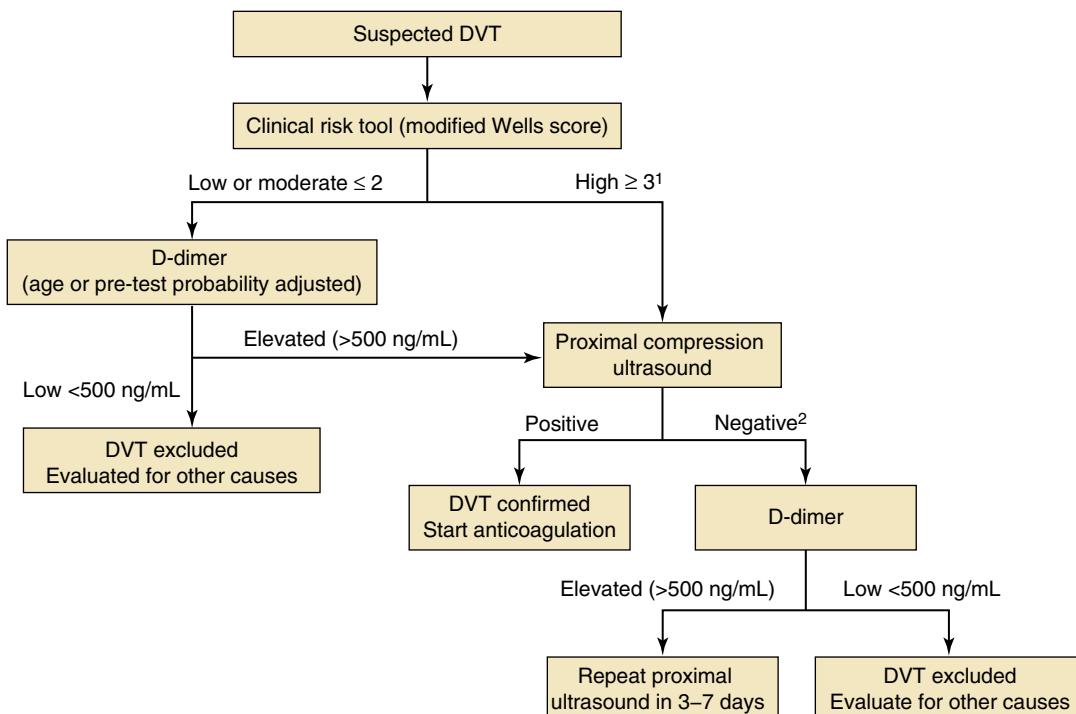
## Extended Treatment

There are a number of anticoagulation options for the extended treatment phase of DVT including continued therapeutic dose anticoagulation, reduced dose apixaban or rivaroxaban, or aspirin. The AMPLIFY-EXT and EINSTEIN CHOICE trials showed that extended treatment with apixaban 2.5 mg BID or rivaroxaban 10 mg daily, respectively, were as effective as therapeutic dose DOACS in the prevention of recurrent VTE

and superior to placebo and aspirin, respectively. There was no difference in major bleeding rates between patients treated with therapeutic or prophylactic dose rivaroxaban or aspirin in EINSTEIN CHOICE and therapeutic or prophylactic dose apixaban or placebo in AMPLIFY-EXT.<sup>140,158,204</sup> Notably, patients in both studies had completed at least 6 months of anticoagulation and there was clinical equipoise about their need for continued anticoagulation. Therefore, reduced doses of apixaban and rivaroxaban have not been sufficiently studied in some populations requiring extended anticoagulation, such as patients with active cancer. Clinical trials of reduced doses versus standard doses for extended therapy in CAT are ongoing.

Platelet inhibition can play a role in the long-term management of VTE.<sup>205–207</sup> The WARFASA and ASPIRE trials showed low-dose aspirin was associated with a 32% reduction in VTE recurrence and a 34% reduction in major vascular events compared to placebo without a significant increase in bleeding. However, both rivaroxaban 20 mg and rivaroxaban 10 mg daily were superior to aspirin in preventing recurrent VTE in the extended phase of therapy in the EINSTEIN CHOICE trial. Thus, secondary prevention with aspirin may be most appropriately limited to patients who have ① completed therapeutic anticoagulation for their DVT and for whom anticoagulation is no longer indicated, available, or who have a ② separate indication for aspirin with an unacceptable bleeding risk on both antiplatelet and anticoagulation therapy.<sup>208</sup>

## CHAPTER ALGORITHM



Diagnostic algorithm for evaluation of patients with suspected DVT. This algorithm can be utilized for patients who are deemed at risk for DVT. Clinical risk tools should not be utilized in patients for whom there is no concern for DVT nor to assess for DVT in hospitalized patients. Values for D-dimer given in fibrinogen equivalent units (FEUs).

<sup>1</sup>If imaging is delayed, start therapeutic anticoagulation in high-risk patients without a contraindication.

<sup>2</sup>If initial imaging is whole leg ultrasound and is negative, DVT is excluded (do not measure D-dimer or repeat imaging).

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment

ANTHONY J. COMEROTA and FAISAL AZIZ

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Acute deep venous thrombosis (DVT) of the lower extremity represents a disease spectrum ranging from asymptomatic calf vein thrombosis to the painful, blue, swollen limb of phlegmasia cerulea dolens resulting from extensive thrombosis involving the iliofemoral venous segment, thereby obstructing the main venous drainage of the lower extremity. This chapter reviews the evidence evaluating whether post-thrombotic morbidity can be reduced by adopting treatment strategies of thrombus removal.

## POST-THROMBOTIC SYNDROME

### Morbidity

PTS is the clinical condition defined by the signs and symptoms resulting from acute DVT. This is usually the consequence of ambulatory venous hypertension resulting from valve reflux and/or chronic luminal obstruction. Studies have shown that patients with PTS have a significant reduction in their quality of life (QoL).<sup>1,2</sup> The severity of the patient's acute DVT is predictive of post-thrombotic morbidity, especially when it involves the iliofemoral (IF) segment. Patients with IFDVT are

a clinically relevant subset of patients with acute DVT. They have occlusion of their single venous outflow channel from the leg, often resulting in severe post-thrombotic morbidity when treated with anticoagulation alone. In a prospective observational study of anticoagulation for acute DVT, IFDVT was found to be the most powerful predictor of severe PTS (HR 2.23).<sup>3-6</sup> Labropoulos et al.<sup>7</sup> monitored venous pressures in patients with PTS after treatment for their acute DVT. They found that patients who were treated for IFDVT had the highest venous pressures. This confirmed prior observations that IFDVT patients treated by anticoagulation alone had ambulatory venous hypertension, with 40% demonstrating venous claudication and up to 15% developing venous ulceration within 5 years.<sup>3-5</sup> The morbidity of PTS escalates with ipsilateral thrombotic recurrence.<sup>8</sup> A meta-analysis of outcomes after treatment for acute DVT demonstrated that recurrence occurs more commonly in patients harboring a large burden of thrombus.<sup>9</sup>

### Etiology

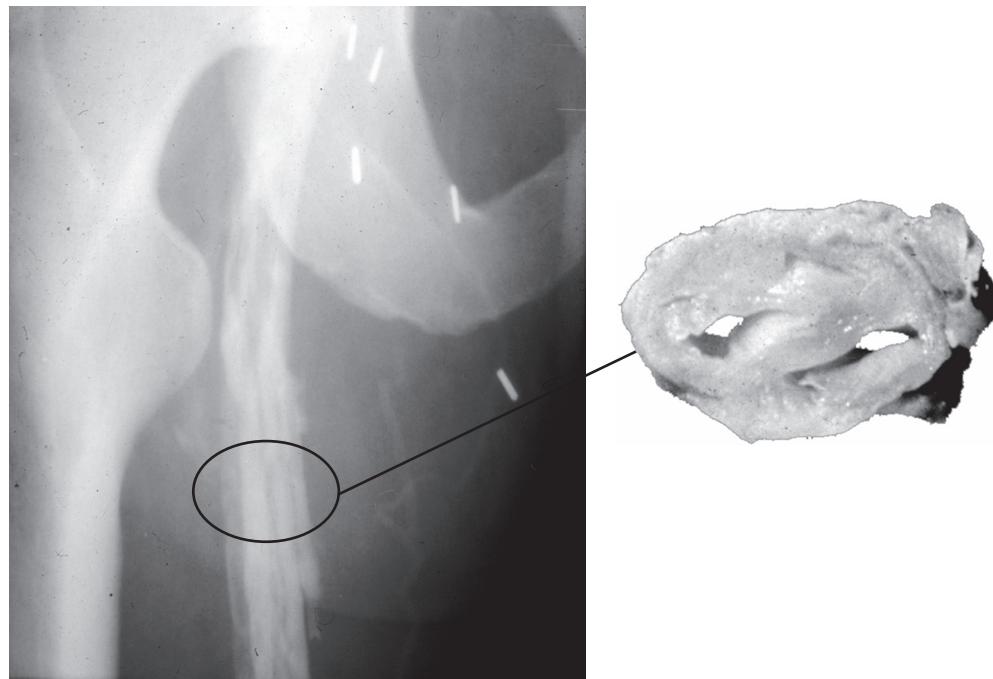
The pathophysiology of post-thrombotic venous disease is ambulatory venous hypertension, defined as elevated venous

pressure during exercise.<sup>10,11</sup> Ambulatory venous pressure is linearly linked to the consequences observed with chronic post-thrombotic venous disease, such as swelling, pigmentation, and lipodermatosclerosis.<sup>12</sup> Microcirculatory changes leading to dermal breakdown follow.

The anatomic components contributing to ambulatory venous hypertension are **venous valvular incompetence** and **luminal obstruction**. The most severe post-thrombotic morbidity is associated with the highest venous pressures, which often occur in patients with both valvular incompetence and luminal venous obstruction.<sup>10,13</sup> Although valvular function can be reliably assessed with ultrasound, techniques are not yet available to assess the relative contribution of venous obstruction to the pathologic venous hemodynamics leading to clinical post-thrombotic morbidity (Fig. 149.1). Neither ascending phlebography performed and interpreted by a skilled radiologist nor the maximal venous outflow test performed in an accredited vascular laboratory identified venous obstruction in the patient presented (see Fig. 149.1). A cross-section of the proximal femoral vein removed during a classic Linton procedure clearly showed recanalization channels through what was once occlusive thrombus, resulting in chronic obstruction of a large percentage of the luminal surface area. Venous hemodynamics can be affected before imaging techniques detect obstruction. Our inability to noninvasively quantify obstruction has led physicians to underappreciate its contribution to post-thrombotic pathophysiology. **Luminal**

venous obstruction causes the most severe forms of PTS, especially when it involves the common femoral and iliac veins. Obstruction of the distal popliteal vein is also associated with significant PTS. Therefore, treatment strategies for **thrombus removal** should be developed during the initial encounter in patients with severe symptoms, and, if successful, can eliminate obstruction, and should significantly reduce the incidence of PTS. We and others have observed that successful elimination of thrombus can preserve venous valve function.<sup>14</sup>

Experimental observations in canine models of acute DVT have shown that successful thrombolysis preserves endothelial function and valve competence.<sup>13,15</sup> These experimental observations appear to translate into improved clinical outcomes when put into the perspective of natural history studies of acute DVT treated with anticoagulation alone. Investigators have found that distal valve incompetence can develop in patients with persistent venous obstruction treated with anticoagulation alone, even when the distal veins are not initially involved with thrombus.<sup>16</sup> When spontaneous lysis occurred, defined as clot resolution within 90 days, valve function was frequently preserved.<sup>17</sup> These investigators confirmed that the combination of valvular incompetence and venous obstruction was associated with the most severe post-thrombotic morbidity.<sup>18,19</sup> It is intuitive that elimination of acute venous thrombus restores luminal patency and increases the likelihood that valve function will be preserved.



**Figure 149.1** Post-thrombotic venous disease illustrating the inability to identify obstruction as part of the pathophysiology of chronic venous disease. This patient had had iliofemoral deep venous thrombosis 10 years earlier and was treated with anticoagulation alone. Severe post-thrombotic syndrome developed, and the patient underwent multiple hospitalizations for venous ulceration. An ascending phlebogram showed recanalization of the iliofemoral venous system; however, the radiologist's interpretation was that there was "no obstruction" of the deep venous system, and a 3-second maximal venous outflow test was "normal." A classic Linton procedure was performed and showed (*inset*) the cross-section of the femoral vein at the corresponding location on the phlebogram, just below the profunda femoris vein.

## RATIONALE FOR THROMBUS REMOVAL

There is a reasonable body of evidence supporting a strategy of thrombus removal, especially in patients with IFDVT. When a strategy of thrombus removal is successful, venous patency is restored, valve function can be preserved, QoL is improved, and the risk of recurrence is reduced. Qvarfordt and Eklof<sup>20</sup> measured compartment pressures in patients presenting with acute IFDVT before and after operative venous thrombectomy. Compartment pressures (a surrogate for venous pressures) were pathologically elevated upon presentation, consistent with pressures associated with acute compartment syndrome. The high pressures normalized following operative thrombectomy. These important observations documented significant physiologic benefit by restoring the main venous outflow to the lower extremity.

Scandinavian investigators randomized patients with IFDVT to operative venous thrombectomy plus arteriovenous fistula (AVF) and anticoagulation or to anticoagulation alone. This multicenter randomized trial demonstrated that patients undergoing venous thrombectomy enjoyed improved iliac vein patency ( $P < 0.05$ ), lower venous pressure ( $P < 0.05$ ), less edema ( $P < 0.05$ ), and fewer post-thrombotic symptoms ( $P < 0.05$ ) than did patients receiving anticoagulation alone.<sup>21,22</sup> Patients undergoing venous thrombectomy were more likely to retain venous valve function in the femoropopliteal segment than those treated by anticoagulation alone. This observation is consistent with that reported by Killewich and co-authors, who demonstrated that persistent proximal obstruction leads to distal valve incompetence in veins not initially involved with thrombus and that elimination of iliofemoral thrombosis maintains distal valve function.<sup>16</sup>

Evidence suggests that catheter-directed thrombolysis (CDT) may be of benefit, particularly in patients with IFDVT.<sup>23–27</sup> A case-controlled study demonstrated significantly improved QoL in IFDVT patients treated by CDT versus anticoagulation alone.<sup>28</sup> In a subsequent analysis, the QoL benefit associated with CDT directly correlated with the volume of thrombus removed.<sup>23</sup> The more residual thrombus at the end of CDT, the worse the QoL. There was also a correlation with objective measures of PTS: the greater the degree of lysis, the fewer symptoms of PTS observed.<sup>26</sup>

Baekgaard et al.<sup>29</sup> followed 103 patients for 6 years after being treated with CDT for IFDVT. They reported that 86% of veins were patent without reflux and only 6% of patients developed recurrence during the 6-year follow-up period.

Pharmacomechanical techniques have been shown to improve outcomes compared with CDT using the drip technique alone, with shortened treatment time, reduced dose of lytic agent, and reduced length of ICU and hospital stay.<sup>29–31</sup>

### Recurrence

An underappreciated but important benefit of successful thrombus removal is the reduction in the rate of recurrent DVT. As mentioned earlier, patients with IFDVT have an exceptionally

high recurrence rate compared with those having less extensive thrombosis.<sup>9,32</sup> Hull et al.<sup>9</sup> performed a systematic review and showed that treated patients with a large thrombus burden had a greater risk of recurrence than those with a smaller thrombus burden. As noted previously, Baekgaard and colleagues<sup>29</sup> observed an unexpectedly low 3-year recurrence after CDT for IFDVT. Aziz and Comerota<sup>26</sup> observed that patients with IFDVT treated with catheter-directed techniques appeared to have a low recurrence rate. Upon further analysis, the benefit accrued to those patients who had successful thrombus removal, whereas those with the bulk of the thrombus remaining (unsuccessful lysis) had a significantly higher recurrence rate.

### Valve Function

Vogel et al.<sup>14</sup> addressed the issue of whether pharmacomechanical techniques compromised valve function, presumably due to direct valve injury. In a sequential analysis of CDT versus pharmacomechanical thrombolysis (PMT), there did not appear to be any adverse effect on valve function. The important observations were that valves functioned best in patients who had successful thrombolysis. An interesting observation was that 35% of the veins in the noninvolved limbs had incompetent valves. This suggests that in a third of patients, valve dysfunction predates the onset of the acute DVT. This was confirmed in a prospective, nested case-controlled study.<sup>33</sup>

## STRATEGIES FOR THROMBUS REMOVAL: ENDOVASCULAR

Pharmacomechanical thromolytic techniques are becoming increasingly popular and should be considered in those patients with symptomatic IFDVT who have no contraindication to thrombolytic therapy.<sup>21,24,34–37</sup>

### Thrombolytic Therapy

Initial attempts at pharmacologic resolution of acute DVT used systemic thrombolysis. Early studies involving systemic delivery of plasminogen activators resulted in high rates of bleeding complications and less than optimal lytic results. Many patients were treated for infrainguinal DVT; therefore, even when lytic therapy was successful, the benefits were not as apparent as in patients with IFDVT. A summary of studies comparing anticoagulation with systemic thrombolysis has been reported.<sup>38</sup> Results were disappointing, considering the increased bleeding risk. However, an important observation demonstrated the improved long-term outcomes in patients with phlebographically successful systemic thrombolysis. Catheter-based procedures have rapidly replaced systemic thrombolysis as the preferred method of thrombus removal in patients with extensive DVT.

### Intrathrombus Catheter-Directed Thrombolysis

During the process of thrombosis, Glu-plasminogen binds to fibrin, which is converted to Lys-plasminogen. This modification produces more binding sites for plasminogen activators

and therefore more efficient production of plasmin. The basic mechanism of thrombolysis is the activation of fibrin-bound plasminogen and resultant production of plasmin. It is intuitive that delivery of the plasminogen activator within the thrombus (1) is more effective and potentially safer than systemic infusion of plasminogen activators. Additionally, intrathrombus delivery (2) protects plasminogen activators from circulating plasminogen activator inhibitor and, more importantly (3), protects the active enzyme plasmin from neutralization by circulating antiplasmin. This neutralization of circulating plasminogen is so effective that the half-life of plasmin in the systemic circulation is only a fraction of a second (see Ch. 43, Thrombolytic Agents).

Numerous reports have demonstrated good outcomes of CDT for acute DVT.<sup>38</sup> In general, when patients with acute iliofemoral DVT are treated, success rates in the range of 75% to 90% can be anticipated. The rate of bleeding complications generally ranges from 5% to 11%. Fortunately, serious distant bleeding is uncommon and intracranial bleeding a rarity. Most bleeding complications are localized to the venous access site. Symptomatic PE during infusion is uncommon and fatal PE rarely observed.

A report by Chang and co-workers<sup>38</sup> documented the benefit of sequential intrathrombus bolus dosing of rt-PA without a continuous infusion in a small group of patients (12 lower extremities with acute DVT). His careful observations lend credence to the benefit of high-pressure bolus dosing (pulse-spray) infusion of plasminogen activators into the acute thrombus. These observations underscore the importance of saturating the thrombus with a plasminogen activator and the effective activation of intrathrombus Lys-plasminogen.

#### Outcomes from the National Venous Registry

The National Venous Registry reported patients treated with lytic therapy for acute DVT, with 71% having IFDVT.<sup>39</sup> Although significant advances in treatment have been made since the publication of this report, a number of the early observations remain important. There was a significant correlation ( $P < 0.001$ ) of thrombosis-free survival associated with initial therapy. At 1 year, 78% of the patients with initially complete clot resolution had patent veins versus only 37% of patients who had less than 50% lysis. In the group of patients with first-time IFDVT who initially had successful thrombolysis, 96% of the veins remained patent at 1 year (4). Initial lytic success also correlated with valve function at 6 months. Of patients with less than 50% thrombolysis, 62% had venous valvular incompetence, whereas 72% with complete lysis had normal valve function ( $P < 0.02$ ).

A cohort-controlled QoL study was performed to determine whether lytic therapy altered QoL in patients with IFDVT in the National Venous Registry.<sup>40</sup> Results demonstrated that CDT was associated with better QoL than anticoagulation alone. QoL was directly related to initial success of thrombolysis. Patients who had a successful lytic outcome reported a better Health Utilities Index, improved physical functioning, less stigma of chronic venous disease, less health distress, and fewer overall post-thrombotic symptoms. Not surprisingly, patients in whom CDT failed had outcomes similar to those treated

with anticoagulation alone. As mentioned earlier, successful thrombus elimination appears to have reduced the risk of recurrence.

#### Pharmacomechanical Thrombolysis

Despite the fact that CDT achieves successful thrombus burden reduction, duration of thrombolysis can be unacceptably long. The risk of systemic bleeding and costs of care can be prohibitive. The effectiveness of CDT was succinctly characterized by Sillesen and colleagues<sup>41</sup> when they reported that 93% of their patients were successfully treated and discharged with patent veins and that more than 90% of the patients discharged with patent veins had normal venous valve function at 1 year. The treated patients had a mean duration of symptoms of just 7 days, and patients with symptoms exceeding 14 days were excluded. Therefore, lysis would be expected quickly in these patients because they truly represented acute DVT.

Mechanical techniques alone or in combination with thrombolysis have been developed to more rapidly clear the venous system. Vedantham and associates evaluated the effectiveness of mechanical thrombectomy alone or in combination with pharmacologic thrombolysis in 28 limbs of patients with acute DVT.<sup>42</sup> They evaluated multiple devices, including the Amplatz (ev3, Inc., Plymouth, MN), Trerotola (Arrow International, Reading, PA), and Oasis (Boston Scientific/Medi-tech, Natick, MA) catheters. Venographic scoring was performed at each step of the procedure. Around 26% of the thrombus was removed by mechanical thrombectomy alone, whereas adding a plasminogen activator solution to the mechanical technique (pharmacomechanical) removed 82% of the thrombus. This tabulation includes patients with more chronic occlusion who did not initially respond. Mechanical thrombectomy alone was successful in removing intraprocedural thrombus, which is generally gelatinous and not cross-linked with fibrin. The average infusion time was approximately 17 hours per limb, and 14% of patients had major bleeding complications.

Lin and co-authors reported their 8-year experience with PMT (via a rheolytic thrombectomy catheter).<sup>32</sup> Of their 98 patients, 46 received CDT alone and 52 underwent PMT. Pharmacomechanical thrombolysis with the AngioJet catheter was associated with significantly fewer phlebograms, shorter ICU stays, shorter hospital stays, and fewer blood transfusions. Bleeding complications were not different between the two groups. A smaller patient group treated by rheolytic thrombectomy was reported by Kasirajan and associates, who demonstrated that catheter-based mechanical thrombectomy alone was less effective than combined PMT.<sup>43</sup>

#### Ultrasound-Accelerated Thrombolysis

Parikh and coauthors reported their initial clinical experience with ultrasound-accelerated thrombolysis in 53 patients treated for acute DVT with the EKOS EndoWave (Bothell, WA) system.<sup>30</sup> Both upper- and lower-extremity DVT patients were included in this report, and a variety of lytic agents were used. Complete lysis ( $\geq 90\%$ ) was observed in 70% of patients and overall lysis (complete and partial) in 91%. The median

infusion time was 22 hours, and 4% of the patients had major complications, which were essentially puncture site hematomas. The authors' impression was that as compared with historical controls (a weakness of this report), treatment time and the doses of lytic agents were reduced with ultrasound-accelerated thrombolysis.

A randomized trial which objectively evaluated the benefit of adding ultrasound-accelerated thrombolysis (USAT) to CDT for IFDVT was reported by Engelberger et al.<sup>40</sup> They randomized patients with IFDVT to CDT alone (ultrasound infusion catheter without ultrasound activation) versus USAT. Patients' thrombus was quantified at baseline. Patients received 20 mg of rtPA over 1.5 hours and a repeat phlebogram performed with residual thrombus quantified by a physician blinded to treatment allocation. Patients receiving CDT alone had 54% lysis and those with USAT had 55% lysis ( $P = 0.91$ ). A one-year follow-up demonstrated that the addition of intravascular ultrasound to conventional catheter-directed thrombolysis for the treatment of acute iliofemoral DVT did not have any impact on relevant clinical or duplex outcomes.

### Endovascular Aspiration Thrombectomy

Aspiration thrombectomy can also be an effective therapy for thrombus removal, using large-sized catheters or sheaths for aspiration of thrombus. Jia et al.<sup>44</sup> performed a retrospective analysis on 68 patients with IFDVT treated with aspiration thrombectomy. A retrievable IVC filter was placed in all patients. Large-sized catheters (either a 9-F guiding catheter [Vista Brite Tip Guiding Catheter, Johnson & Johnson, Miami, FL] or a 10-F OptEase retrieval catheter [Cordis, Miami, FL]) was advanced over a 0.035-in guide wire with the catheter tip placed in either the iliac or femoral vein. The guide wire was then removed, and the catheter slowly pulled back while aspirating the catheter with a large syringe. This process was repeated until thrombus was completely removed. The authors reported a 100% technical success rate. Aspiration alone was successful in 47 patients; the remaining 21 required additional thrombolysis, and 32 required venous stenting. At a mean follow-up of 21.9 months, 11% recurrent thrombosis was found.

### RANDOMIZED TRIALS OF CATHETER-DIRECTED THROMBOLYSIS

The CaVenT trial<sup>45</sup> reported the long-term outcome after anticoagulation plus additional CDT versus anticoagulation alone for acute IFDVT. These investigators randomized 209 patients. Their primary endpoint was iliofemoral patency at 6 months and PTS at 2 years. CDT was performed with the UniFuse catheter (AngioDynamics, Latham, NY). Alteplase was infused at a dose of 0.01 mg/kg per hour for a maximum of 96 hours. The alteplase was prepared by mixing 20 mg in 500 mL of 0.9% NaCl. This would result in a 70-kg man being infused with 0.7 mg of recombinant tissue plasminogen activator (rt-PA) in 17.5 mL of infusate per hour. This appears to be an

unusually small volume of infusate, which might disadvantage effective thrombolysis.

The mean duration of thrombolysis was 24 hours; 43% had complete thrombolysis, 37% had partial thrombolysis, and 10% were deemed unsuccessful. Patients receiving CDT had a mean clot resolution of 82%. Patients treated with additional CDT had significantly improved iliofemoral venous patency at 6 months ( $P = 0.012$ ) and less PTS at 2 years ( $P = 0.047$ ). The authors reported that lower thrombus scores at completion of CDT were associated with increased patency ( $P < 0.04$ ) and that patency of the iliofemoral venous system correlated with a reduction in PTS ( $P < 0.001$ ). There was an absolute risk reduction in PTS of 14.4% in patients receiving CDT. Major bleeding complications occurred in 3.3% of patients undergoing CDT. Only one inferior vena cava filter was used in this group and there was no symptomatic pulmonary embolism (PE) observed.

These results demonstrate a significant benefit in those patients receiving additional CDT. The actual benefit might have been substantially greater if all patients entered into this trial had IFDVT. In reality, only 45% of the patients randomized to thrombolysis and 36% of those in the anticoagulation group had IFDVT. The authors calculated that the number needed to treat (NNT) to prevent one PTS was seven. In their 5-year analysis of clinical outcomes, the NNT to prevent one PTS was 4. This was due to continued deterioration of post-thrombotic morbidity in the anticoagulation group.

The ATTRACT Trial<sup>37</sup> (NCT00790335) is the largest randomized trial to date designed to evaluate whether a strategy of acute thrombus removal using pharmacomechanical catheter-directed thrombolysis (PCDT) plus anticoagulation reduces the incidence of PTS compared to patients assigned to anticoagulation alone. This NHLBI funded clinical trial randomized 692 patients with proximal DVT to PCDT plus anticoagulation ( $N = 336$ ) versus anticoagulation alone ( $N = 355$ ). Upon entry into the study, patients were stratified by extent of their thrombosis (iliofemoral vs. femoral-popliteal DVT), prior to treatment randomization (Fig. 149.2). The primary efficacy outcome was any PTS (Villalta score  $>4$ ) at 2 years post-treatment. The primary safety outcome was major bleeding. Clinically important secondary outcomes were resolution of acute pain and swelling, moderate to severe PTS and quality of life at 2 years (Veins QOL Symptoms). Patients randomized to PCDT were treated with rt-PA at a dose of 0.01 mg/kg per hour, not to exceed 1 mg/h. The total dose of rt-PA could not exceed 35 mg and the duration of infusion could not exceed 30 hours.

Overall results indicated that there was no difference in any PTS at 2 years between those randomized to PCDT and those randomized to anticoagulation alone, 47% and 48% respectively. Major bleeding was low in both groups, but significantly higher with PCDT, 1.7% compared to 0.3% in the anticoagulation group,  $P = 0.049$ . Fewer patients in the PCDT group developed moderate to severe PTS (Villalta score  $>9$ ) at 2 years compared to the anticoagulation group,  $P = 0.035$ . Although there was a trend toward improved QOL in the PCDT group at 2 years, the difference did not reach significance,  $P = 0.08$ . These data rendered this trial a negative study. However,

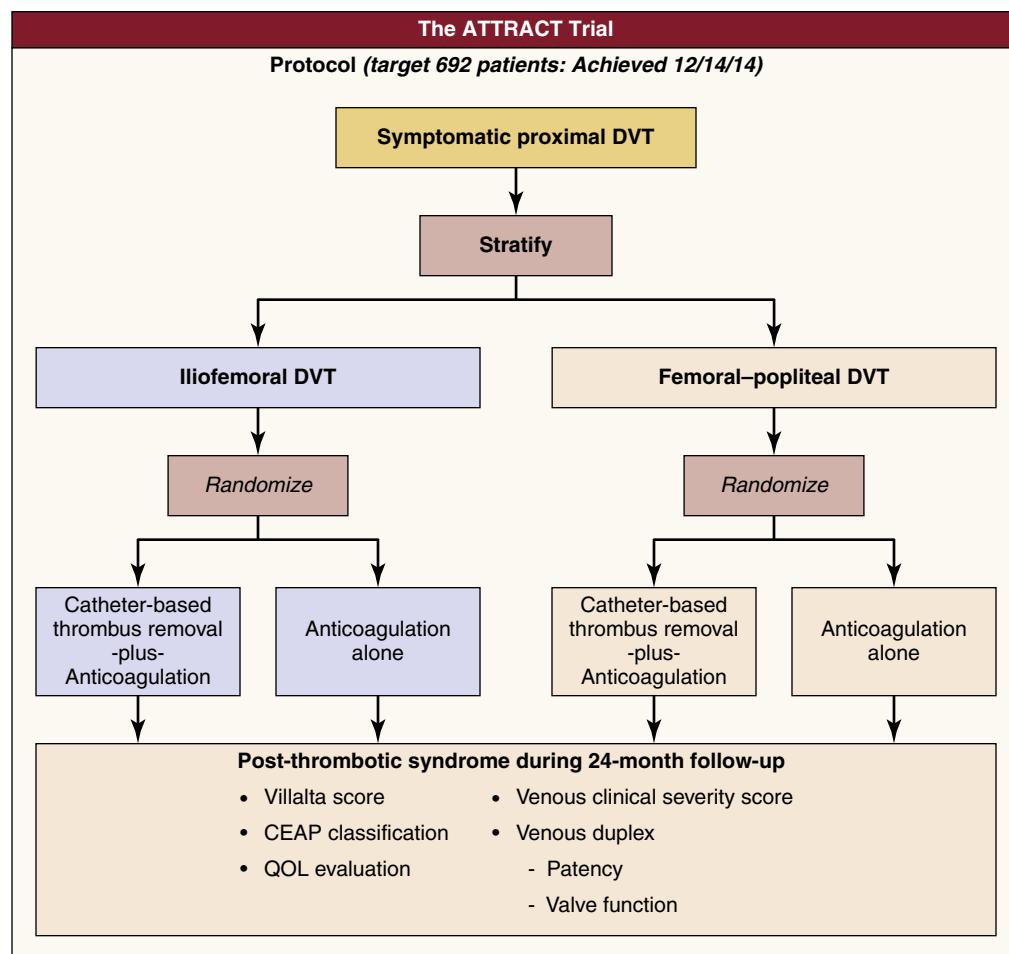


Figure 149.2 Basic Design of ATTRACT.

clinicians recognized that there was major value in examining whether there were outcome differences in patients with femoral–popliteal DVT versus those treated for iliofemoral DVT.

Kearon et al.<sup>46</sup> analyzed patients with femoral–popliteal DVT who were randomized in ATTRACT ( $N = 300$ ). Over a 24-month follow-up, there was no difference in any PTS, moderate or severe PTS or general or disease-specific quality of life. Major bleeding occurred more frequently in the PCDT patients ( $P = 0.06$ ). There appeared to be no signal that PCDT offered benefit to patients with femoral–popliteal DVT.

Comerota et al.<sup>28</sup> reported the results of patients presenting with iliofemoral DVT who were randomized in ATTRACT ( $N = 391$ ). The mean dose of rt-PA was 21 mg and the mean time of infusion was 22 hours. The mean amount of thrombus resolution was 86%. The primary endpoint of any PTS was no difference between groups, 49% in the PCDT group versus 51% in the anticoagulation group, using the Villalta score. However, if the VCSS were used, the primary endpoint of any PTS would have been met, favoring PCDT. PCDT led to reduced PTS severity as shown by lower mean Villalta and VCSS scores ( $P < 0.01$ ) and fewer patients with moderate–severe PTS (Villalta > 9,  $P = 0.021$ ) or severe PTS ( $P = 0.048$ ). From baseline, PCDT led to greater reduction in leg pain and swelling ( $P < 0.01$ ) at 10 and 30 days, and greater improvements in

venous disease-specific quality of life ( $P = 0.029$ ). In patients having PCDT, major bleeding within 10 days occurred in 1.5% versus 0.5% ( $P = 0.32$ ) and recurrent venous thromboembolism was observed in 13% versus 9.2% ( $P = 0.21$ ).

Physicians have questioned why the primary endpoint was not reached in patients with IFDVT. By protocol, any thrombus extending into the common femoral vein (even if nonocclusive) would be defined as iliofemoral DVT. An additional explanation may be that any PTS defined by the Villalta score may have been too sensitive for a primary endpoint. If a different outcome measure, such as the VCSS, were chosen as the primary endpoint, the results would have been positive. Another important observation is that 14% of IFDVT patients entered the trial with a normal Villalta score and 33% entered the trial with a mild Villalta Score. Since the goal of early treatment with a strategy of thrombus removal is to avoid moderate or severe PTS, that goal was achieved as a clinically meaningful endpoint.

The CAVA Investigators<sup>47</sup> sought to evaluate whether CDT with ultrasound-accelerated thrombolysis (USAT) using urokinase was more effective than anticoagulation alone in patients with IFDVT. One hundred and fifty-two patients with IFDVT were studied. Seventy-seven were randomized to USAT infusing urokinase at a 250,000 IU bolus followed by a continuous

infusion dose of 100,000 IU/h for a maximum of 96 hours, or 75 patients treated with conventional anticoagulation. At 12 months, post-thrombotic syndrome occurred in 22 (29%) of patients allocated to additional ultrasound-accelerated thrombolysis vs. 26 (35%) receiving standard anticoagulation ( $P = 0.42$ ). Major bleeding occurred in 4 (5%) in the intervention group and no major events in patient receiving standard anti-coagulation. There was no difference in QOL between the two treatment groups.

## OPERATIVE VENOUS THROMBECTOMY

Venous thrombectomy for iliofemoral venous thrombosis provides effective short- and long-term outcomes with relatively few complications. Pooled data from reports of iliofemoral venous thrombectomy indicate that the early and long-term patency rates of the iliofemoral venous segment is 75% to 80% versus 30% in patients treated by anticoagulation alone.<sup>4</sup> Femoropopliteal venous valve function is preserved in the majority of patients if patency of this segment is preserved or restored (Table 149.1).

The Scandinavian investigators reported a randomized trial of operative venous thrombectomy versus anticoagulation alone in patients with IFDVT.<sup>21–23</sup> Patients underwent systematic follow-up with venous imaging and physiologic measurements. Six-month, 5-year, and 10-year follow-up showed that patients randomized to venous thrombectomy had improved patency ( $P < 0.05$ ), lower venous pressure ( $P < 0.05$ ), less leg edema ( $P < 0.05$ ), and fewer post-thrombotic symptoms ( $P < 0.05$ ) than did patients treated with anticoagulation alone.

Rodriguez et al.<sup>48</sup> reported their experience treating 71 patients with IFDVT. They compared the results of 40 patients treated with a hybrid operative thrombectomy with 31 treated with catheter-directed thrombolysis. The hybrid operative thrombectomy included balloon catheter thrombectomy, completion venogram, and balloon venoplasty and stenting if needed. An AVF was not performed.

The investigators reported eight major bleeds in patients with CDT compared with none in the operative thrombectomy group ( $P = 0.04$ ) and CDT patients had a longer length of hospital stay (13.3 vs. 10 days;  $P = 0.028$ ). At 2-year follow-up there was no difference in femoropopliteal reflux. Although operative thrombectomy patients had a lower clinical class of their CEAP score, there was no difference in their Villalta scores (2.1 vs. 1.9,  $P = 0.8$ ).

### Venous Thrombectomy Technique

The principles of venous thrombectomy follow those of basic vascular surgical technique: remove the thrombus, provide unobstructed outflow from the iliofemoral venous segment into the vena cava and unobstructed inflow from the infrainguinal venous segment, correct any underlying lesions, and prevent rethrombosis (Box 149.1).

TABLE 149.1

### Venous Thrombectomy with Arteriovenous Fistula: Long-Term Iliac Vein Patency

Author/Year	No.	Follow-Up (Months)	Patent Iliac Vein (%)
Plate et al., 1984	31	6	76
Piquet et al., 1985	57	39	80
Einarsson et al., 1986	53	10	61
Vollmar, 1986	93	53	82
Juhan et al., 1987	150	102	84
Torngren and Swedenborg, 1998	54	19	54
Rasmussen et al., 1990	24	20	88
Eklof and Kistner, 1996	77	48	75
Neglen et al., 1991	34	24	88
Meissner et al., 1996	27	12	89
Pillny et al., 2003	97	70	90
Hartung et al., 2008	29	63	86
Holper et al., 2010	25	68	84
Rodriguez et al., 2017	40	36	76
Total	796	54 (mean)	80 (mean)

Modified from Comerota AJ, Gale SS. Surgical venous thrombectomy for iliofemoral deep vein thrombosis. In: Greenhalgh RM, ed. *Towards Vascular and Endovascular Consensus*. London: BIBA Publishing; 2005. Used with permission.

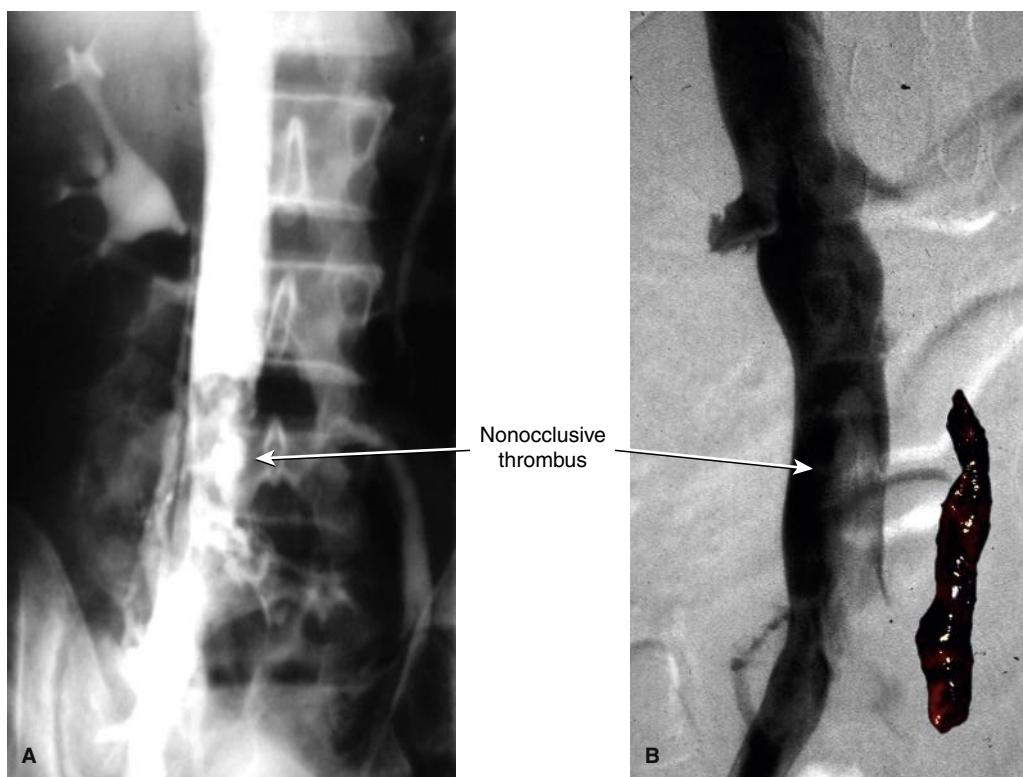
### PRINCIPLES

BOX 149.1

### Overview of the Technique of Contemporary Venous Thrombectomy

- Identify the cause of the extensive venous thromboembolic process
  - Complete thrombophilia evaluation
  - Rapid CT scan of the chest, abdomen, and pelvis
- Define the full extent of the thrombus
  - Venous duplex examination
  - Contralateral iliacavogram, MRV, or spiral CT
- Prevent pulmonary embolism (numerous techniques)
  - Anticoagulation
  - Vena caval filter (if nonocclusive caval clot)
  - Balloon occlusion of the vena cava during thrombectomy
  - Positive end-expiratory pressure during thrombectomy
- Perform complete thrombectomy
  - Iliofemoral (vena cava) thrombectomy
  - Infrainguinal venous thrombectomy (if required)
- Ensure unobstructed venous inflow to and outflow from the thrombectomized iliofemoral venous system
  - Infrainguinal venous thrombectomy (if required)
  - Correct iliac vein stenosis (if present)
- Prevent recurrent thrombosis
  - Arteriovenous fistula
  - Continuous therapeutic anticoagulation
  - Catheter-directed postoperative anticoagulation (if infrainguinal venous thrombectomy is required)
  - Extended oral anticoagulation

CT, computed tomography; MRV, magnetic resonance venography.



**Figure 149.3** (A) Contrast iliocavogram shows nonocclusive thrombus in the vena cava and illustrate the importance of imaging to detect the proximal extent of thrombus. In (B), the outlined area shows where the adjacent thrombus was extracted from the vena cava by balloon catheter thrombectomy. The proximal vena cava was protected with the balloon catheter (see Fig. 149.6).

Preoperative anticoagulation is generally initiated with unfractionated heparin (UFH) because it has a short half-life and can be controlled more easily than low-molecular-weight heparin or direct factor Xa inhibitors. The full extent of thrombus (distal and proximal) should be identified (**vena caval filtration** is not routinely used except in patients who have **nonocclusive thrombus extending into the vena cava** (Fig. 149.3). Vena cava filters and proximal balloon occlusion of the cava during thrombectomy are reasonable options.

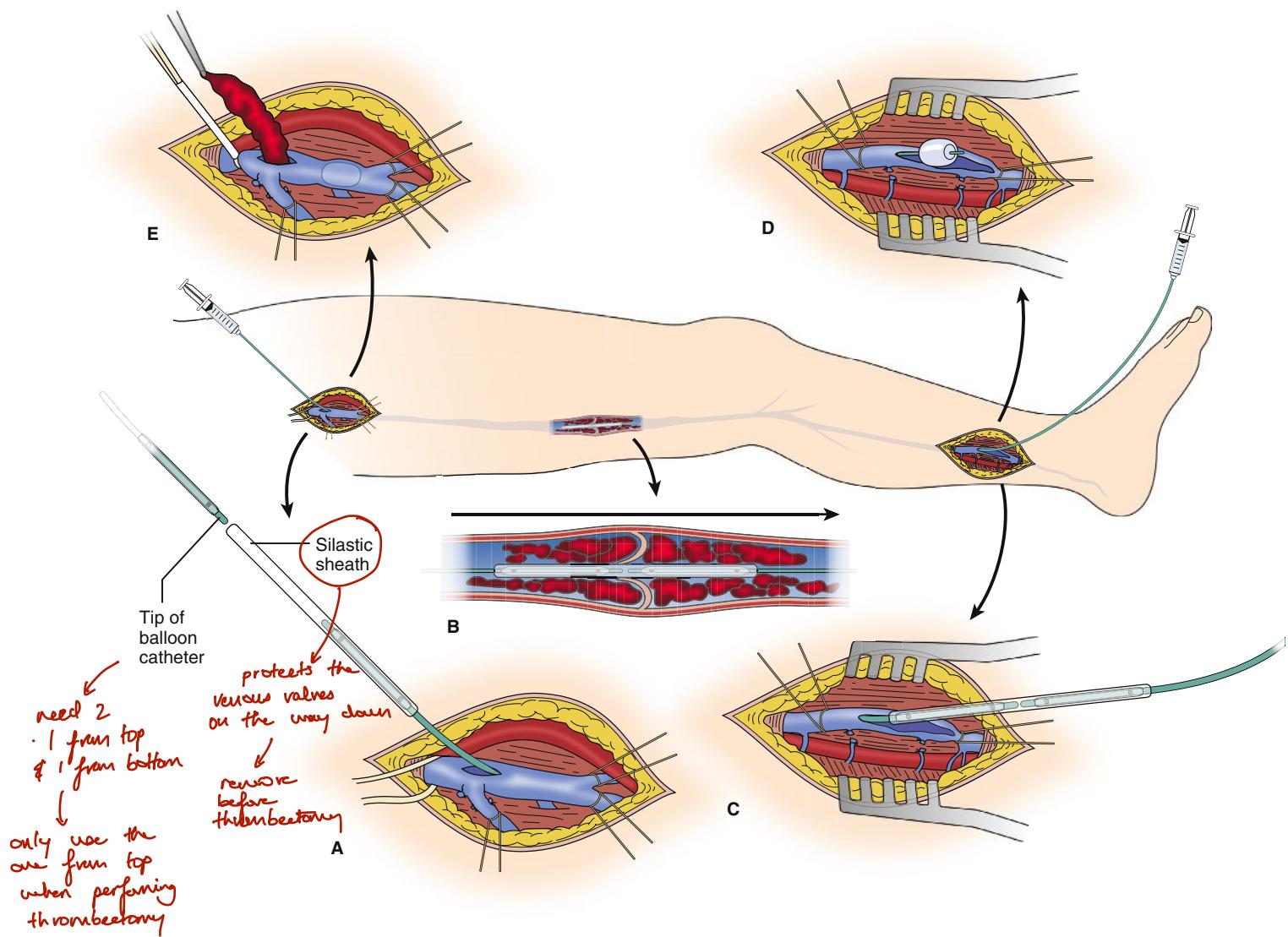
The **thrombectomy** is performed under fluoroscopic guidance with the **balloon** of the venous thrombectomy catheter filled with contrast material. The entire abdominal vena cava and pelvic venous system must be in the fluoroscopic field. An autotransfusion device should be available. General anesthesia is recommended. A longitudinal inguinal incision exposes the common femoral vein, femoral vein, saphenofemoral junction, and profunda femoris vein or veins (Fig. 149.4A). A longitudinal venotomy is made in the common femoral vein to ensure access to the origin of the saphenous and profunda femoris branches.

If **infrainguinal thrombus** is present, the leg is elevated and compressed with a tightly wrapped rubber bandage. The foot is dorsiflexed, and the calf and thigh are squeezed. If all infrainguinal thrombus is removed, balloon thrombectomy of the iliofemoral venous system then proceeds.

If the infrainguinal thrombus persists, a direct infrainguinal thrombectomy is required. A cut-down is performed to expose

the distal posterior tibial vein. A no. 3 Fogarty catheter is advanced from the distal posterior tibial vein to and through the common femoral venotomy. The Silastic stem of an intravenous catheter (12- to 14-gauge) is amputated from its hub and slid halfway onto the balloon catheter exiting the common femoral venotomy. Another balloon catheter (no. 4 Fogarty) is placed in the opposite end of the Silastic sheath (see Fig. 149.4A). Pressure is applied to the two balloons by a single operating surgeon to ensure that the catheters remain secure inside the sheath. The no. 4 balloon catheter is guided distally through the thrombus and venous valves (Fig. 149.4B) to the level of the posterior tibial venotomy (Fig. 149.4C). The infrainguinal venous thrombectomy is then performed, with passage repeated as necessary (Fig. 149.4D and E). Alternatively, ultrasound-guided posterior tibial vein access is obtained and a guide wire advanced to the common femoral venotomy. An over-the-wire balloon catheter is advanced distally to perform the balloon catheter infrainguinal thrombectomy. Upon completion of the thrombectomy, a sheath is passed into the posterior tibial vein for completion venogram and postoperative infusion.

After the infrainguinal balloon catheter thrombectomy, the infrainguinal venous system is flushed by placing a large red rubber catheter into the proximal posterior tibial vein and vigorously flushing with a heparin–saline solution via a bulb syringe to hydraulically force residual thrombus from the deep venous system (Fig. 149.5). Frequently, an impressive amount of thrombus will be expelled with this maneuver.



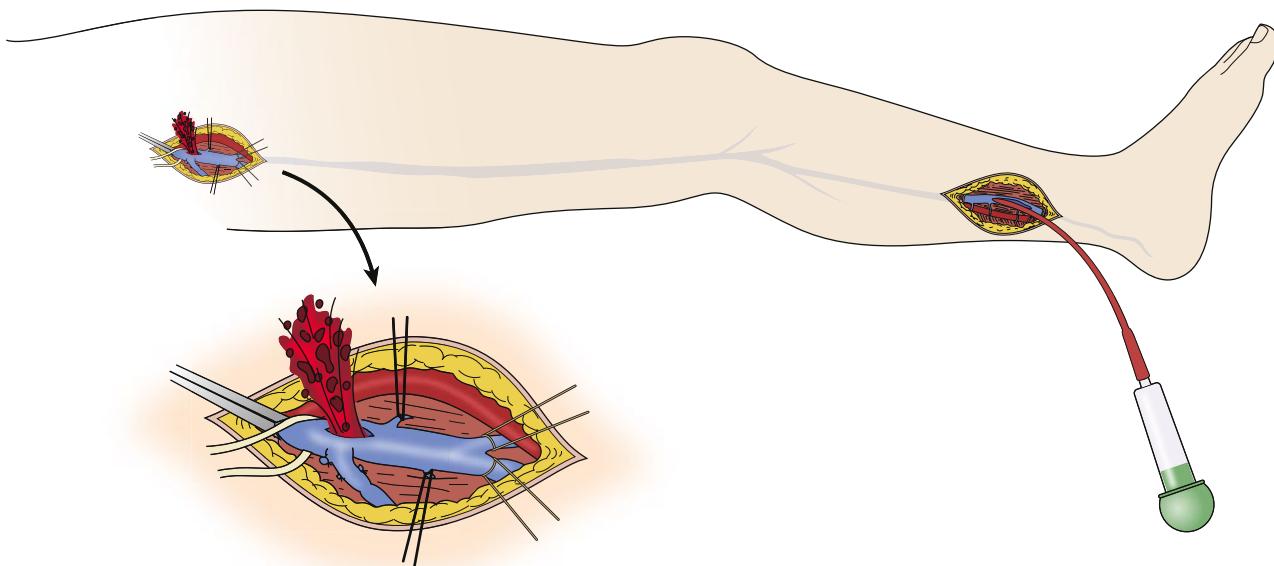
**Figure 149.4** Operative Thrombectomy for Acute Venous Thrombosis. (A) Longitudinal inguinal incision to expose the common femoral vein, femoral vein, saphenofemoral junction, and profunda femoris vein. (B and C) The balloon catheter is guided distally through the thrombosed venous valves and clotted veins to the level of the posterior tibial venotomy. (D and E) Performance of infrainguinal venous thrombectomy, with passage of the balloon catheter repeated as necessary.

Once the infrainguinal venous system is adequately cleared, a vascular clamp is applied below the femoral venotomy and the infrainguinal venous system is filled with dilute plasminogen activator solution consisting of 4 mg of rt-PA in 200 mL of saline. The plasminogen activator solution remains in the infrainguinal veins for the remainder of the procedure. This amount of local rt-PA will bind to fibrin-bound plasminogen in residual thrombus and promote further residual clot dissolution; however, it will not cause a systemic lytic response. If the infrainguinal venous thrombectomy is not successful because of chronic thrombotic disease of the femoral vein, the femoral vein is ligated and divided below the profunda femoris vein. Patency of the profunda is ensured by direct thrombectomy if necessary.

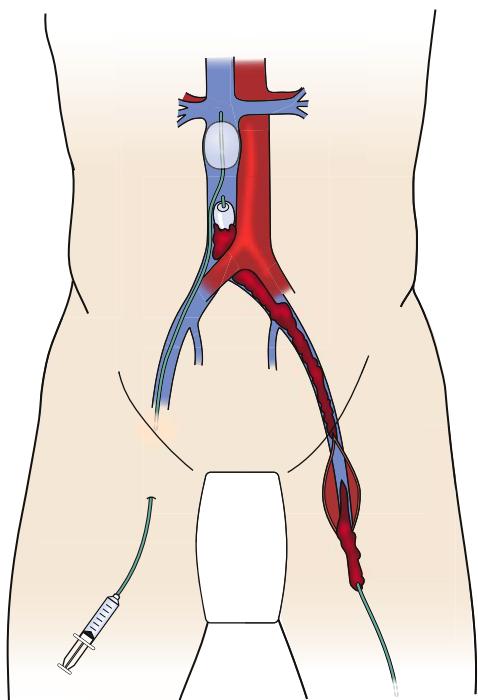
Iliofemoral venous thrombectomy is then performed by passing a no. 8 or 10 venous thrombectomy balloon catheter

partially into the iliac vein for several passes to remove the bulk of the thrombus before advancing the catheter into the vena cava. The proximal thrombectomy is always performed under fluoroscopic guidance with contrast material in the balloon, especially if a vena caval filter is present, there is clot in the vena cava, or resistance to catheter passage is encountered. During this part of the procedure, the anesthesiologist applies positive end-expiratory pressure to further reduce the risk of PE. If a clot is present in the vena cava, caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus as an alternative to vena caval filtration (Fig. 149.6).

After completion of the iliofemoral venous thrombectomy, intraoperative phlebography/fluoroscopy is performed to evaluate for underlying iliac vein stenosis and assess the nature of the venous drainage into the vena cava. Intravascular ultrasound is often better than single-view phlebography for detecting iliac



**Figure 149.5** After infrainguinal balloon catheter thrombectomy, flushing of the infrainguinal venous system with a heparin–saline solution is performed by placing a large red rubber catheter into the proximal posterior tibial vein and flushing vigorously with a bulb syringe.



**Figure 149.6** If a clot is present in the vena cava, caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus as an alternative to vena caval filtration.

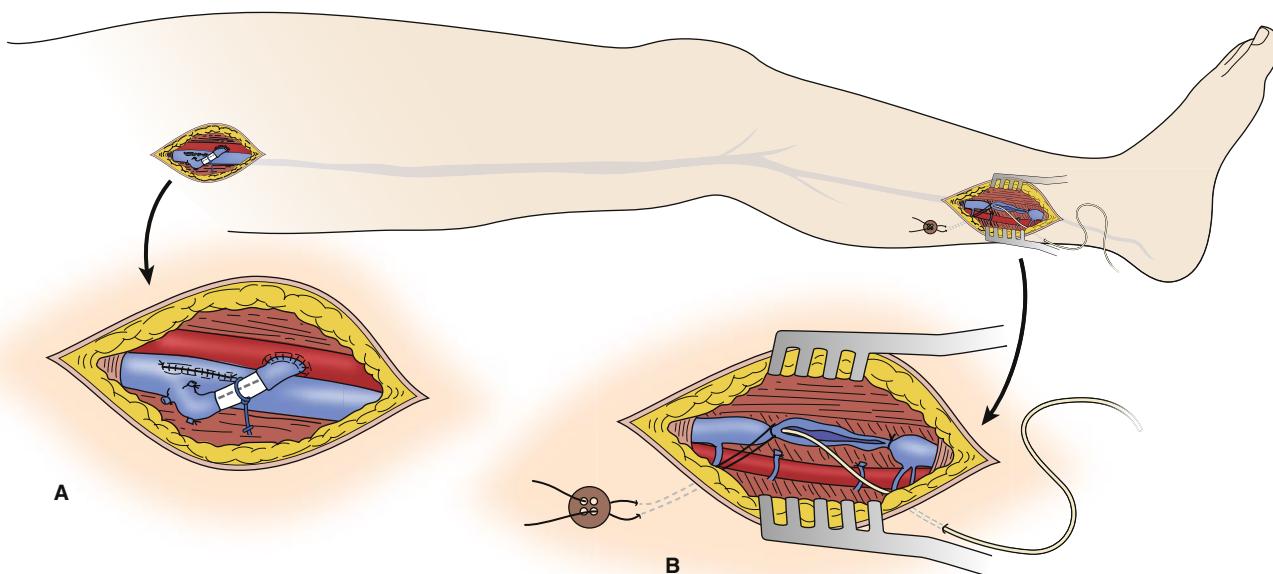
vein stenosis. Any underlying iliac vein stenosis is corrected by balloon angioplasty and stenting if venous recoil occurs. If an iliac vein stent is used, a 12-mm or larger-diameter stent is recommended for the external iliac vein and 16-mm or larger for the common iliac vein.

Once the venotomy is closed, an end-to-side AVF is constructed by anastomosing the amputated end of the proximal saphenous vein or a large proximal branch of the saphenous vein to the side of the superficial femoral artery. The anastomosis should be limited to 3.5 to 4.0 mm in diameter. The purpose of the AVF is to increase venous velocity but not venous pressure. Common femoral vein pressure is recorded before and after the AVF is opened. No increase in pressure should be observed when the clamps are removed and the AVF is opened. If the pressure increases, the proximal iliac vein should be re-evaluated for residual obstruction and the proximal lesion corrected. If the pressure remains elevated, the AVF is constricted to decrease flow and normalize pressure.

A piece of polytetrafluoroethylene or bovine pericardium is placed around the saphenous AVF and a large permanent monofilament ligature (no. 0) is looped and clipped, with approximately 2 cm left in the subcutaneous tissue (Fig. 149.7A). This will serve as a guide for future dissection in the event that operative closure of the AVF becomes necessary; however, most do not.

A diligent search for transected lymphatics is performed. A closed suction drain is placed in the wound to evacuate any serosanguineous fluid that may accumulate postoperatively. The drain exits through a separate puncture site adjacent to the incision. The wound is closed with multilayered running absorbable sutures to achieve hemostatic and lymphostatic wound closure and ensure elimination of dead space.

The distal posterior tibial vein is ligated. In patients with a posterior tibial venotomy, a small infusion catheter (pediatric feeding tube) is brought into the wound via a separate stab incision in the skin and inserted and fixed in the proximal posterior tibial vein (Fig. 149.7B). This catheter is used for postoperative anticoagulation with UFH and predischarge phlebography. Anticoagulation via this catheter ensures



**Figure 149.7** (A) Placement of a piece of polytetrafluoroethylene or Silastic around the saphenous arteriovenous fistula. A large permanent monofilament suture is looped and clipped, with approximately 2 cm left in the subcutaneous tissue. (B) Placement of a small infusion catheter (pediatric feeding tube) into the wound via a separate stab incision in the skin. It is inserted and fixed in the proximal posterior tibial vein.

maximum heparin concentration in the thrombectomized veins, which can be achieved with doses less than those required for systemic anticoagulation. A 2-0 monofilament suture is looped around the proximal posterior tibial vein (and catheter), and both ends exit the skin. The ends of the suture are passed through the holes of a sterile button, which is secured snugly to the skin when the catheter is removed. This obliterates the proximal posterior tibial vein at the time of catheter removal and eliminates the risk of bleeding. As mentioned, before removal of the catheter, an ascending phlebogram is performed through the catheter to assess patency.

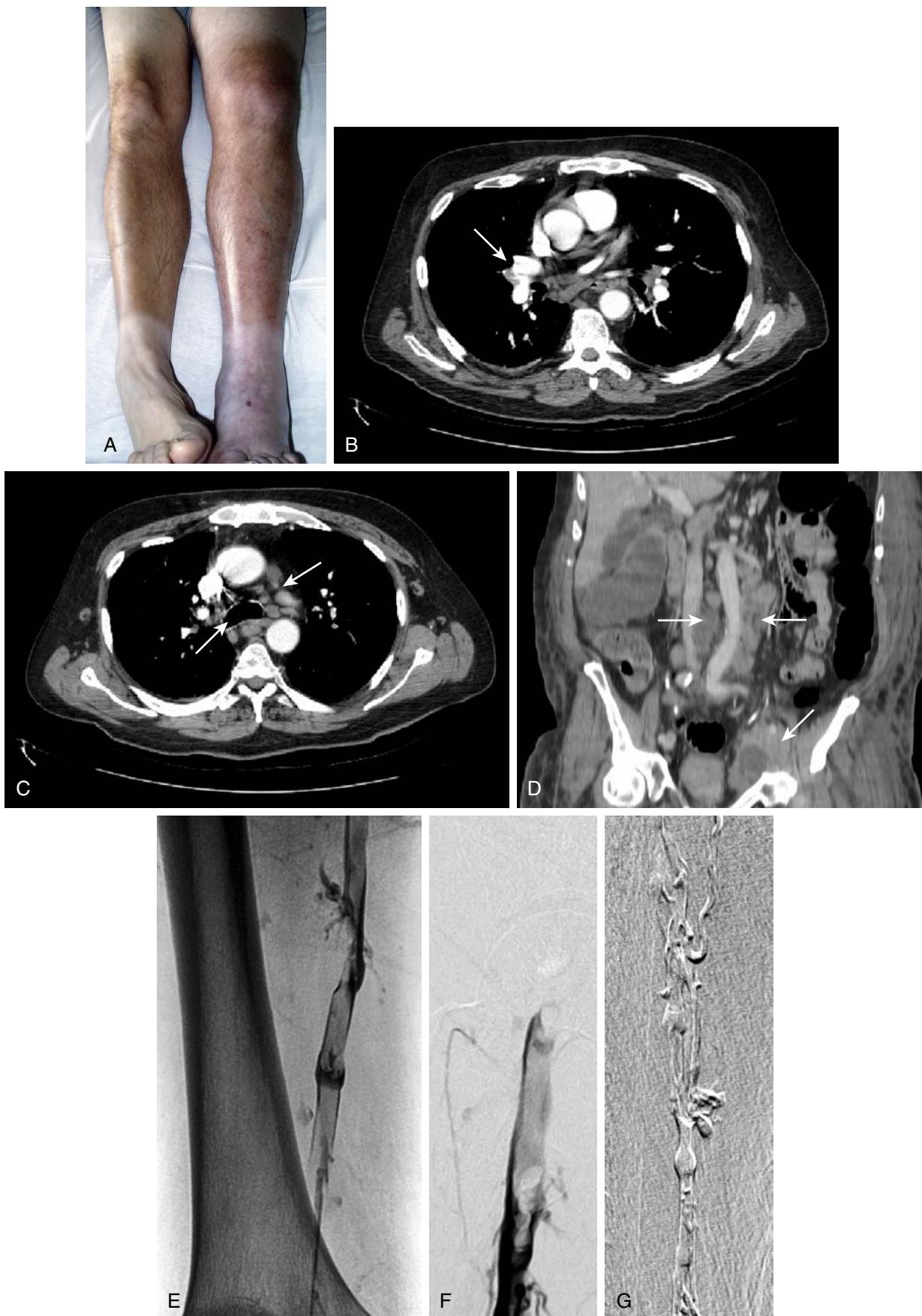
Antibiotic ointment is applied to all wounds beneath sterile dressings. The patient's leg is wrapped snugly with sterile gauze and multilayered elastic bandages from the base of the toes to the groin. The posterior tibial vein catheter exits between the layers of the bandage.

Anticoagulation is continued with UFH at 800 IU/h through the posterior tibial vein catheter attached to a pump on an intravenous pole with wheels so that the patient can ambulate. Before removal of the posterior tibial vein catheter, an ascending phlebogram is performed. Anticoagulation with warfarin or an oral anticoagulant is begun when the patient awakens and resumes oral intake. Oral anticoagulation is continued for an extended period, for 1 year and often indefinitely.

If an IVC filter was used, it is removed early after completion of the procedure. When the patient is fully recovered and back to baseline activity, repeat venous duplex and venous function studies are performed to evaluate patency and vein valve function, which serve as a baseline for future studies.

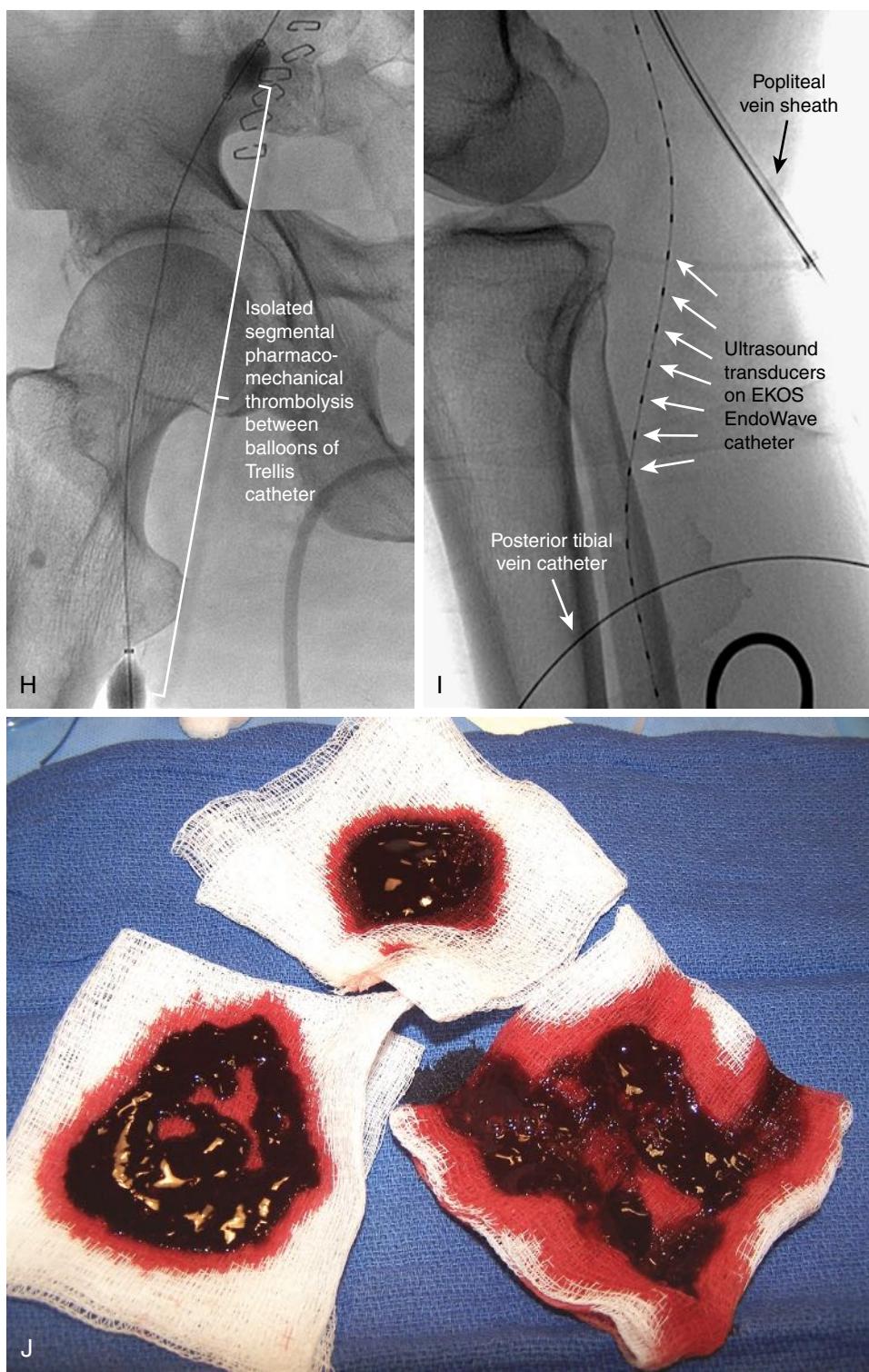
## CHOOSING THE APPROPRIATE TREATMENT OPTION

Patients with IFDVT should be considered for a strategy of thrombus removal if they have moderate or severe signs/symptoms at presentation. Our current approach to patients with IFDVT is summarized in the chapter algorithm below, and by the patient described in Figure 149.8. In general, our approach is to offer moderately to severely symptomatic patients with IFDVT a strategy of thrombus removal unless a reason exists otherwise. Individuals with occlusive thrombus of the common femoral vein have effectively obliterated venous drainage from the lower extremity and are subject to severe post-thrombotic morbidity. Although most patients in whom acute DVT is diagnosed are treated as outpatients, those with occlusion of the common femoral vein should be admitted and considered for a strategy of thrombus removal.



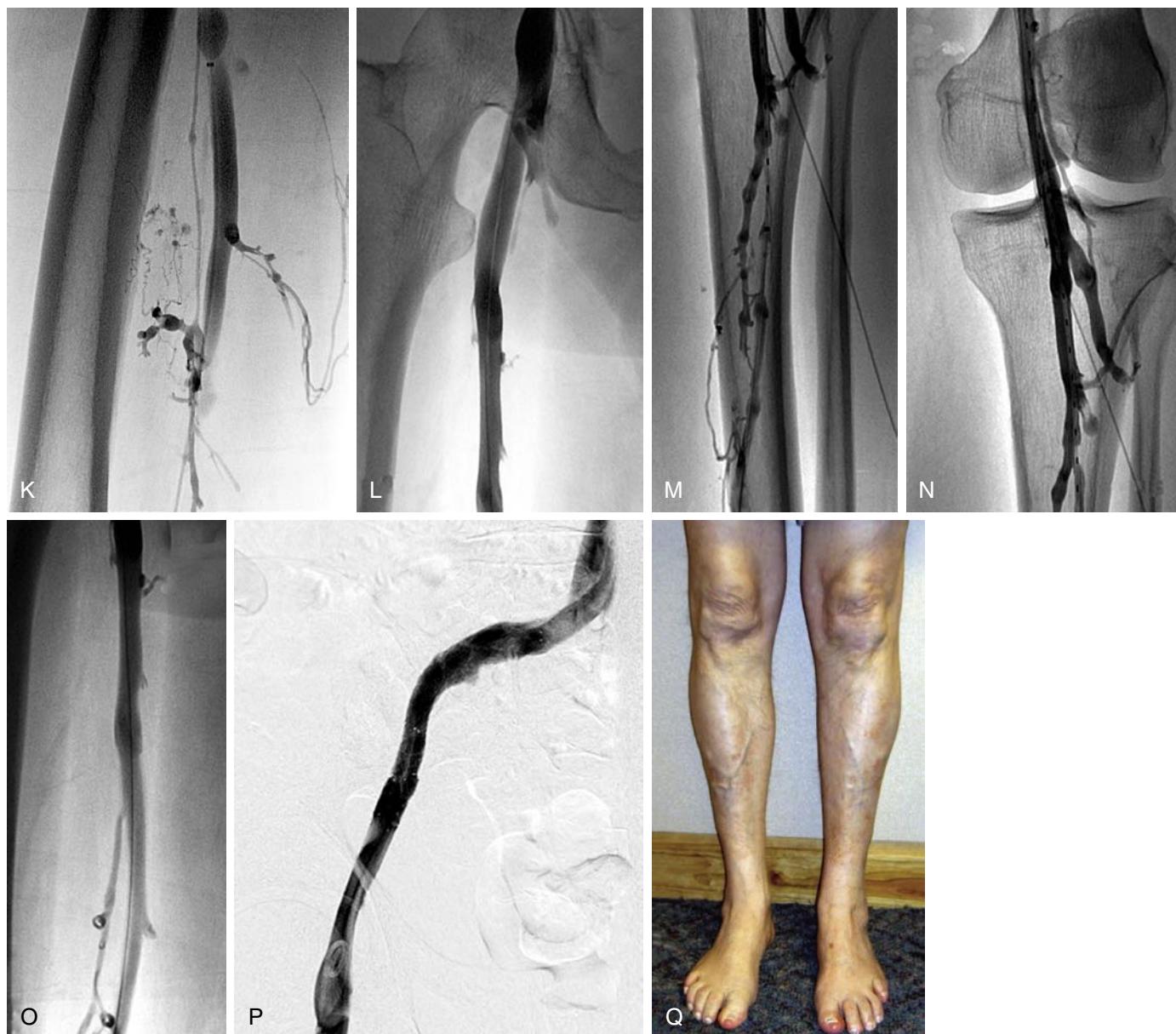
**Figure 149.8** A 65-year-old man was referred with phlegmasia cerulea dolens of his left leg (A) 36 hours after major abdominal laparotomy. Venous duplex demonstrated clot in the posterior tibial veins extending to the external iliac vein. A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis was performed and demonstrated asymptomatic pulmonary emboli (B) and mediastinal (C, arrows), and pelvic lymphadenopathy (D, arrows). The extensive thrombus is demonstrated by a catheter phlebogram of the femoral vein (E and F) and the silhouette of the calf thrombus (G) by the catheter in the posterior tibial vein at the ankle.

*Continued*



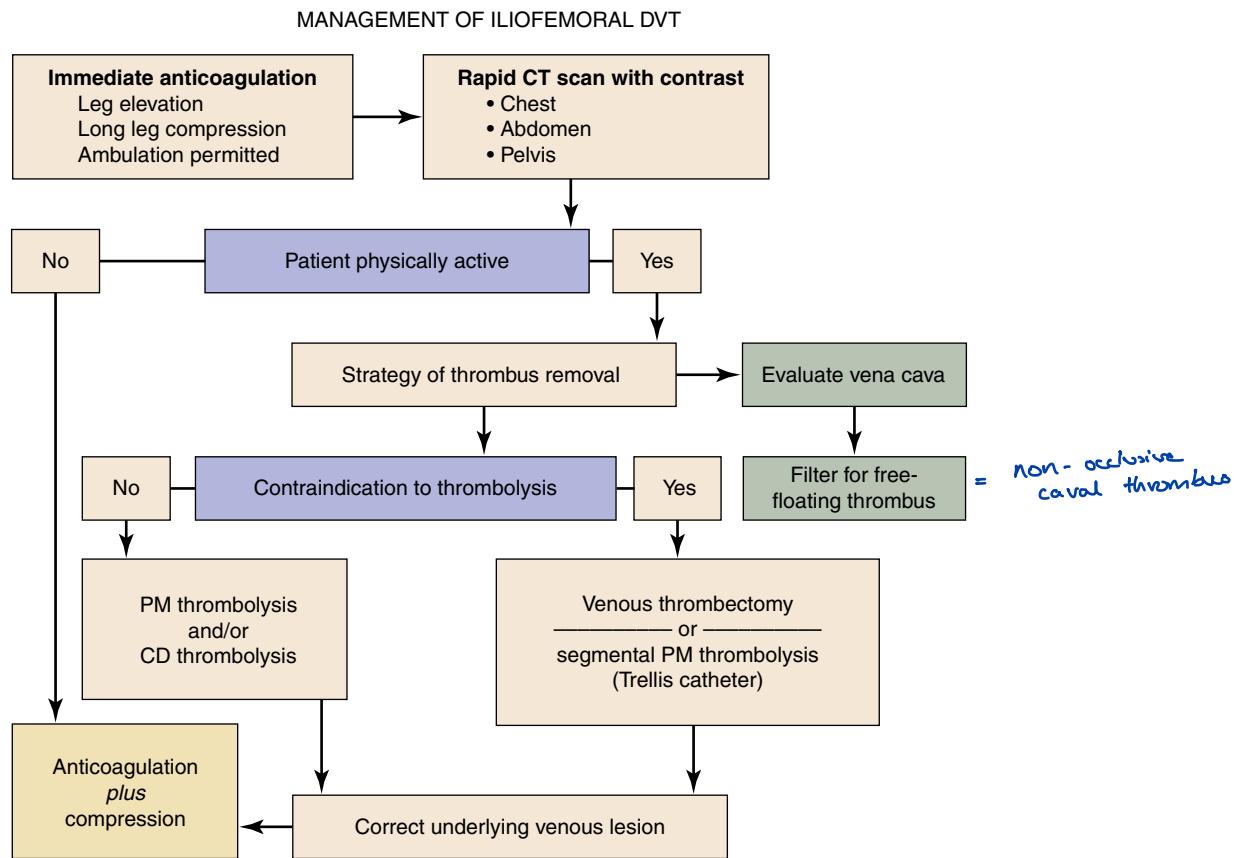
**Figure 149.8 cont'd** The bulk of the thrombus from the proximal popliteal vein to the common iliac vein was treated with the Trellis catheter via an ultrasound-guided popliteal vein approach (H). The clot in the posterior tibial and popliteal veins was treated with the EKOS EndoWave system (I). Liquefied and fragmented thrombus resulting from ISPMT was aspirated via the Trellis catheter (J).

*Continued*



**Figure 149.8 cont'd** Segmental phlebography is performed to check the results of treatment before moving to an adjacent thrombosed segment (**K** and **L**). Residual thrombus is removed by rheolytic thrombectomy with the AngioJet, and the iliac vein compression is treated with a stent. A completion phlebogram shows patency of the calf, popliteal, femoral, and iliac veins as well as supple valve cusps, thus suggesting that valve function persists (**M–P**). The patient was treated with systemic chemotherapy for his underlying lymphoma. At 16 months (**Q**) the patient was asymptomatic, had no post-thrombotic symptoms, maintained lower extremity venous patency with normal valve function, and fortunately had no evidence of lymphoma recurrence.

## CHAPTER ALGORITHM



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Comerota AJ, Kearon C, Gu CS, Julian JA, Goldhaber SZ, Kahn SR. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis. *Circulation*. 2019;139:1162.

*This is the analysis of 391 patients in the ATTRACT Trial with acute iliofemoral DVT. Those randomized to PCDT had more rapid relief of pain and swelling, had less moderate and severe post-thrombotic syndrome and had better disease-specific quality of life.*

Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomized controlled trial. *Lancet*. 2012;379(9810):31–38.

*This randomized trial of CDT added to anticoagulation versus anticoagulation alone for patients with IFDVT demonstrated significant benefit (reduced PTS) of CDT. The reduced post-thrombotic morbidity was directly correlated with patency of the iliofemoral venous segment.*

Kahn SR, Kearon C, Julian JA, et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost*. 2005;3(4):718–723.

*This prospective evaluation of patients with acute DVT was the strongest predictor of severe post-thrombotic syndrome (PTS). The odds ratio for patients with IFDVT to develop PTS was 2.23.*

Plate G, Akesson H, Einarsson E, Ohlin P, Eklof B. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. *Eur J Vasc Surg*. 1990;4(5):483–489.

*The Scandinavian investigators report the long-term follow-up of patients with IFDVT randomized to operative thrombectomy and AVF with anticoagulation versus anticoagulation alone. Patients randomized to operative thrombectomy had better patency, lower venous pressures, and less post-thrombotic morbidity.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Acute Upper Extremity and Catheter-Related Venous Thrombosis

ENRICO ASCHER, ANIL P. HINGORANI, and NATALIE A. MARKS

INTRODUCTION 1985

CLINICAL FINDINGS 1985

DIAGNOSTIC STRATEGIES 1986

RISK FACTORS AND PREVENTION 1986

Biomarkers 1986

Role of Thromboprophylaxis 1986

Catheter/Patient-Related Causes 1987

TREATMENT 1987

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CHAPTER ALGORITHM 1988

## INTRODUCTION

Acute upper extremity deep venous thrombosis (DVT) characterizes a disease process that ranges from an acutely swollen and painful extremity to one that is asymptomatic. This condition can be classified as either primary or secondary. Primary upper extremity DVT is related to either effort thrombosis (i.e. Paget–Schroetter syndrome – see Ch. 12<sup>6</sup>) Thoracic Outlet Syndrome: Venous) or an idiopathic cause. Secondary upper extremity DVT develops in patients with either cancer or an indwelling central venous catheter. As the prevalence of central venous catheter placement increases, secondary thromboses are increasingly outnumbering those related to primary causes.

The prevalence of acute upper extremity DVT, based on a prospectively collected registry – The Computerized Registry of Patients with Venous Thromboembolism (RIETE) – is approximately 4.4% of all DVTs. Almost half of the cases in that registry are catheter-related.<sup>1</sup> Furthermore, studies have documented that in comparison with lower extremity DVT, patients who suffer from upper extremity DVT have a higher mortality rate (up to 48% vs. 13% at 6 months). The high mortality rates in this population are reflective of the associated severe comorbidities rather than the central catheter or the thrombosis itself.<sup>2,3</sup> Subsequent data have demonstrated similar outcomes between upper extremity DVT and lower extremity DVT.<sup>4,5</sup>

In the United States alone, greater than five million catheters are inserted yearly to administer fluids, antibiotics, nutrition, and provide hemodialysis needs.<sup>6</sup> With an increasing number

of central venous catheters inserted, the overall incidence of catheter-related venous complications including thrombosis, sepsis, pulmonary embolism (PE) and death is simultaneously becoming a considerable issue. There is clearly an elevated incidence of thrombosis in cannulated veins versus noncannulated veins. This was demonstrated in an autopsy study as the risk of venous thrombosis among cannulated versus noncannulated vessels was 36% vs. 1.6%, respectively.<sup>7,8</sup> This chapter focuses on acute upper extremity catheter-related deep venous thrombosis.

## CLINICAL FINDINGS

Most patients with catheter-related upper extremity DVT are asymptomatic. For example, in a study documenting catheter-related thrombosis in cancer patients, the authors demonstrated that asymptomatic thrombi were present in 29% of patients (range 5% to 62%) vs. symptomatic thrombi in 12% of patients (range 5% to 54%).<sup>7</sup>

Erythema, pain or swelling located at neck, chest or arm are a few of the common symptoms, if present.<sup>9–15</sup> In patients with significant disease, there is often tremendous engorgement of the veins along the chest wall or the extremity. In rare instances, phlegmasia cerulean dolens has been reported.<sup>16,17</sup>

Pulmonary embolism is known to occur in 5% to 20% of patients with upper extremity DVT. A prospective study of patients with upper extremity DVT routinely performed ventilation–perfusion scans to determine the prevalence of PE among

all patients with upper extremity DVT. The scans demonstrated that 13 out of 86 (15.1%) patients developed a PE. The most common underlying comorbidity for these patients was cancer (31.4%). Additionally, Montreal et al., found that the higher incidence of PE (20%) occurred in the patients that had DVT associated with an underlying indwelling catheter.<sup>18,19</sup>

**Post-thrombotic syndrome**, consistent with a painful and swollen extremity after the acute episode, is also known to occur after upper extremity DVT. In a retrospective study by Hingorani et al., 13-month follow-up of 170 patients yielded 4% prevalence of symptoms associated with PTS. However, others have reported the incidence of post-thrombotic syndrome to be as high as 35%.<sup>2</sup>

## DIAGNOSTIC STRATEGIES

(1) Duplex ultrasonography is the mainstay for diagnosis of most upper extremity DVT. It is noninvasive and more cost-effective than other diagnostic modalities. The diagnosis is confirmed with augmentation maneuvers without appropriate response, noncompressibility of the venous segment, or the signal echogenicity in B-mode along a venous segment.<sup>2</sup>

A 2009 review article demonstrated duplex ultrasonography to be 86% to 100% specific and 78% to 100% sensitive in the diagnosis of upper extremity DVT. The thromboses that diminished the sensitivity of the duplex ultrasonography were those that incompletely assessed the veins, or located at the proximal subclavian or brachiocephalic veins. Furthermore, a prospective study in 66 patients with leukemia evaluated the role of ultrasonography and venography to evaluate patients with asymptomatic upper extremity DVT. These patients underwent bilateral venography and duplex ultrasound evaluation. The authors found an overall prevalence of 29% upper extremity DVT in this cohort. They then concluded that the sensitivity of their ultrasound (37%) was far inferior to venography (79%). It was also determined by these authors that the most common missed thrombotic sites were internal jugular vein during venography and subclavian vein during duplex ultrasonography.<sup>11</sup> It was also their recommendation that in those patients with suspected thrombosis, but without a confirmed diagnosis based on one test, additional testing with or without the use of adjunctive maneuvers should be performed (see Chapter Algorithm).

We recommend that if the duplex ultrasound fails to reveal a thrombus and clinical suspicion is elevated for acute upper extremity DVT, one should obtain venography by either computer tomography (CT) or magnetic resonance (MR). Although catheter-directed venography is seldom used, it remains the gold standard to determine central thrombosis.

## RISK FACTORS AND PREVENTION

### Biomarkers

Biomarkers along with clinical exam and blood tests are often utilized to identify patients at high risk for thrombosis. In a

2014 study by Kleinjan et al., the authors aimed to generate a management strategy for patients based on a risk assessment score.<sup>20</sup> They utilized the Clinical Decision Score to predict upper extremity DVT based on a single point assigned to: presence of catheter in a venous system, localized pain, or unilateral edema. If another diagnosis was at least as likely to be present as thrombosis, a negative point was assessed to the patient and resulted in risk of 12%, 20%, or 70% for 1, 2, or 3 points, respectively.

A prospective study by Boersma et al. evaluated 212 patients with a 9% incidence of catheter-related thrombosis. The authors determined that patients with symptomatic thrombosis presented with elevated levels of factors VIII ( $P = 0.023$ ), white blood cell count ( $P = 0.042$ ), and plasminogen activator inhibitor-1 ( $P = 0.008$ ).<sup>21</sup> The authors advocated the use of thromboprophylaxis use in this selected population.

### Role of Thromboprophylaxis

While limited prior series had shown promise with the use of chemical thromboprophylaxis using anticoagulation for all patients with central catheters, published guidelines and most recent data have failed to support the idea. A study by Timsit et al. in 1998 demonstrated that age  $\geq 65$  years ( $P = 0.001$ ), internal jugular vein placement ( $P = 0.005$ ) and absence of therapeutic anticoagulation at time of catheter placement ( $P = 0.04$ ) were all associated with increased risk of thrombosis.<sup>22</sup> Further support of anticoagulation prophylaxis comes from small series of cancer patients evaluated by D'Ambrosio et al. Their analysis determined a lower risk of symptomatic catheter-related thrombosis than control among patients that received anticoagulation for prophylaxis (RR = 0.61, 95% CI, 0.42 to 0.88).<sup>13</sup> Additionally, in another report dalteparin infusion 2 hours prior to central catheter insertion in cancer patients was associated with a reduced risk of thrombosis.<sup>19</sup> Yet, the results have been largely irreproducible and the role of chemical thromboprophylaxis use prior to or during catheter insertion is not well supported.<sup>7</sup> Therefore, we do not recommend routine anticoagulation for patients with central venous catheters.

Measures to address catheter thrombogenicity have also been examined. Murray et al. demonstrated increased catheter thrombogenicity of polyethylene catheters compared to polyurethane catheters and rigid catheters compared to compliant catheters.<sup>10</sup> A number of authors have also commented that less trauma to vessel wall during insertion and during the life of the implant as well as persistence of catheter to remain in optimal location was paramount in safeguarding catheter-related thrombosis.

Moreover, the role of heparin-bonded catheters remains inconclusive at best, as the prophylactic effects against upper extremity DVT in adults have not been consistent. In 2014, a Cochrane review examined heparin-bonded catheters to non-heparin-bonded catheters in the pediatric population. The review failed to demonstrate a difference in thrombotic outcomes (RR = 0.34, 95% CI, 0.01 to 7.68).<sup>23</sup>

## Catheter/Patient-Related Causes

It is helpful to understand that thrombosis can be due to multiple causes: patient-related, catheter insertion-related or a combination. One of the earliest series to warn against the dangers of indwelling catheters associated with upper extremity DVT was completed in 1970. Tilney and Griffiths documented their 25-year experience and demonstrated that 31 of 48 (65%) of upper extremity DVTs were associated with catheters.<sup>15</sup> In 1998, Horattas et al., documented their cohort of patients with upper extremity DVT and found that 39% were catheter-related and 12% of those patients with upper extremity DVT presented with a pulmonary embolism. Horattas et al. further found that the risk of upper extremity DVT increased with larger catheter diameter, multiple punctures needed during insertion and overall duration of catheter placement.<sup>24</sup>

A patient's history of previous thrombotic event, inherited thrombotic disorders, malignancy and an acute infection have also demonstrated increased risk of thrombosis. A retrospective study evaluated 105 consecutive cancer patients undergoing chemotherapy with clinical suspicion of upper extremity DVT. The authors concluded that patients with acute catheter-related infection were more likely to have deep vein thrombosis than those without acute infection (RR 17.6, 95% CI, 4.1–74.1).<sup>10</sup>

Peripherally inserted central venous catheter (PICC)-associated upper extremity DVT has an incidence of 1.6% to 3.5%. Large PICC diameter ( $\geq 5$  Fr) (OR = 3.9, 95% CI, 1.1–13.9) and concurrent malignancy (OR = 4.1, 95% CI, 1.9–8.9) as demonstrated in a study among all patients that underwent PICC placement over a 1-year period, were found to be associated with a higher risk of development of upper extremity DVT.<sup>25</sup> In a study of fluid analysis model utilizing different PICC diameters, the authors noted a decrease in up to 80% of segmental venous flow rate with use of 6-Fr PICCs.<sup>26</sup> This finding was consistent with a prospective study with an established increased risk of symptomatic DVT in patients with 4-Fr PICC (up to 2.9%) compared to patients with a 6-Fr PICC (up to 9.8%). Another study to demonstrate the flow limit concept was performed in patients with cardiac lead devices. The study retrospectively evaluated patients with implanted cardiac leads and demonstrated a higher risk of upper extremity DVT in patients with multiple pacemaker leads (27%) vs. a single pacemaker lead (7%) (RR = 3.8, 95% CI, 1.0–15.0).<sup>27</sup>

Additionally, catheter site selection and distal tip position have also been demonstrated to be of great significance. The French National Federation of Cancer Centers workgroup on Standards, Options, and Recommendations established their guidelines on prevention of catheter-related thrombosis by reviewing 36 publications over an almost three-decade period (1990–2007).<sup>28</sup> Their analysis found that catheter position is one of the most important factors and recommended the distal tip of all central venous catheters to be located at the junction of right atrium and the superior vena cava.

Systematic review of internal jugular vein versus subclavian vein insertion site for central venous catheters found that internal jugular vein route had a lower rate of malposition (5.3%

vs. 9.3%) (RR = 0.66, 95% CI, 0.44–0.99).<sup>29</sup> Yet, the analysis failed to demonstrate a difference in thrombotic outcomes based on site of insertion. Furthermore, a study evaluating left versus right side central catheter insertion in cancer patients found that the incidence of thrombosis was much more common after left-sided catheter insertion (25.6%) than right-sided catheter insertion (6.8%). This result was reproducible in two additional studies that documented a relative risk in cancer patients of 2.6 and 4.4 for upper extremity DVT occurring after right-sided insertion and left-sided catheter insertion, respectively.<sup>28</sup>

The correlation between the routes of catheter insertion to incidence of DVT was addressed in a 2012 Cochrane review. The authors evaluated three randomized controlled trials and compared internal jugular vein vs. subclavian vein insertion sites of central venous catheters and assessed risk for associated thrombosis.<sup>9</sup> The review failed to find a difference in thrombotic complications (RR = 1.97, 95% CI, 0.87–4.48) between internal jugular or subclavian vein route. The analysis did find a significantly increased risk of thrombosis for femoral vein insertion compared to subclavian vein catheter insertions (RR = 11.53, 95% CI, 2.80–47.52). The authors concluded that subclavian route was preferred to femoral vein insertion for central venous catheters, but no clear thrombotic difference was noted between the internal jugular and the subclavian vein routes.

## TREATMENT

The standard treatment for upper extremity deep vein thrombosis is anticoagulation. This data, to a large part, has been extrapolated from the lower extremity data. In addition, the recent addition of direct oral anticoagulation as an effective and efficacious treatment modality for lower extremity deep vein thrombosis should yield them to be considered as enhanced alternatives to vitamin K antagonists.<sup>30</sup>

American College of Chest Physicians' (ACCP) guidelines recommend upper extremity deep vein thrombosis to be treated with three to six months of anticoagulation and removal of the central catheter if the patient does not require it.<sup>28,31,32</sup> The role of thrombolytic agents or thrombectomy is not clearly established, but the use of this therapy may be beneficial in patients with phlegmasia.<sup>19</sup> Specifically, according to the 2016 *Chest* guidelines the following cohort of patients may benefit from catheter-directed thrombolysis: those with severe symptoms, thrombosis involving most of the subclavian and axillary veins, symptoms present for less than 14 days, good functional status, life expectancy greater than one year, and low risk for bleeding.<sup>31</sup>

Furthermore, superior vena cava filter placement to prevent pulmonary embolism may be considered in a subset of patients that are unable to receive anticoagulation or catheter removal.<sup>12,33,34</sup> It is crucial to note the study by Usoh et al. demonstrated that high degree of caution should be noted in younger male patients that undergo superior vena cava filter placement. They documented that among 154 patients with a mean follow-up of 256 days after filter placement, there were three cases of

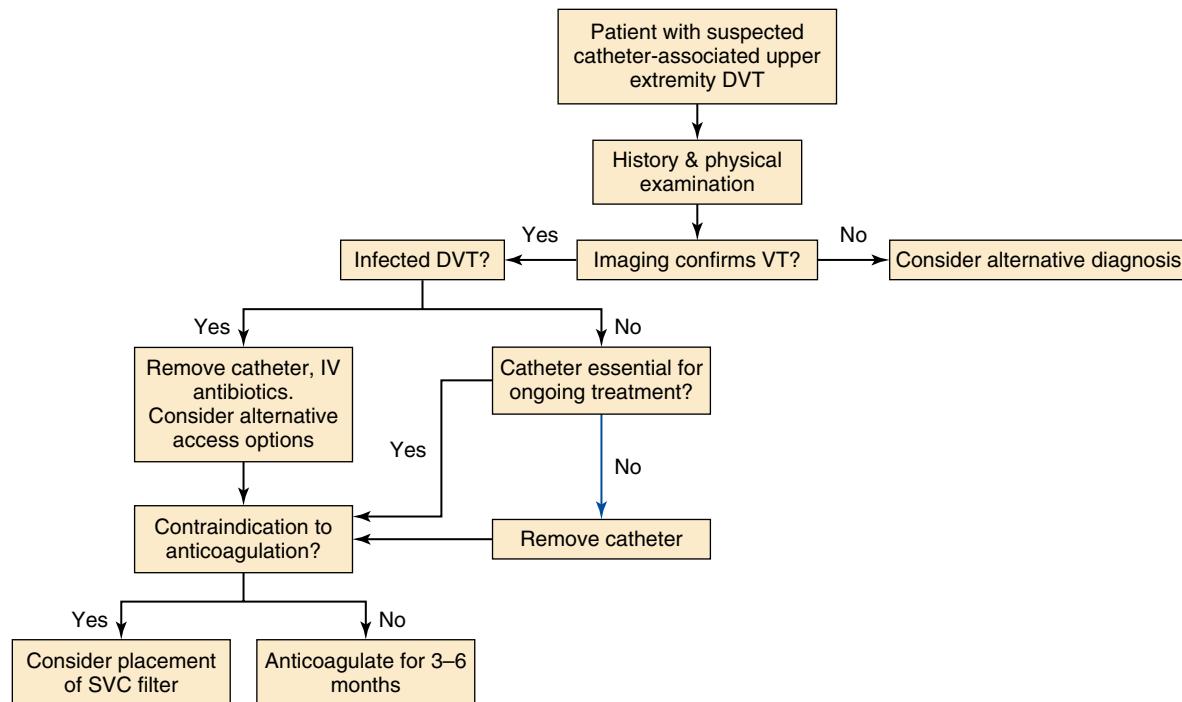
caval perforations. All three cases occurred in males less than 60 years old. No other cases of perforation occurred in older males or females of any age<sup>34</sup> (see Chapter Algorithm).

## CONCLUSION

Acute upper extremity venous thrombosis occurs frequently after insertion of indwelling catheters. Although most

patients with this condition may remain asymptomatic, some will develop a classic clinical picture including pain, erythema, swelling and even signs of pulmonary embolism. If possible, the indwelling catheter should be removed. However, if the patient does not have a safe alternative, the catheter can be left in place. The current treatment guidelines recommend full anticoagulation for a period of 3–6 months.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Superficial Thrombophlebitis and its Management

SUMAN M. WASAN

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Superficial venous thrombophlebitis (SVT) has been the focus of increased attention because of growing recognition of the potential morbidity and mortality associated with it. Although a global disorder, SVT develops in approximately 125,000 people per year in the United States; nonetheless, it is underestimated because many cases go unreported.<sup>1</sup>

It has been historically assumed that SVT is a self-limited process of little consequence and of small risk. However, new evidence on the natural history of SVT has led to improvements in evaluation and treatment. A meta-analysis reported a 6% to 44% incidence of deep venous thrombosis (DVT), a 20% to 33% incidence of asymptomatic pulmonary embolism (PE), and a 2% to 13% incidence of symptomatic PE in patients in whom SVT is diagnosed.<sup>2</sup> Improved diagnostic evaluation of SVT with duplex scanning, lung scanning, and blood tests has helped to identify predisposing risk factors and potential complications.

This chapter examines current data regarding SVT and its management, with the goal of improving recognition and treatment of the underlying disorders to prevent recurrence and its life-threatening complications.

## EPIDEMIOLOGY AND PATHOGENESIS

Although SVT is a frequently observed condition, its incidence and prevalence have never been adequately assessed. The classic Tecumseh Community Health Study from 1973 reported that

the incidence of SVT increases with age from 0.05 per 1000 per year in males in their third decade to 1.8 per 1000 per year in their eighth decade. In females the incidence similarly rises from 0.31 per 1000 per year to 2.2 per 1000 per year from their third decade to their eighth decade.<sup>3</sup> A more recent retrospective cohort study from the Netherlands reported an SVT rate in primary care of 1.3 per 1000 person-years with a 4.1% rate of venous thromboembolic sequelae, more frequent in active cancer patients and less in those with varicose veins.<sup>4</sup> Other studies have also demonstrated an increased prevalence of SVT in females.<sup>5,6</sup>

Overall, the incidence of lower extremity SVT has been reported to be 3% to 11% in the general population. A useful classification is the recognition that SVT may occur in two forms, those with, and those without varicose veins, or alternatively, SVT may be primary, involving the vein wall only, or secondary, involving a more systemic inflammatory process. Primary SVT is most common in the saphenous veins and their tributaries, followed by the upper extremity cephalic and basilic veins. The greater saphenous vein (GSV) is affected in 60% to 80% of cases, followed by the small saphenous vein (SSV) in 10% to 20%, and bilateral lower extremity SVT in 5% to 10%.<sup>7</sup> Patients with varicose veins are affected far more frequently than in the general population, with a prevalence of SVT ranging from 4% to 62%.<sup>3,6,7</sup>

Risk factors can be classified in accordance with Virchow's triad: endothelial injury from trauma or insertion of venous catheters; venous stasis as seen in varicosities; and

hypercoagulable states such as factor V Leiden, prothrombin G mutation, protein C and protein S deficiency, antithrombin III abnormalities, and malignancies including both solid tumors and hematologic conditions of Hodgkin lymphoma, leukemia, thrombocytosis, polycythemia vera, cryoglobulinemia, and nocturnal paroxysmal hemoglobinuria.<sup>7,8</sup> Patients in whom SVT develops without an inciting physical event or varicosities may need to be fully evaluated for the presence of such disorders.

Other secondary causes for the development of SVT include the use of oral contraceptives, hormonal replacement therapy, pregnancy, obesity, prolonged immobilization, recent surgery, trauma, sclerotherapy, history of venous thromboembolism, and some drugs (e.g., diazepam, amiodarone, vancomycin, heroin, some chemotherapy). Intravenous catheter use with or without bacterial infection places patients more at risk for the development of SVT.<sup>3,6-9</sup> In addition, patients with autoimmune disorders, including systemic lupus erythematosus and vasculitis, such as Behcet and Buerger disease, have also been identified as being susceptible to the development of SVT. A 2006 review of 2319 patients with Behcet disease found that 14.3% of these patients have vascular involvement. Of these 332 patients, 53.3% had SVT and 29.8% had DVT.<sup>10</sup> Patients with Buerger disease appear to have an increased incidence of SVT because the inflammatory process involves small arteries and veins of the extremities. It can be diagnosed from biopsy findings of acute superficial thrombophlebitis showing the characteristic acute phase lesion – inflammation of all three layers of the vessel wall with occlusive cellular thrombosis.<sup>11</sup>

The main concern related to SVT is the likelihood that the thrombus will extend into the deep veins, causing DVT and potential PE. Several older studies have evaluated this risk especially in relation to the proximity of GSV SVT to the deep veins. Chengelis et al. followed 263 patients with isolated SVT and performed follow-up ultrasound at 2 to 10 days (mean 6.3 days).<sup>12</sup> Thirty (11%) patients experienced progression to DVT while not receiving anticoagulation. The most common site was propagation of the SVT in the GSV into the common femoral vein. In a small retrospective review, 185 patients with SVT and 370 age- and sex-matched controls were evaluated.<sup>13</sup> A minority (13%) received nonsteroidal anti-inflammatory drugs (NSAIDs) or rarely low-molecular-weight heparin (LMWH) therapy. At 6 months, overall 2.7% had developed DVT and 0.5% PE. SVT conferred a 10-time increased risk of developing DVT compared with controls without SVT. A more recent meta-analysis found a pooled DVT and PE event rate of 9.3 to 16.6 events per 100 person-years after SVT in the absence of pharmacological treatment.<sup>14</sup> These studies represent an estimate of the natural history of SVT progression. Another focused study evaluated the incidence of PE in 21 patients with isolated SVT in the thigh.<sup>15</sup> Nuclear perfusion lung scans were performed within 3 hours of SVT diagnosis and demonstrated seven patients with PE (33%), including one symptomatic patient. Of note, there were no significant differences in the

distance of the SVT from the common femoral vein, or the presence of common risk factors for thrombosis compared with those with SVT that did not experience a PE. Although a small study, these findings highlight the potential serious consequences of SVT and suggest the need for anticoagulant therapy to prevent these complications.

Two recent large studies have evaluated the epidemiology and natural history of SVT in patients, most of whom received medical therapy. In the POST trial, Decousas et al. prospectively followed a cohort of 844 consecutive patients with symptomatic SVT of the lower limbs confirmed by ultrasound testing.<sup>16</sup> Patients with recent surgery within 10 days or SVT due to sclerotherapy in the previous 30 days were excluded. Patients were initially assessed for concomitant DVT, and then those with isolated SVT (634 patients) were followed with ultrasound again at 10 days and then at 3 months. A secondary outcome was overall mortality at 3 months. DVT or PE was confirmed in 24.9% of patients with SVT (82 patients with proximal DVT, 33 patients with PE). In 41.9% of patients with DVT, both proximal and distal, the DVT was not contiguous with the SVT. Of 634 patients with SVT, 90.5% received one or more anticoagulant medications, mostly therapeutic LMWH. Sixty patients (10.2%) had venous surgery. Fourteen patients were lost to follow-up. Of the remaining 586 patients, 58 had thromboembolic complications (10.2%), including seven with symptomatic proximal DVT, three with PE, and five with extension of SVT to DVT. Multivariate analysis showed that male sex, history of DVT or PE, previous cancer, and no varicose veins were independent risk factors for symptomatic venous thromboembolism (VTE) at 3 months including recurrence or extension of SVT. A more recent analysis of the ICARO study confirmed similar risk factors of male sex and cancer for progression of isolated SVT to DVT and PE.<sup>17</sup>

A recent pooled analysis of the POST study and the OPTIMEV trials involving 1074 cases revealed that in symptomatic patients with SVT, only male sex significantly and independently increased the risk of VTE recurrence after multivariate analysis. Cancer and saphenofemoral/popliteal junction proximity were associated with VTE recurrence on univariate analysis.

The OPTIMEV study evaluated 788 patients with SVT of 8256 patients that were referred for VTE.<sup>18</sup> The median age of these patients was 65 years, 36% were men and 16% were inpatients. Similar to the POST study, 29% were found to have concomitant DVT. Patients with both SVT and DVT had risk factors of presence of nonvaricose veins involved, age greater than 75 years, inpatient status, and active cancer, compared with isolated SVT, which was independently associated with anticoagulant treatment at inclusion and pregnancy or postpartum state. Compared with SVT of varicose veins, SVT in nonvaricose veins was a strong risk factor for concurrent DVT but did not convey a higher risk of 3-month adverse outcomes of death, VTE recurrence, or bleeding. In this study, 76% of those with isolated SVT were treated with anticoagulants, including 92.5% with full-dose LMWH. A follow-up analysis

revealed that cancer patients with SVT have a poor prognosis similar to that of patients with cancer-related DVT suggesting that these patients may require a longer duration of anticoagulant therapy.<sup>19</sup>

More recently, there has been greater awareness of the presence of hypercoagulable states in patients with SVT. These patients have a higher probability of developing DVT and recurrent SVT and may require long-term anticoagulation to prevent complications. Milio et al. evaluated 107 patients with unprovoked SVT for common thrombophilic conditions.<sup>20</sup> The patients underwent duplex evaluation at baseline and every 48 hours for 8 days, with notation whether the SVT occurred in varicose or nonvaricose veins. In the overall cohort, factor V Leiden was detected in 22.4%, MTHRF in 17.7%, and factor II G20210 mutation in 8.4%. Patients with thrombophilia and SVT in nonvaricose veins had a higher rate of extension of thrombus to deep veins. However, because all patients were treated with either LMWH or NSAIDs and the results were not analyzed by treatment group, it is difficult to draw definitive conclusions regarding the role of thrombophilia and DVT extension. Similar studies have supported the presence of acquired and inherited thrombophilic disorders as being a risk factor for the development of SVT, such as factor V Leiden and prothrombin (G20210A) gene mutations; deficiencies of antithrombin, heparin cofactor 2, protein C, and protein S; lupus anticoagulant; anticardiolipin antibodies; and abnormal fibrinolytic activity.<sup>3,6,10,11,21–23</sup>

An analysis published in 2014 including 1294 patients with SVT concluded that in patients with SVT not associated with varicose veins, malignancy, or autoimmune disease, thrombophilia screening may be considered due to a higher incidence of thrombus progression.<sup>24</sup>

Although a number of studies have described the pathophysiology and various changes that take place in leukocyte–vessel wall interactions, cytokines/chemokines, and various other factors involved in the development and resolution of DVT, there is a paucity of studies exploring these mechanisms in SVT. In a study of 68 patients with leg SVT who were treated with low and intermediate doses of dalteparin, acute phase SVT showed elevated high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukins 6, 8 and 10 (IL-6, IL-8, IL-10), and markers of fibrinolytic activity tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1) and fibrinogen that were reduced with treatment. Higher inflammatory markers were negatively correlated with thrombus recanalization at 12 weeks.<sup>25</sup>

## CLINICAL PRESENTATION

Evaluation for SVT by physical examination is based on the presence of erythema and tenderness in the distribution of the superficial veins and with the thrombosis being suspected by a palpable cord. Pain, erythema, and swelling are the most common symptoms.<sup>26</sup> There are a number of conditions discussed later that present unique risk factors or clinical presentations of SVT.

## Superficial Thrombophlebitis with Varicose Veins

The most common predisposing risk factor for the development of SVT is varicose veins. Because it has been reported that DVT will develop in only 3% to 20% of SVT patients with varicose veins as compared with 44% to 60% of SVT patients without varicose veins,<sup>27,28</sup> it appears that patients with varicose veins may have a different pathophysiology from those without varicose veins.

SVT involving varicose veins may remain localized to the cluster of tributary varicosities or may extend into the GSV.<sup>6,7,11,29,30</sup> SVT of varicose veins themselves may occur without antecedent trauma. SVT is frequently found in varicose veins in conjunction with venous stasis ulcers. This diagnosis should be confirmed by duplex ultrasound because the degree of SVT may be much greater than that based solely on clinical examination. SVT in varicosities may manifest as tender nodules with localized induration and erythema.

## Traumatic Thrombophlebitis

Traumatic SVT is often seen in individuals using illicit drugs or undergoing drug therapy in a hospital or outpatient setting. It is associated with direct endothelial injury from the intravenous catheter used for the infusion of medications and irritating solutions, particularly when the indwelling catheter has been in place for long periods. Its onset is usually heralded by the development of pain, tenderness, and erythema at the site of catheter insertion or infusion. Treatment usually consists of cessation of the infusion, removal of the offending access device, and sometimes anticoagulation depending on the severity of symptoms and underlying hypercoagulable condition. The induration may take weeks to months to resolve.

## Septic and Suppurative Thrombophlebitis

Suppurative SVT (SSVT) is also associated with the use of an intravenous cannula; however, SSVT may cause additional morbidity because of its association with septicemia. Signs and symptoms of SSVT include pus at an intravenous site, fever, leukocytosis, and local intense pain.<sup>31</sup> Aerobic, anaerobic, and mixed infections have been reported in SSVT. Organisms associated with SSVT include *Staphylococcus aureus*, *Pseudomonas* species (spp.), *Klebsiella* spp., *Enterococcus* spp., *Fusobacterium* spp., and recently, fungi such as *Candida* spp.<sup>31</sup> Treatment begins with removal of the foreign body and intravenous administration of antibiotics. Excision of the vein is rarely needed to clear the infection, although occasionally speeds up the healing process.

## Migratory Thrombophlebitis

Migratory thrombophlebitis was first described by Jadioux in 1845 as an entity characterized by repeated thrombosis developing in superficial veins at varying sites but most

commonly in the lower extremity.<sup>30</sup> This entity may be associated with carcinoma (Trousseau syndrome) and may precede diagnosis of the carcinoma by several years. Consequently, evaluation for occult malignancy is warranted when the diagnosis of migratory thrombophlebitis is made. Migratory thrombophlebitis also occurs in the presence of some forms of vasculitis such as Behcet disease, Buerger disease, and polyarteritis nodosa.<sup>8</sup>

### Mondor Disease

Mondor disease is defined as thrombophlebitis of the thoracoepigastric vein of the breast and chest wall (Fig. 151.1). It is thought to be associated with breast carcinoma or hypercoagulable states, although cases have been reported with no identifiable cause.<sup>22</sup> Tender, cordlike structures can be seen extending from the lower portion of the breast toward the costal margin or in the anterolateral aspect of the breast.<sup>32</sup> The condition is considered benign and self-limited lasting 4–8 weeks,<sup>33</sup> and treatment is conservative, rarely involving systemic anticoagulation.<sup>34</sup>

The term *Mondor disease* has also been applied to SVT of the dorsal vein of the penis. This phenomenon occurs in patients with DVT, after hernia operations, and in association with excessive sexual intercourse. Treatment consists of NSAIDs and dorsal penile vein resection if the symptoms are refractory.<sup>35</sup>

### Small Saphenous Vein Superficial Thrombophlebitis

Although the bulk of attention has been focused on SVT of the GSV, SVT of the SSV is also clinically significant. SSV



**Figure 151.1** Mondor disease: superficial thrombophlebitis of the thoracoepigastric vein of the breast.

SVT may progress to popliteal DVT. In a group of 56 patients with SSV SVT, 16% had PE or DVT.<sup>27</sup> In one study, it was found that 65.6% of 32 patients with SSV SVT also had DVT over a 1-year period.<sup>36</sup> Therefore it is crucial that patients with SSV SVT be treated similarly to those in whom GSV SVT is diagnosed – the same careful duplex examination, follow-up, and anticoagulation or ligation if the SVT approaches the popliteal vein.

### Upper Extremity Superficial Thrombophlebitis

Although very little appears in the literature, upper extremity SVT often results from intravenous cannulation and infusion of caustic substances that damage the endothelium. Typically, the basilic or cephalic veins are involved particularly if the catheter is inserted at or near the antecubital fossa. Interestingly, progression of upper extremity SVT to upper extremity DVT or PE is less common when compared with lower extremity SVT.<sup>37</sup> Initial treatment of upper extremity SVT is catheter removal followed by conservative measures with anticoagulation occasionally required. A recent analysis of PICC-related venous thrombosis in cancer patients receiving chemotherapy revealed age >60 and fluorouracil-containing infusion was associated with increased risk of line thrombosis.<sup>38</sup> A smaller study of 127 cancer patients revealed a 48.82% rate of asymptomatic PICC-related thrombosis with 76.5% SVT.<sup>39</sup>

### Superficial Thrombophlebitis After Endovascular Venous Obliteration

Minimally invasive endovascular techniques have emerged and gained popularity as alternatives to GSV ligation and stripping for GSV insufficiency and treatment of varicose veins. Endovenous laser ablation and radiofrequency ablation (RFA) have become widespread because of superior pain scores and feasibility as office-based procedures. In a prospective study of 67 patients undergoing EVLT and 66 patients undergoing RFA of the GSV or SSV, the rate of SVT was 1.5% in the EVLT group compared with 0% in the RFA group.<sup>40</sup> In another prospective study of 155 patients who underwent RFA of the GSV or SSV, only one patient (1.4% treated veins) developed SVT that occurred at a puncture site.<sup>41</sup> The incidence of SVT was higher in 150 patients who underwent SSV RFA (4%).<sup>42</sup> Zuniga et al. also reported a higher incidence of SVT of 10% to 15% in 667 RFA procedures of the GSV.<sup>43</sup> A meta-analysis of 104 studies evaluating the use of endovenous foam sclerotherapy for the treatment of venous disorders found an incidence of SVT of 11%.<sup>44</sup> This is somewhat higher compared with that reported for other endovenous procedures. Similarly, in a large randomized prospective study of 500 consecutive patients comparing EVLT, RFA, foam sclerotherapy, and stripping for GSV varicose veins, SVT occurred in 4 patients (3.2%) undergoing EVLT; 12 (9.6%) patients undergoing RFA; 17 patients (13.7%) with foam sclerotherapy, and 5 patients (4%) with surgical stripping.<sup>45</sup>

UGFS > RFA > EVLA + ⚡

## DIAGNOSIS

A positive diagnosis of SVT is primarily established by identifying the clinical and physical signs described earlier. Typically, pain, erythema, tenderness, and induration corresponding to one or more superficial veins or dilated varicose veins are evidence with possible edema over the inflamed vein. Painful “cords” are palpable, and fever or leukocytosis may be present if associated with a systemic infection. Typically, the inflammatory reaction may last 2 to 3 weeks, and either vein fibrosis or vein recanalization occurs over the ensuing 6 to 8 weeks. Postinflammatory hyperpigmentation may occur and last several months.<sup>8</sup> However, the potential presence of occult or symptomatic DVT or PE concomitantly with SVT warrants further imaging studies. A study of 141 patients with SVT of the GSV found a significantly greater thrombus extension when examined by ultrasound compared to physical exam, affirming the value of imaging for SVT evaluation.<sup>46</sup> A small study found that recurrent SVT correlated with thrombus in tributary veins, but other risk factors of varicose veins, previous DVT, cancer, or hypercoagulable state were not predictive.<sup>47</sup>

Duplex ultrasound scanning has become the initial test of choice for the diagnosis of DVT and evaluation of SVT since first introduced by Talbot in 1982. The availability of reliable duplex ultrasonography of the deep and superficial venous systems has made routine determination of the location and incidence of DVT in association with SVT precise and practical (Fig. 151.2; see Ch. 25, Vascular Laboratory: Venous Duplex Scanning). Furthermore, the extent of involvement of the deep and superficial systems can be more accurately assessed with this protocol. Duplex ultrasound imaging also offers the advantage of being inexpensive and noninvasive and can be repeated for follow-up examination. Because venography may contribute to the onset of phlebitis and duplex imaging affords an accurate diagnosis, venography is not a first choice for investigation. Although initial studies generated enthusiasm for the use of scintigraphy and computed tomographic venography,

their poor specificity and lack of anatomic detail have led to duplex ultrasonography remaining the primary diagnostic modality for SVT.

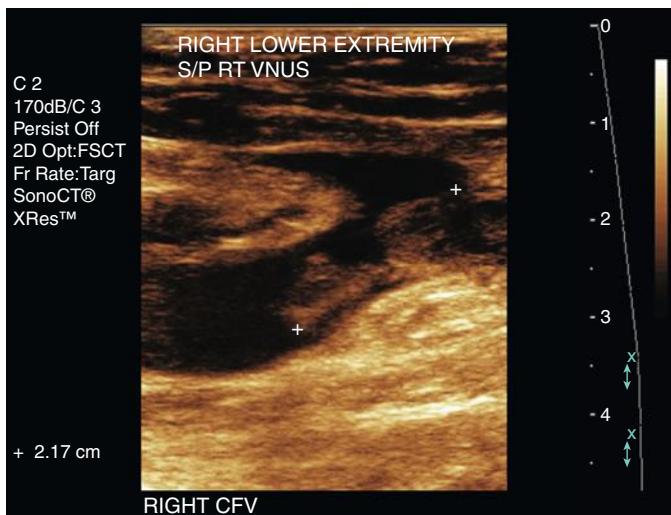
Patients with SVT may or may not have elevated levels of D-dimer, thus offering little assistance with respect to the negative or positive predictive value of the disease. Blood tests in patients with SVT should be directed toward testing for acquired and congenital hypercoagulable states or malignancies if clinically indicated, particularly in patients with nonvaricose vein SVT.

## TREATMENT

Treatment depends on the cause and location of the SVT. The goals of therapy are decreasing the acute symptoms of SVT including pain and erythema and preventing potential serious complications such as DVT and PE, as well as extension or recurrence of SVT. Historically, treatment was dictated by the proximity of the thrombus to the deep veins. Treatment for SVT has evolved from primarily surgical options to emphasis on medical treatment with the introduction of LMWH. Although warm compresses and compression hose have been recommended, there are little data supporting their use. A trial of 73 patients with SVT comparing use of compression stockings for 1 week compared with no compression revealed no difference in quality of life, pain, or use of analgesics, although thrombus regression measured on ultrasound was faster in the compression group.<sup>48</sup>

### Low-Molecular-Weight Heparin and Direct Oral Anticoagulants

One of the first trials evaluating modern medical management of SVT was the STENOX trial, a randomized double-blind trial of 427 patients with acute SVT of at least 5 cm length of the legs.<sup>49</sup> Patients were randomized to receive enoxaparin 40 mg daily, enoxaparin 1.5 mg/kg daily, oral tenoxicam 20 mg daily, or placebo for 8 to 12 days. Follow-up ultrasound was performed between day 8 and 12. The study excluded patients who were at high risk, such as those with thrombophilia; a history of DVT, PE, or SVT; two or more episodes of SVT; a history of venous sclerotherapy; or pregnancy. The overall rate of DVT by day 12 was 3.6% placebo group, 0.9% enoxaparin 40 mg group, 1% enoxaparin 1.5 mg/kg group, and 2.1% tenoxicam group. The study found that 30% of patients in the placebo group eventually had the combined outcome of extension of the SVT toward the saphenofemoral junction, recurrent SVT, and progression to DVT or PE by day 12. Fifteen percent of the NSAID group, 8% of those receiving 40 mg enoxaparin, and 7% of those receiving 1.5 mg/kg enoxaparin had the combined outcome for thrombotic events showing that all active treatment groups significantly reduced DVT and SVT progression. At 3-month follow-up after cessation of therapy, there was still a significant decrease in the combined outcome of DVT and SVT in the active treatment groups, but not in DVT alone. There were no episodes of major bleeding or



**Figure 151.2** Ultrasound image of thrombophlebitis with free-floating thrombus extending from the great saphenous vein into the femoral vein.

death during the study. Overall, this study showed a significant risk for DVT and SVT extension in the absence of medical treatment and suggested that LMWH, used either as a prophylactic or treatment dose, was the most effective therapy for prevention of thrombotic complications. Furthermore, the results suggest that the duration of therapy required further evaluation because most of the recurrent VTE events in the treatment groups occurred after active treatment halted.

Since publication of the STENOX trial in 2003, there have been four additional randomized trials evaluating the use of medical therapy for the treatment of SVT. The Vesalia investigators randomized 164 consecutive patients with acute SVT of the GSV not within 3 cm of the saphenofemoral junction (SFJ) to nadroparin fixed prophylactic dose (2850 units) subcutaneously versus body weight-adjusted therapeutic doses of nadroparin for 1 month in a double-blind double-dummy fashion.<sup>50</sup> The main outcome of VTE complications at 3 months occurred in 7 prophylactic dose patients compared with six treatment dose patients (NS). No patients in either group developed major bleeding.

The CALISTO study group randomized 3002 patients with acute SVT not within 3 cm of the SFJ to fondaparinux 2.5 mg subcutaneously daily or placebo for 45 days. At 47 days follow-up,<sup>51</sup> the primary combined outcome of symptomatic VTE, death, extension to the SFJ, or symptomatic SVT recurrence occurred in 13 or 1502 patients (0.9%) of the fondaparinux group and 88 of 1500 patients (5.9%) receiving placebo. Major bleeding occurred in one patient in each group. Except for the outcome of death, all components of the primary outcomes were significantly reduced in the fondaparinux group.

A post hoc analysis revealed that SVT extension occurred in 3.6% of patients and DVT/PE occurred in 9.3% and 8.9%, respectively, in the placebo group compared with less than 1.0% SVT extension and no DVT/PE in the fondaparinux group. This analysis supported the conclusion that symptomatic SVT extension confers significant morbidity whether near the deep saphenous junction or not. Fondaparinux treatment was associated with less consumption of medical resources related to thromboembolic complications.<sup>52</sup>

Rathbun et al. randomized 72 patients with acute SVT of the upper or lower limb regardless of proximity to the deep veins to dalteparin 200 units/kg body weight (maximum dose, 18,000 units) day 1 then 10,000 units daily for up to 13 additional days versus ibuprofen 800 mg three times daily for up to 14 days with the primary outcome of SVT extension or VTE at 14 days and 3 months.<sup>53</sup> Four patients receiving ibuprofen compared with no patients receiving dalteparin had thrombus extension at 14 days ( $P = 0.05$ ); however, there was no difference in thrombus extension at 3 months. Both treatments significantly reduced pain. There were no episodes of major or minor bleeding during the trial. Of note, extension of thrombus during the time after ibuprofen and dalteparin were discontinued suggested that the treatment duration of 14 days may have been too brief or that there is a rebound phenomenon after the medication is halted. A study of 147 consecutive patients who received tinzaparin for 60 versus 90

days showed a reduced incidence of recurrent thrombosis in the extended duration group that remained significant out to a year follow-up suggesting longer duration therapy for SVT is preferred.<sup>54</sup>

(4)

Finally, most recently, Cosmi et al. randomized 664 patients with SVT of the GSV or SSV or tributaries of at least 4 cm in length to parnaparin either 8500 IU daily for 10 days followed by placebo for 20 days (group A), or 8500 IU daily for 10 days followed by 6400 IU daily for 20 days (group B) or 4250 IU daily for 30 days (group C) in a double-blind fashion. The primary outcome of the composite of symptomatic and asymptomatic DVT, symptomatic PE, and relapse and/or symptomatic or asymptomatic SVT recurrence in the first 33 days with 60 days follow-up occurred in 15.6% group A, 1.8% group B, and 7.3% group C. No major hemorrhages occurred. The authors concluded that an intermediate dose of parnaparin for 30 days was superior to either 30-day prophylactic dose or 10-day intermediate dose treatment of SVT.<sup>55</sup>

A post hoc analysis for evaluation of risk factors showed that previous VTE, SVT, and/or family history of VTE were associated with the measured composite outcome. After LMWH treatment was stopped, the absence of varicose veins, previous VTE/SVT, or family history of VTE were associated with the outcomes. The authors suggested that these patients may deserve a higher intensity or longer duration of anticoagulant treatment.<sup>56</sup>

(5) The SURPRISE phase 3b trial compared fondaparinux 2.5 mg versus rivaroxaban 10 mg daily for 45 days for 472 patients with symptomatic SVT not within 3 cm of the saphenofemoral junction and one additional risk factor. At 45 days follow-up, rivaroxaban was found to be noninferior for the primary composite endpoint of recurrent VTE and all-cause mortality. There were no major bleeds in either group. The authors concluded that rivaroxaban 10 mg was a less burdensome and expensive treatment option for SVT compared to LMWH.<sup>57</sup> A second clinical trial for treatment of SVT in Canada compares rivaroxaban 10 mg to placebo; the study has completed enrollment with results pending (RASET trial; NCT 02123524).

## Nonsteroidal Anti-inflammatory Medications

In addition to the trials discussed previously, the effectiveness of NSAIDs for SVT treatment has been the focus as part of a Cochrane systematic review.<sup>2</sup> Five trials overall (including STENOX) were evaluated. This analysis found that NSAIDs significantly reduced the risk of SVT extension or recurrence by 67% (OR 0.33; 95% CI 0.16–0.68), compared with placebo. However, there was no difference in the rate of VTE or resolution of symptoms. No episodes of major bleeding were recorded in these trials.

A JAMA clinical evidence synopsis of treatment for lower extremity SVT concluded that LMWH and NSAIDs are associated with lower rates of SVT extension or recurrence, but the effect on the reduction of symptomatic VTE was inconclusive. The authors stated that the data regarding topical or surgical therapy were inconclusive.<sup>58</sup>

## Surgery

For SVT within 1 cm of the saphenofemoral junction, management by high saphenous ligation with or without saphenous vein stripping has been suggested to be the treatment of choice because of the recognized potential for extension into the deep system and embolization.<sup>12,59–62</sup> There have been only two randomized trials over the past 15 years that have evaluated surgery for the treatment of SVT. The first was a prospective study consisting of 444 evaluable patients randomized to six different treatment plans for the management of superficial thrombophlebitis: compression only; early surgery, with and without stripping; low-dose subcutaneous heparin; LMWH; and oral anticoagulant treatment.<sup>63</sup> Patients with SVT and large varicose veins but without any suspected/documentated systemic disorder were included in this study. Criteria for inclusion were venous incompetence (by duplex investigation), a tender indurated cord along a superficial vein, and redness and heat in the affected area. Exclusion criteria were obesity, cardiovascular or neoplastic diseases, nonambulatory status, bone/joint disease, problems requiring immobilization, age older than 70 years, and the presence of superficial thrombophlebitis without varicose veins. Color duplex ultrasound scans were used to detect concomitant DVT and to determine extension or reduction of SVT at 3 and 6 months.

The incidence of SVT extension at 3 and 6 months was higher in the elastic compression alone group and in the saphenous ligation alone group ( $P < 0.05$ ) compared with the groups with medical therapy or surgical therapy with ligation and stripping. There was no significant difference in the incidence of DVT at 3 months in any of the treatment groups. The results of this study are difficult to evaluate because the details of the treatment protocols were lacking. Furthermore, the exclusion criteria would eliminate many of the patients in whom SVT is routinely diagnosed in clinical practice limiting the generalizability of the findings.

**②** Lozano and Almazan randomized 60 patients with above-knee GSV SVT to saphenofemoral disconnection under local anesthesia with short-term compression bandage or enoxaparin 1 mg/kg twice daily for 1 week and then once daily for 3 weeks.<sup>64</sup> All patients in the trial were instructed to use compression stockings. Although the rate of VTE was less in the enoxaparin group (RR 0.2; 95% CI: 0.01–4), it did not reach statistical significance. The rate of wound infections was 6.7% (2/30 patients) in the surgical group. A systematic review of six studies included 246 patients altogether that received GSV ligation with or without stripping compared to 88 patients that received intravenous heparin followed by vitamin K antagonist for 6 weeks to 6 months and showed no difference in SVT progression, DVT, or PE. The overall surgical complication rate including hematoma, seroma, or infection was 7.7%.<sup>65</sup>

## Topical Therapy

As part of the previously mentioned Cochrane systematic review, seven trials that included topical treatment for SVT were evaluated.<sup>2</sup> One of these small trials compared the use

of a novel liposomal heparin spray versus LMWH (Clexane 40 mg daily subcutaneously) in 46 outpatients. The main outcomes measures of erythema size and duplex assessment of thrombus regression were comparable in the two groups; however, there were three cases of DVT in the heparin spray-gel group compared with one in the LMWH group.<sup>66</sup> To date, no further follow-up studies have been published and the spray is not available for commercial use. A more recent smaller study of 84 patients compared heparin topical solution to heparin topical gel and showed less infusion-induced phlebitis in the topical solution group.<sup>67</sup> Other topical treatments that have been evaluated include methythioadenosine, diclofenac gel, and Etofenak gel. Although these treatments did demonstrate reduction in local signs and symptoms, none of these studies evaluated the effect on VTE or SVT extension.

Other therapies that have been evaluated in small trials include oral vasotonin, venoruton, oral heparan sulfate, oral sulodexide, oxyphenbutazone, oral vitamin K antagonists, enzyme therapy, and desmin.<sup>2</sup> Most provided local symptomatic relief. The most recent Cochrane systematic review that included analysis of 33 randomized controlled trials for treatment of SVT concluded that both LMWH and NSAIDs reduced the incidence of extension or recurrent SVT without any significant effect on VTE and further research is necessary to define the role of direct oral anticoagulants (DOACs) in the treatment of SVT. Topical treatments improved local symptoms.<sup>66,68</sup>

To summarize, LMWH and rivaroxaban seem to provide the best outcomes for treatment of SVT with the least complications. However, questions remain regarding the duration of therapy, with 1 week likely being too short. Currently, there are no updated societal guidelines for the treatment of SVT and the most recent American College of Chest Physicians guidelines (2012) were not updated in 2016 and give the following recommendations for treatment of patients with SVT of the lower limb<sup>69</sup>:

1. In those with SVT at least 5 cm in length, the use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation (Grade 2B).
2. In those with SVT who are treated with anticoagulation, fondaparinux 2.5 mg daily over a prophylactic dose of LMWH is suggested (Grade 2C).

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Kearon C, Akl E, Comerota A, et al. Antithrombotic therapy for VTE Disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e474S.

*The most recent ACCP guidelines 2012 state low-level recommendations for the treatment of symptomatic SVT: 8.1.1. In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (grade 2B). 8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (grade 2C). The updated 2016 ACCP guidelines do not change these recommendations.*

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*This double-blind study of 427 patients with symptomatic SVT compared the efficacy of enoxaparin prophylactic and therapeutic dose with NSAID and placebo for prevention of SVT progression and VTE and found all active treatments superior to placebo. Interestingly, there was no difference in outcomes for prophylactic and therapeutic enoxaparin.*

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*This multicenter, prospective, controlled, double-blind, double-dummy trial, 164 patients with great saphenous vein SVT were randomized to receive fixed versus weight-adjusted nadroparin for 1 month. Therapeutic weight-adjusted nadroparin was found to be no more effective in preventing SVT progression and VTE at 3-month follow-up.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Pulmonary Embolism: Presentation, Natural History, and Treatment

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## INTRODUCTION

Acute pulmonary embolism (PE) is a partial or complete occlusion of the pulmonary arteries, with hemodynamic consequences determined by the size and location of the embolus, preexisting cardiopulmonary disease, and the severity of ventilation and oxygenation compromise. Acute PE is the third leading cause of cardiovascular mortality, with well over 100,000 deaths per year in the United States.<sup>1</sup> Recent registries and cohort studies suggest that approximately 10% of all patients with diagnosed acute PE will die within 3 months after diagnosis.<sup>2,3</sup> Despite being the most preventable cause of hospital mortality and despite advances in diagnosis and management, it accounts for 5% to 10% of in-hospital deaths.<sup>4</sup>

In the majority of patients with PE, the cause is lower extremity or pelvic venous thrombosis. The physical obstruction of the pulmonary arteries is accompanied by hypoxic vasoconstriction and release of potent pulmonary arterial vasoconstrictors, which further increase pulmonary vascular resistance and right ventricular (RV) afterload. The increasing RV afterload can cause RV hypokinesis and dilation, tricuspid regurgitation, and ultimately RV failure with subsequent life-threatening reduction in coronary perfusion and cardiac output. Although in the majority of the survivors pulmonary thromboemboli will gradually resolve, in some patients, it may organize into fibrotic deposits permanently occluding the pulmonary arteries, leading to chronic pulmonary hypertension and RV dysfunction.

## CLINICAL PRESENTATION

The clinical presentation varies from asymptomatic (incidentally diagnosed) to fatal. Development of symptoms depends on the embolic burden and the severity of any underlying cardiopulmonary disease. The diagnosis of PE is never made in approximately 70% of those who survive the initial event. Thus, it is critical that a high level of suspicion is maintained.

In most patients, PE is suspected on the basis of dyspnea, chest pain, presyncope or syncope, and/or hemoptysis. The onset of dyspnea may be acute and severe usually representing a PE in the main or lobar vessels; in small peripheral PE, it is often mild and may be transient. Chest pain is a frequent symptom and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction. In central PE, chest pain may have a typical angina character, possibly reflecting RV ischemia and requiring differential diagnosis with acute coronary syndrome or aortic dissection. Hemoptysis can occur with pulmonary infarction.

Common clinical signs include tachypnea, tachycardia, rales or decreased breath sounds, jugular venous distension, and rarely fever mimicking pneumonia. Half of the patients will also present with symptoms of leg deep venous thrombosis (DVT) or rarely with symptoms of upper extremity DVT. Arterial hypotension and shock are rare (<10%) but critical clinical presentations because they indicate central PE and/or a severely reduced hemodynamic reserve. Syncope is infrequent but may occur regardless of the presence of hemodynamic instability.<sup>5</sup>

## DIAGNOSIS

A high index of suspicion is required for the diagnosis of PE because symptomatology is nonspecific and overlaps with other pathologies, such as acute coronary syndromes, aortic dissection, pericardial tamponade, new onset arrhythmia, pneumonia, and pneumothorax.<sup>6,7</sup> Clinical impression alone has a sensitivity and specificity of 85% and 51%, respectively.<sup>8</sup> For this reason, clinical prediction algorithms have been developed. Various laboratory and imaging tests are complimentary of the clinical suspicion.

### Laboratory Tests

Routine blood tests in patients with PE are nonspecific and may include leukocytosis, elevated LDH and AST, CRP, and ESR. Plasma D-dimer levels, preferably using a high-sensitivity assay, are useful in patients who are unlikely to have PE or the clinical probability is low or intermediate to reduce unnecessary computed tomography pulmonary angiography (CTPA) or lung scans. In these cases, a normal D-dimer level (<500 µg/L or <10 µg/L × age when >50 years old) practically excludes PE. On the contrary, a positive D-dimer test is associated with a notoriously low specificity and should prompt further testing.

Biomarkers of RV dysfunction include troponin and brain natriuretic peptide (BNP). Their diagnostic value is limited because they are neither sensitive nor specific. However, in

patients with confirmed PE, cardiac troponin (TnT or TnI) and BNP (or its precursor NT-proBNP) tests are recommended for further stratification of patients at intermediate risk (see below).<sup>9,10</sup> The standard cutoff values for TnT, TnI, and BNP are 0.1 ng/mL, 0.4 ng/mL, and 90 pg/mL, respectively, although they may vary depending on the assay and the lab. Similar to D-dimers, age-adjusted and not standard values are better predictors of adverse outcomes for troponin (e.g., high sensitivity TnT is prognostic at 45 pg/mL instead of 14 pg/mL for patients older than 75 years).<sup>11</sup> NT-proBNP has its optimal prognostic value when it exceeds 600 pg/mL instead of the previously proposed 300, 500, or 1000 pg/mL.<sup>12</sup> An alternative novel marker of myocardial injury is the heart-type fatty acid-binding protein emerging as a significant predictor of mortality in patients with intermediate risk PE.<sup>13-15</sup>

Arterial blood gases are also nonspecific and do not assist in the diagnosis of PE. However, hypoxemia may have a prognostic value for confirmed PE as an indicator of anticipated complications, respiratory failure, or death.<sup>16</sup> Pulse oximetry is a more reasonable noninvasive alternative, at least for the low- or intermediate-risk patients.

### Electrocardiogram

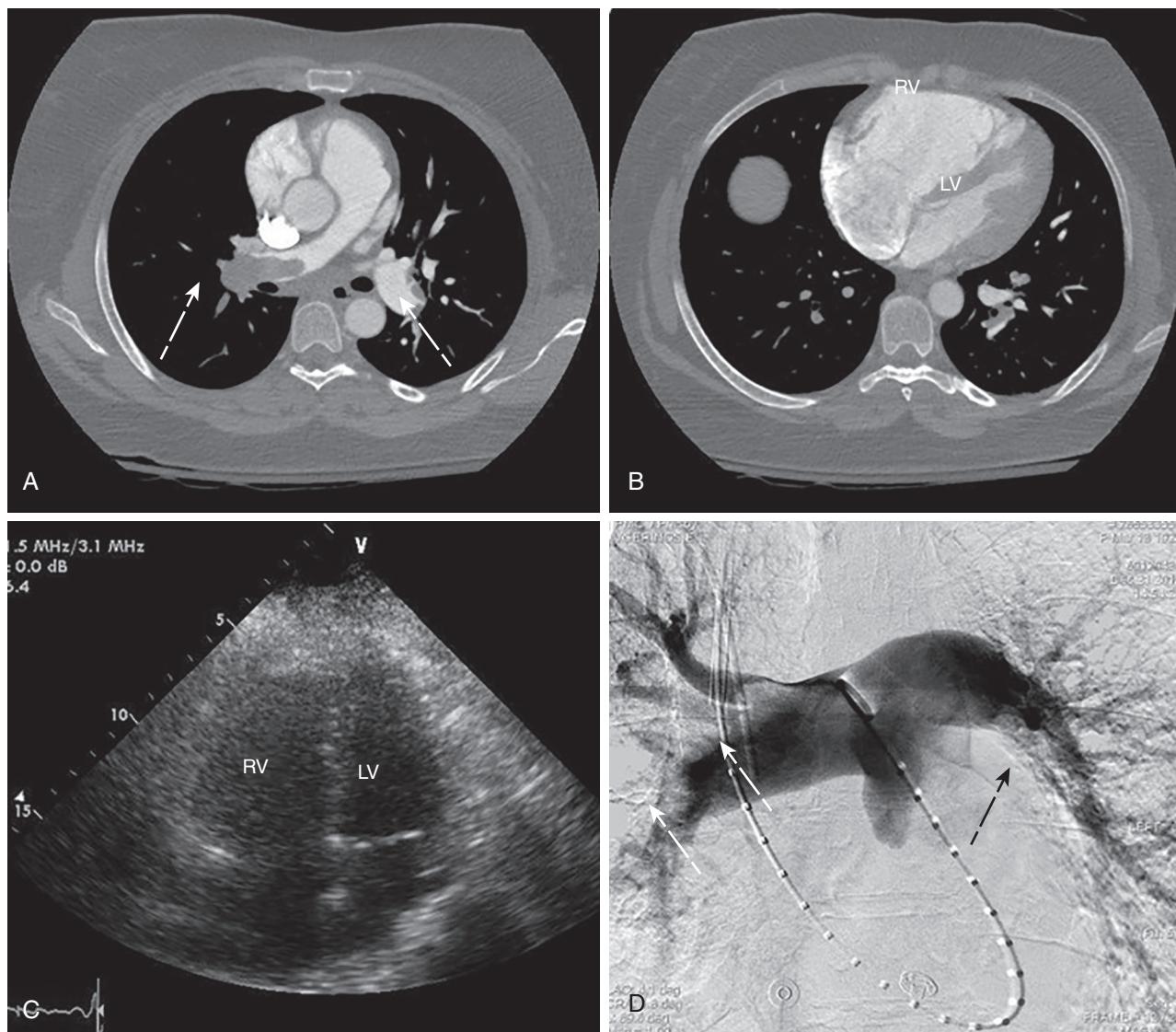
Electrocardiographic changes associated with acute PE are neither sensitive nor specific. They are similar to all other causes of pulmonary hypertension (e.g., acute bronchospasm, pneumothorax). The S1Q3T3 (prominent S wave in lead I, Q wave and inverted T wave in lead III) pattern is a sign of acute RV overload (acute cor pulmonale) and reflects strain; it is seen in less than 20% of diagnosed PEs. The greatest utility of the ECG in a suspected PE is to rule out acute myocardial infarction.

### Chest X-Ray

Chest radiographs are not sensitive or specific for PE but can rule out alternative diagnoses (e.g., pneumothorax). Frequently, patients with PE have a normal chest X-ray. Atelectasis or parenchymal density and pleural effusion are probably the most frequent findings. Radiographic signs such as the Fleischner sign (enlarged pulmonary artery), Hampton hump (peripheral wedge of airspace opacity – lung infarction), Westermark sign (regional oligemia), and knuckle sign (abrupt tapering or cutoff of a pulmonary artery) are rare but should raise the suspicion of PE.<sup>17</sup>

### Computed Tomographic Arteriography

Computed tomographic pulmonary angiography (CTPA) is the method of choice for imaging the pulmonary vasculature in patients with suspected PE (Fig. 152.1A). It allows adequate visualization of the pulmonary arteries down to at least the segmental level and has a high predictive value, particularly when combined with clinical probability. Based on the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II trial, CTPA has a sensitivity of 83% and a specificity of 96%



**Figure 152.1** Pulmonary Embolism (PE) and Right Ventricular Imaging. (A) PE is primarily diagnosed with CT pulmonary arteriogram; notice bilateral main pulmonary and segmental arteries with thrombus. (B) RV dilatation as seen in the CT pulmonary arteriogram. (C) Transthoracic echocardiogram four-chamber view showing RV dilatation. (D) Pulmonary arteriogram; notice bilateral main pulmonary and segmental arteries with thrombus (arrows). *LV*, left ventricular; *RV*, right ventricular.

and several studies have demonstrated its efficiency as a stand-alone imaging test for confirming or excluding PE.<sup>18–22</sup>

CTPA, particularly if it is electrocardiogram gated, can further serve as a prognostic tool for the severity and outcomes of PE.<sup>18–26</sup> Heart chamber dimension measurements may detect RV enlargement as an indicator of RV dysfunction, typically defined as a right-to-left ventricular end-diastolic dimensional ratio  $\geq 0.9$  (Fig. 152.1B).

## Echocardiogram

Transthoracic echocardiography (TTE) is the most common first-line examination to diagnose the signs of RV dysfunction but cannot definitely diagnose PE because an elevated RV pressure may be the result of other conditions such as pulmonary hypertension and RV infarction. Echocardiography is most

useful in patients with diagnosed PE, for prognostic purposes. Confirmation of RV dysfunction is a key determinant of PE prognosis because it seems to increase the risk of death by at least twofold.<sup>27</sup>

RV/LV end-diastolic diameter ratio has been commonly used as an indicator of RV dysfunction, defined as RV/LV end-diastolic ratio greater than 1, but its reproducibility is only fair because the ventricular walls cannot always be well defined (Fig. 152.1C).<sup>28,29</sup> Tricuspid annular plane systolic excursion (TAPSE) is a quantitative echocardiographic parameter that is the least user dependent and most reproducible. Another sign of RV dysfunction is the depressed contractility of the RV free wall compared with the RV apex (McConnell sign), reported to retain a high positive predictive value for PE, even in the presence of preexisting cardiorespiratory disease.<sup>28–30</sup> Finally a relatively rare finding suggestive of PE is thrombus in the RV,

also known as thrombus in transit. Thrombus in the pulmonary arteries can be seen with transesophageal echocardiography.

Overall, echocardiography is not recommended as part of the routine diagnostic workup in patients with suspected PE, unless they are hemodynamically unstable. On the other hand, confirmation of RV dysfunction may justify emergency reperfusion treatment for PE if immediate CTPA is not feasible.<sup>6</sup>

## Other Imaging Modalities

Ventilation/perfusion (V/Q) scans are rarely used currently unless the patient with a suspected PE is pregnant or has renal insufficiency that prohibits CTPA. V/Q scanning is a highly sensitive but poorly specific study for the diagnosis of PE. When the V/Q scan is inconclusive (and CTPA contraindicated), magnetic resonance pulmonary angiography can be a reasonable alternative, acknowledging the complexity of the protocol, suboptimal resolution, and low sensitivity. Finally, invasive pulmonary angiography is a historical “gold standard,” that currently would be justified for diagnostic purposes only provided that some kind of catheter-directed intervention (CDI) is planned (e.g., catheter thrombolysis or aspiration thrombectomy) upon confirmation of PE (Fig. 152.1D).

Lower extremity venous duplex will show a DVT in 30% to 50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing. Among patients who have symptoms or clinical signs of DVT, only half will have it confirmed by ultrasound (see Ch. 148, Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment). Patients with acute symptomatic PE and confirmed DVT have an almost twofold higher risk of short-term death when compared with those without a DVT.<sup>6,31</sup>

## Diagnostic Strategies

Several explicit clinical prediction rules have been developed to improve stratification and care. These rules apply to non-pregnant hemodynamically stable patients. Hemodynamically unstable patients with suspected PE are expected to receive an expeditious life-saving reperfusion therapy (e.g., systemic thrombolysis), skipping a potentially time-consuming probability assessment. For these hemodynamically stable patients in whom PE is suspected, following clinical and laboratory assessment, the pretest probability is most frequently assessed using the Wells or modified Geneva scores, both of which have been simplified and validated (Table 152.1).<sup>32–37</sup>

Among patients who are likely to have PE based on these scores or unlikely but with a D-dimer level  $\geq 500 \text{ ng/mL}$ , CTPA is the imaging modality of choice. If negative, no further testing is required; if positive, treatment (anticoagulation) should be initiated. While awaiting the CTPA, initiation of empiric anti-coagulation can be individualized based on the clinical scenario. Patients who are unlikely to have PE do not require a CTPA but a sensitive D-dimer test. If the levels are less than 500 ng/mL, no further testing is required (see Chapter Algorithms).

**TABLE 152.1** Probability Scores for Pulmonary Embolism

Wells Score	PROBABILITY SCORE	
	Original	Simplified
Previous PE or DVT	1.5	1
Heart rate $\geq 100 \text{ bpm}$	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1

Clinical Probability		
Three-level Score		
Low	0–1	n/a
Intermediate	2–6	n/a
High	$\geq 7$	

Two-level Score		
PE unlikely	0–4	0–1
PE likely	$\geq 5$	$\geq 2$

Revised Geneva Score	Original	Simplified
Previous PE or DVT	3	1
Heart rate	3	1
75–95 bpm	5	2
$\geq 95 \text{ bpm}$		
Surgery or fracture within the past month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral edema	4	1
Age $> 65 \text{ years}$	1	1

Clinical Probability		
Three-level Score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	$\geq 11$	$\geq 5$

Two-level Score		
PE unlikely	0–5	0–2
PE likely	$\geq 6$	$\geq 3$

DVT, deep venous thrombosis; PE, pulmonary embolism.

## RISK STRATIFICATION

PE severity should be based on an individual estimate of PE-related early mortality risk rather than the extent of pulmonary vascular obstruction. Although it is attractive to stratify types of acute PE on the basis of the anticipated mortality, this

approach is hampered by the presence of comorbidities; for example, a non-high risk PE might be associated with a high mortality risk in a patient with obstructive airway disease or congestive heart failure.<sup>38</sup> Despite this relative weakness, PE risk stratification guides major treatment decisions in all major guideline documents.<sup>6,39,40</sup>

PE is classified as low, intermediate (or submassive), and high (or massive) risk based on the anticipated 30-day mortality rate. The terms “submassive” and “massive” were initially suggested on the basis of angiographic burden of emboli by use of the Miller Index, but these are now of limited use as the embolic burden is a poor indicator of mortality.<sup>41,42</sup>

With small variations in their definitions as given by societal guidelines, low-, intermediate-, and high-risk PE are defined as follows:

- **Low risk:** normotensive patients without imaging evidence of RV dysfunction or elevated cardiac biomarkers. Approximately 40% of all PE patients fall into this category. They have excellent short-term prognosis with a mortality rate approximately 1% to 2% or less.<sup>39,43</sup>
- **Intermediate risk:** normotensive patients with either imaging evidence of RV dysfunction or elevated cardiac biomarkers or both. This group constitutes approximately 55% of all PEs, and the mortality rate ranges between 3% and 15%.<sup>39,44–46</sup>
- **High risk:** hemodynamically unstable patients with sustained shock or hypotension (<90 mm Hg) or cardiac arrest. These patients are rare, approximately 5%, but in-hospital mortality

ranges between 15% and 30% or may exceed 60% for those requiring cardiopulmonary resuscitation.<sup>3,45–48</sup>

Several scoring systems have been devised for risk stratification, the most widely used being the Pulmonary Embolism Severity Index (PESI) and its simplified version, as well as the Bova and FAST scores for patients without hemodynamic instability (Table 152.2).<sup>38,49</sup> The prediction is enhanced when these scores are combined with imaging or laboratory findings, because there is no single test with sufficient positive predictive value that could justify an aggressive treatment. Within the intermediate-risk category, further risk assessment can be elaborated focusing on the status of the RV and/or on cardiac biomarkers (Table 152.3). Multiple observational studies and meta-analyses have suggested that the combination of clinical variables (e.g., tachycardia, mild hypotension), myocardial injury (e.g., high troponin), and RV dysfunction (e.g., RV dilatation, high BNP) particularly in those with concomitant DVT, identifies the more severe intermediate-risk patients with acute PE.<sup>50</sup> The European Society of Cardiology has introduced the terms intermediate low and intermediate high risk, with intermediate high risk encompassing patients having both imaging findings of RV dysfunction and positive biomarkers (troponin or BNP/proBNP).<sup>6,50–53</sup>

## TREATMENT

The main goal of therapy is to prevent mortality; it has been suggested that thrombolysis may prevent late PE

**TABLE 152.2** Pulmonary Embolism Risk Stratification Based on the Pulmonary Embolism Severity Index (PESI)

Predictor	PESI SCORING		BOVA SCORE		FAST SCORE	
	Original	Simplified	Elevated trop.	2	H-FABP ≥6 or elevated trop.	1.5
Age	Age in years	1 (if >80 years)	Elevated trop.	2	H-FABP ≥6 or elevated trop.	1.5
Men	10	–	RV dysfunction	2	Syncope	1.5
Cancer	30	1	Pulse ≥110 bpm	1	Pulse ≥100 bpm	2
Heart failure	10	1	Syst BP 90–100 mm Hg	2		
Chronic lung disease	10					
Pulse ≥110 bpm	20	1	Low risk	≤4		<3
Systolic pressure <100 mm Hg	30	1	Intermediate–high risk	>4		≥3
Respiratory rate ≥30	20	–				
Temperature <36°C	20	–				
Altered mental status	60	–				
Saturation <90%	20	1				
<b>Risk</b>						
Very low risk (class I)	≤65	0				
Low risk (class II)	66–85					
Intermediate risk (class III)	86–105	≥1				
High risk (class IV)	106–125					
Very high risk (class V)	≥126					

H-FABP, heart-type fatty acid-binding protein; RV, right ventricle.

**TABLE 152.3**

## Imaging and Laboratory and Clinical Tests for Risk Stratification of Pulmonary Embolism (PE)

	Markers of Non-Low Risk PE	Remarks
Echocardiogram	RV/LV EDD >1 TAPSE ≤1.6 cm TRJV >2.6 m/s <sup>-1</sup> Estimated RVSP ≤52 mm Hg McConnell sign + IVC collapsibility >50% + RV hypokinesia + Leftward shifting of IVS +	RV dysfunction parameters have been identified as independent predictors of death. With the exception of TAPSE, the complex geometry of the RV and the subjective nature of the measurements are limiting factors.
CT angiogram	RV/LV EDD ≥0.9	RV dilatation has been identified as independent predictor of death. No clear association has been shown for clot burden.
Lower leg duplex	DVT +	Proximal DVT in patients with symptomatic PE is an independent predictor of death (OR 1.9; 95% CI 1.5–2.4).
Troponin	TnT >0.1 ng/mL TnI >0.4 ng/mL	High troponin levels are independent predictors of death. Limited detection time-window (peak at 8 h). Optimal cutoff values are yet to be defined. High sensitivity assays and age-adjusted values may be more accurate.
BNP	>90 pg/mL	High levels predict death (OR 6.5; 95% CI 2.0–2.1)
Pro-BNP	>600 pg/mL	High levels predict death (OR 6.3; 95% CI 2.2–18.3)
HFAB	>6 µg/l	Novel biomarker with significant prognostic value for mortality (OR 40.8; 95% CI 11.8–140.1).
PESI	Original: ≥86 (class III–V) Simplified: ≥1	Validated widely used clinical score.

BNP, brain natriuretic peptide; CI, confidence interval; CT, computed tomography; DVT, deep venous thrombosis; EDD, end-diastolic diameter; HFAB, heart-type fatty acid-binding protein; IVC, inferior vena cava; IVS, interventricular septum; LV, left ventricle; OR, odds ratio; PESI, Pulmonary Embolism Severity Index; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TRJV, tricuspid regurgitant jet velocity.

sequelae and improve functional capacity but this remains unclear.<sup>4,6,39–41,54–59</sup> Late PE sequelae include a wide spectrum of symptoms ranging from dyspnea on exertion to advanced chronic thromboembolic pulmonary hypertension (CTEPH).

## Initial Supportive Therapies

Although patients classified as low-risk PE do not require any specific support, it is vital that those with intermediate- or high-risk PE receive supportive treatment. The initial approach to patients suspected with PE should assess hemodynamic stability; if a patient is unstable (or borderline stable), general support should be provided while diagnostic evaluation is ongoing. In the setting of hypotension, intravenous fluid should be administered in small volumes (500–1000 mL of normal saline) to avoid overloading an otherwise stretched RV. Should the fluid challenge fail, vasopressor therapy should follow. In cardiogenic shock norepinephrine is the most suitable agent because it is less likely to cause tachycardia and exacerbate hypotension.

## Anticoagulation

Unless contraindicated, all patients with acute PE should receive systemic anticoagulation with the objective of preventing both early death and a recurrent symptomatic or fatal event. Anticoagulation should be initiated during the

diagnostic workup in patients with intermediate or high clinical probability of PE. The standard duration of anticoagulation should cover at least 3 months (see Ch. 41, Anticoagulant Therapy).<sup>6,39,40</sup>

In the acute PE phase, parenteral anticoagulation (unfractionated heparin, low-molecular-weight heparin [LMWH], or fondaparinux) should be initiated first, followed by the parallel administration of a vitamin K antagonist (warfarin) for at least 5 days and until INR reaches the desired therapeutic level (2.0–3.0). Direct oral anticoagulants, factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), and direct thrombin inhibitors (dabigatran) do not require monitoring and dose adjustments or prolonged bridging therapy. These agents are noninferior to warfarin.

## Inferior Vena Cava Filter

As a general guideline, inferior vena cava (IVC) filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs and in patients with objectively confirmed recurrent PE despite adequate anticoagulation.<sup>6,39,40</sup> Current guidelines are against the routine use of IVC filters in patients who can be anticoagulated. However, because it is uncertain if there is benefit to placing an IVC filter in anticoagulated patients with severe PE (e.g., hypotension), this recommendation against insertion may not apply to this select subgroup (see Ch. 153, Vena Cava Interruption).<sup>59</sup>

## Thrombolysis

Thrombolysis is reserved for high-risk and selected cases of intermediate-risk PE.<sup>6,39,40,60</sup> The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for up to 14 days. The standard route for administration of lytics is intravenous through a peripheral line; however, catheter-directed lytic administration directly into the pulmonary arterial tree is increasingly common. Contraindications to thrombolysis in PE patients have not been exclusively studied in this patient population but have been extrapolated from patients with myocardial infarction.<sup>39,61</sup> It is unclear to what extend these apply for catheter-directed thrombolysis, and preliminary data are controversial regarding bleeding events in the setting of a “contraindication” (see Ch. 43, Thrombolytic Agents).<sup>62–66</sup>

### Systemic Thrombolysis

Systemic intravenous thrombolysis is universally recommended for high-risk PE but remains controversial for intermediate-risk PE. The most widely suggested regimen is 100 mg alteplase (recombinant tissue plasminogen activator [rtPA]) over 2 hours. Other rtPA forms such as reteplase and desmoteplase have been tested against alteplase in acute PE, with similar results in terms of hemodynamic parameters; tenecteplase has been tested against placebo (heparin alone) in patients with intermediate-risk PE.<sup>66,67,68</sup> Heparin infusion may be held during thrombolysis.

An analysis of the US nationwide inpatient sample (1999–2008), including 72,230 patients, demonstrated an all-cause (47% vs. 15%) and PE-related (42% vs. 8.4%) mortality benefit for thrombolysis in massive PEs.<sup>69</sup> A large meta-analysis of thrombolysis for PE reported pooled data from 16 trials including 2115 patients (1775 intermediate risk).<sup>70</sup> Thrombolysis was associated with lower mortality risk compared with standard anticoagulation (2.17 vs. 3.89%,  $P = 0.01$ ). The mortality benefit persisted when the analysis was limited to patients with intermediate-risk PE (1.39% vs. 2.92%,  $P = 0.03$ ). However, thrombolysis was associated with higher rates of major bleeding (9.24 vs. 3.42%,  $P < 0.001$ ) and intracranial hemorrhage (1.46 vs. 0.19%,  $P = 0.002$ ). The increased major bleeding was primarily driven by patients older than 65 years. A meta-analysis (1990–2013, 440 patients) suggested that a low-dose protocol (e.g., 50 mg) has similar efficacy and may be safer than the standard 100 mg dose.<sup>71</sup> Interestingly, despite the marked reduction of case fatality rate with systemic thrombolysis in unstable patients, only 30% receive it, partly because of various contraindications to lytics and concerns for complications.<sup>49,69</sup>

### Catheter-Directed Interventions

The limitations and complications of systemic thrombolysis are driving contemporary practice toward CDIs (thrombolytic and nonthrombolytic techniques) as a first-line treatment in the appropriate clinical setting as a way to provide the benefits and minimize adverse events of systemic thrombolytic therapy. Despite the publication of the first comparative studies (CDIs vs.

anticoagulation or vs. high- or low-dose systemic lysis), there is lack of sufficient robust evidence to confirm the assumption of combined efficacy and safety, particularly in the high-risk population.<sup>41,62,71,72</sup>

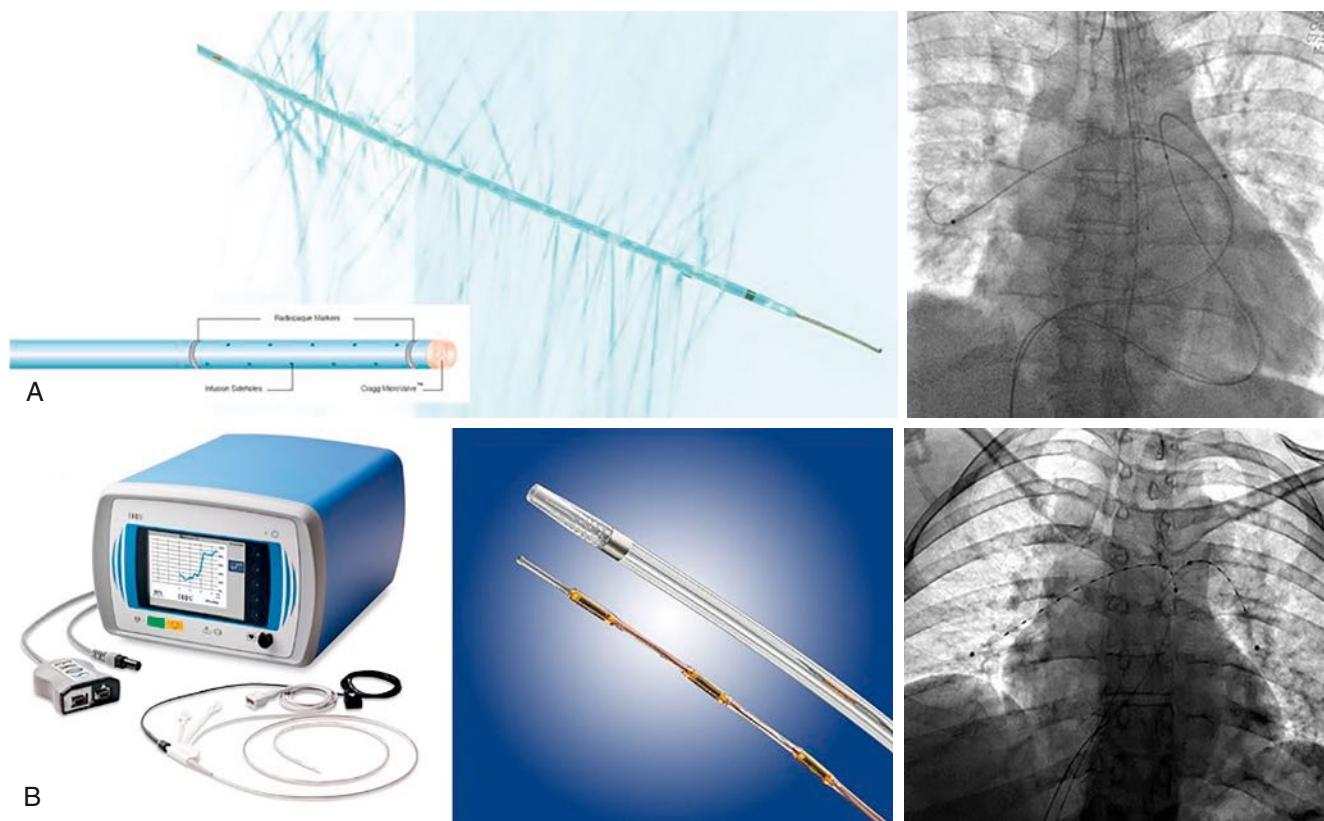
The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial was the first randomized controlled trial to include CDIs for intermediate-risk PE comparing standardized fixed-dose ultrasound-assisted thrombolysis (USAT) (10 mg of tPA per lung for 15 hours) and anticoagulation with anticoagulation alone.<sup>73</sup> In the USAT group but not in the anticoagulation group, the mean RV/LV ratio was significantly reduced at 24 hours but became comparable between the two groups at 90 days. The RV systolic function was significantly improved in the USAT group versus the heparin group at both 24 hours and 90 days. In both study groups, minor bleeding complications were rare, and there were no major bleeding complications. However, in real-world practice, CDIs are not risk-free procedures.<sup>62,63,66,70,71</sup> The pooled major bleeding rate from 20 studies (1168 patients) was 6.7% for high-risk and 1.4% for intermediate-risk PE.<sup>62</sup> This is similar to that obtained from the U.S. nationwide inpatient sample analysis (4.9%) and our experience (6.2%).<sup>66</sup> Catheter interventions can be related to unique adverse events like heart and lung injuries, contrast-induced nephropathy and other device-related complications.<sup>66</sup> The stroke rate in the majority of studies is less than 1%. A learning curve related to technical skills and patient selection criteria seems to have an effect in minimizing failures and complications.<sup>74</sup>

CDIs should be provided in selected patients where appropriate expertise is available. These interventions appear to be safer than systemic thrombolytics for the treatment of acute PE, but they are definitely not as safe as initially thought. As a general rule, whenever thrombolysis is considered as a treatment option, either in the setting of high- or intermediate-risk PE, CDIs may be the only alternative for patients at a high bleeding risk (e.g., recent surgery) and can be considered a reasonable alternative in patients at low risk for bleeding.<sup>74,75</sup>

### Technical Considerations for Catheter-Directed Interventions

Contemporary CDIs are variable and can be performed with or without thrombolysis. The latter include thrombus fragmentation and/or aspiration techniques, with no lytic agents, for patients with absolute contraindications to thrombolysis; evidence on their efficacy and safety has been growing over the recent years.<sup>39,62,64,76–78</sup> Thrombolytic and nonthrombolytic techniques are complimentary and equally effective when used appropriately.<sup>74–76</sup> Each technique has strengths and weaknesses along with a different complication profile. Thrombolytics can be administered through low profile catheters but need time and may be associated with systemic bleeding; suction thrombectomy techniques require large profile devices that need to cross the heart with risk of injury or arrhythmias and a limited action on the distal pulmonary arterial run-off.

The standard technique involves administration of local thrombolytics through a multi-sidehole catheter placed unilaterally or bilaterally into the pulmonary artery thrombus



**Figure 152.2** Catheter-Directed Thrombolysis. (A) Five-French standard multi-sidehole catheter. (B) Ultrasound-assisted thrombolysis catheter, EkoSonic (Endovascular System, EKOS Corporation, Bothell, WA). The catheter is composed of a 5.2-F multi-sidehole infusion catheter and a microsonic core wire containing the ultrasound elements.

(transjugular or transfemoral). The use of ultrasound to enhance thrombolytic permeation of large emboli holds currently the highest level of evidence in both efficacy and safety.<sup>77</sup> The EkoSonic Endovascular System (EKOS Corporation; Bothell, WA) combines a multi-sidehole drug-infusion catheter with a multielement ultrasound core wire and was approved by the U.S. Food and Drug Administration (FDA) for use in patients with PE (Fig. 152.2). However, the clinical superiority of USAT over conventional catheter-directed thrombolysis has not been proven.<sup>64,79</sup> Short lytic times (6–12 hours) and doses (1 mg/hr per catheter) are typically enough,<sup>80</sup> though termination should be better decided based on objective improvement of vital signs and hemodynamic or echocardiographic parameters. Catheters are pulled out at the bedside.

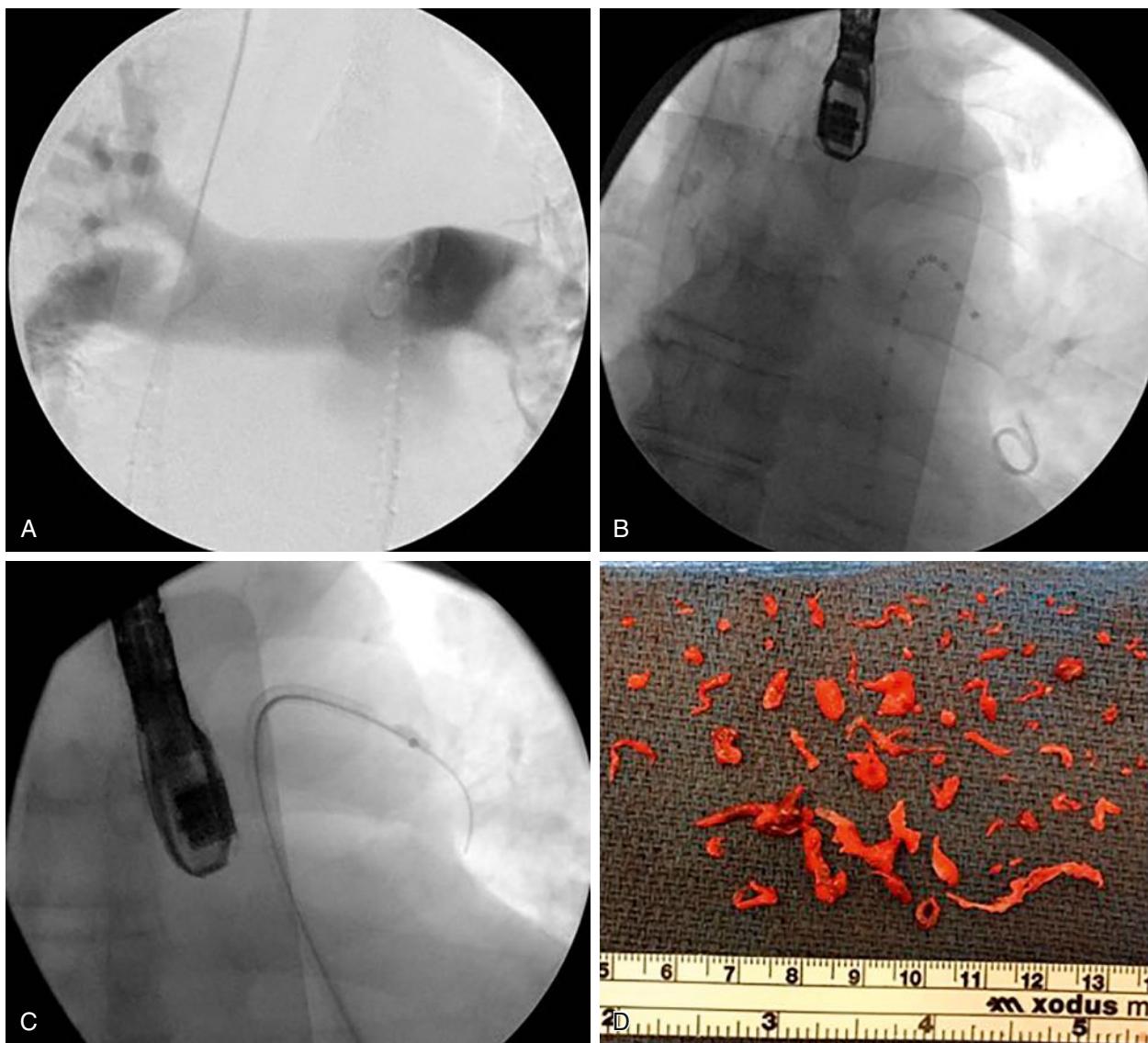
It remains unclear at what rate heparin infusion should be maintained during lytic infusion. Some recommend DVT therapeutic heparin protocols; others recommend minimal heparin (500 units/hour) just to prevent sheath thrombosis. Our group has established a therapeutic low-dose heparin protocol (atrial fibrillation protocol: target aPTT 60–80 seconds).

Rotating pigtail or balloon embolectomy catheters have been broadly reported in the past for thrombus fragmentation.<sup>41</sup> Because fragmentation may lead to distal clot embolization, adjunctive aspiration thrombectomy and subsequent lysis may be needed. The rationale of fragmentation is that it allows exposure of a greater embolic surface area to the lytic drug's effect; otherwise local thrombolytic infusion will be no more

efficacious than systemic delivery because it tends to rapidly wash into nonoccluded arteries.<sup>41</sup> Thrombus aspiration can be performed as an adjunct to any CDI or as a stand-alone technique using dedicated large-bore suction devices. The simplest aspiration technique, though not as effective, is by using any 5- to 9-F end-hole catheter, or dedicated steerable aspiration catheters 10 to 14 F in size (Fig. 152.3).

The FlowTriever (Inari Medical Inc., Irvine, CA) is an FDA-approved mechanical thrombectomy device now available in its third generation configuration<sup>77,78,81</sup> (Fig. 152.4). It consists of a flexible large-bore aspiration 0.035 guide catheter 20 or 24 F (T20 and T24), and a catheter system of self-expanding nitinol discs (6–10, 11–14, and 15–18 mm), which can be advanced through the aspiration sheath to mechanically engage thrombi. The side port tubing of the sheath connects to a 60-cc locking syringe that can generate up to 29 mm Hg negative pressure. Given the large bore access, the T20 sheath can remove up to 104 mL/sec, the T24 up to 143 mL/sec. A smaller T16 sheath/catheter is available but not recommended for routine use given its small suction power. It is complimentary to the larger sheaths to reach more distal targets.

The Indigo CAT-8 system (Penumbra, Inc., Alameda, CA) is also FDA approved for use in PE<sup>77,78</sup> (Fig. 152.5). It has three components: a catheter, a separator, and a vacuum pump. The catheter is 8 F and needs to be introduced through a 9- or 10-F long sheath positioned in the main PA. The separator wire allows thrombus fragmentation and mobilization as well



**Figure 152.3** Massive pulmonary embolism (right ventricular strain and hemodynamic decompensation) on a patient with recent surgery and with intrapulmonary bleed due to the pulmonary infarct. (A) Intraoperative pulmonary angiogram indicating bilateral thrombus (L>R). (B) Pigtail rotation within the major clot burden. (C) Aspiration thrombectomy using a 10-F Pronto catheter (Vascular Solutions, Minneapolis, MN). (D) Extracted thromboembolic material. (Figure obtained with permission from Avgerinos ED, Chaer RA. Catheter-directed interventions for pulmonary embolism. *J Vasc Surg*. 2015;61:559–565.)

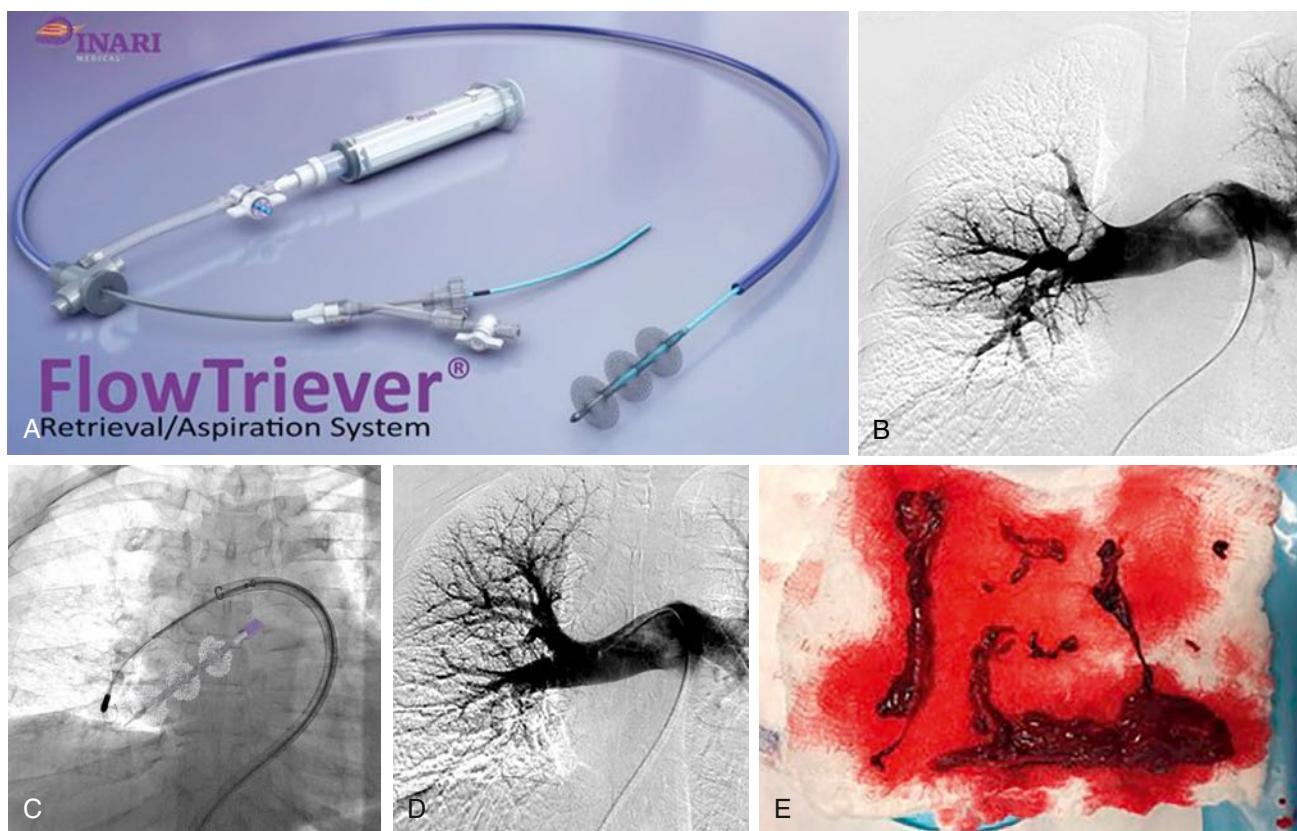
as cleaning of the catheter when it is obstructed by thrombus. The vacuum pump provides continuous suction and can aspirate up to 8 mL/s by applying and maintaining negative pressure of almost –29 mm Hg. A CAT-12 system for more powerful aspiration and a novel vacuum pump detecting brisk flow and automatically shutting off to reduce unnecessary blood losses has been recently released for clinical use.

The AngioVac system (Angiodynamics Inc, Latham, NY) is a powerful suction system that employs an extracorporeal veno-venous circuit that includes a filter between an aspiration and a reinfusing cannula. It is FDA approved for any material extraction from the venous circulation including thrombi and cardiac vegetations. A funnel-shaped distal tip facilitates *en bloc* removal of the embolus. Successful outcomes in the setting of PE have been reported in small case series.<sup>82</sup> The device

requires a 26-F delivery sheath and can be used from the femoral or jugular approach and allows embolectomy without the use of lytic agents (Fig. 152.6). Initial enthusiasm for PE has now subsided due to its rigidity, which makes positioning and advancing in and beyond the pulmonary artery quite challenging. A new generation device specifically for PE is underway.

### Surgical Thrombectomy

Traditionally, surgical pulmonary thromboembolectomy is reserved for patients with documented central PE and refractory cardiogenic shock despite maximal supportive therapy and who have absolute contraindications to or have failed thrombolytic therapy. Surgical thrombectomy aims to rapidly reduce RV afterload by physically removing proximal pulmonary



**Figure 152.4** Intermediate high risk pulmonary embolism with gradual hemodynamic deterioration after recent laparoscopic cholecystectomy. (A) FlowTriever INARI suction thrombectomy system. (B) Pulmonary arteriogram showing thrombus at the right apical trunk and the interlobar artery. (C) Suction thrombectomy using the T20 sheath and the FlowTriever disks. (D) Final arteriogram indicates thrombus clearance. (E) Organized thrombus segments retrieved.

artery thrombi.<sup>80,83–85</sup> Outcomes have improved in the past two decades, with mortality declining from 30% to well below 10% in centers with appropriate expertise.<sup>85–90</sup> Mortality should be anticipated to be significantly higher when surgical thrombectomy follows a failed thrombolysis and even worse after a cardiac arrest; best results are achieved with primary early surgery.<sup>86,89,90</sup>

Surgical embolectomy is performed through a median sternotomy using a normothermic cardiopulmonary bypass. Aortic cross-clamping and cardioplegic cardiac arrest are usually not needed. The main pulmonary artery is opened and the thrombotic material is extracted. The right atrium and ventricle are also explored for possible thrombi and a patent foramen ovale is closed, if present.

### Extracorporeal Membrane Oxygenation

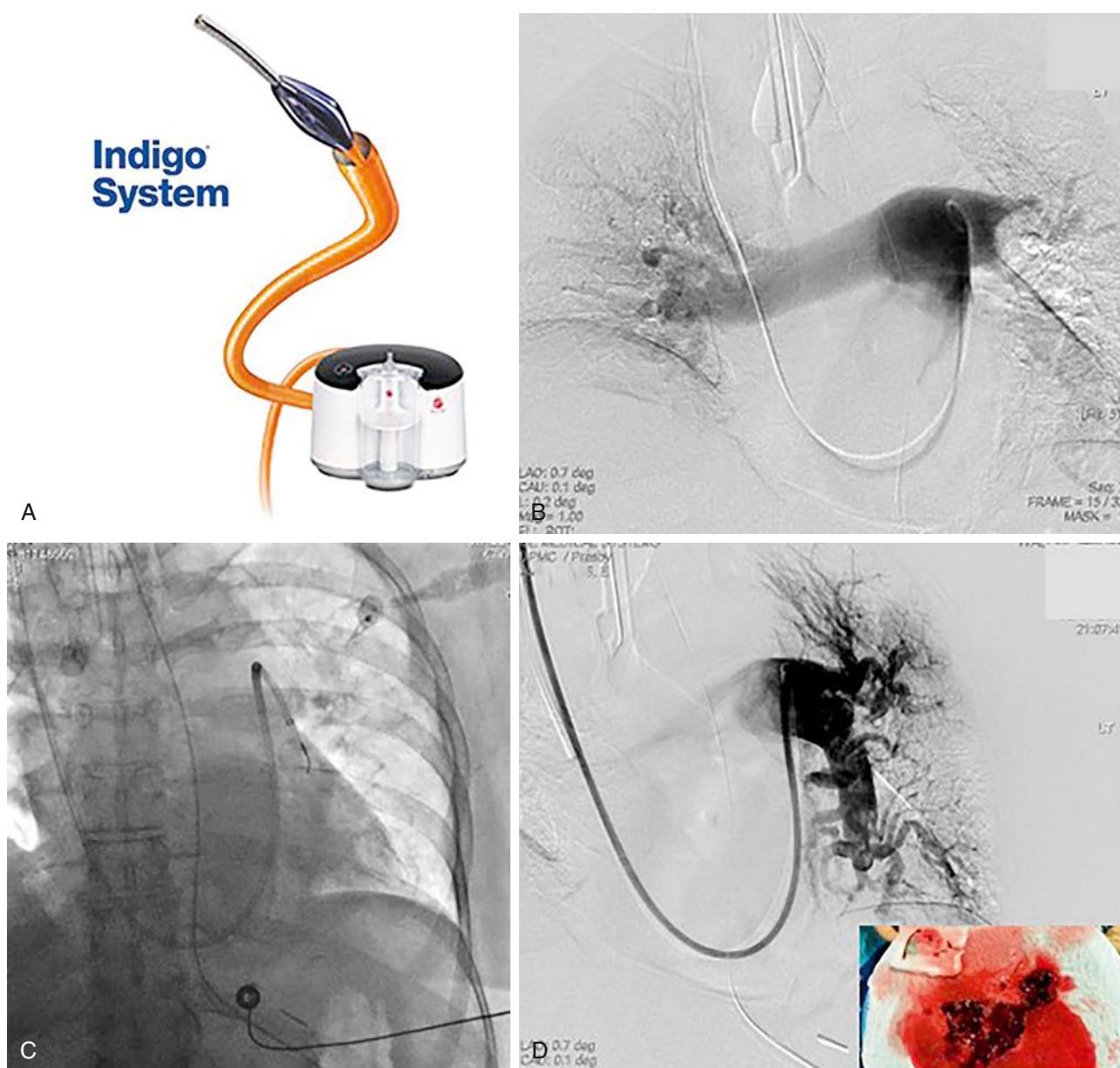
Transportable extracorporeal membrane oxygenation (ECMO) assistance systems with percutaneous femoral cannulation can be helpful in critical situations, ensuring circulation and oxygenation until definitive diagnosis. ECMO unloads the acutely failing right heart, providing effective hemodynamic and respiratory support for patients who develop massive PE until recuperation of the initial pulmonary insult. It has been increasingly used in some centers for unstable PE patients who

are not responding to other treatment modalities or as a bridge for catheter-based or surgical embolectomy.<sup>91</sup>

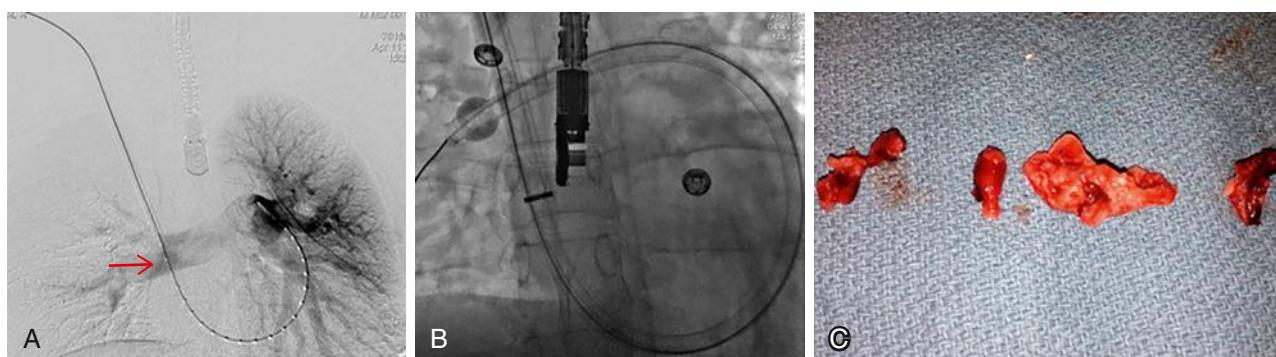
There are no clear prognostic indicators to appropriately select unstable PE patients who are likely to benefit from ECMO support. Although it seems reasonable to offer ECMO as a last resort to PE patients who are otherwise expected to die, this decision has to be reached on an individual basis to avoid providing futile care and wasting resources. Several factors should be considered in this decision, including the patient's comorbidities and the local expertise.

### Early Discharge and Home Treatment

Outpatient treatment of PE, giving the first dose of anticoagulation in the hospital, can be safe and effective in select patients who fulfill certain criteria. Clinical probability scores, mainly the PESI score, are predominately used to preselect these patients. The value of NT-proBNP as a laboratory biomarker for selecting candidates for home treatment has been evaluated, and, among those with clinically defined very-low-risk PE and NT-proBNP levels less than 500 pg/mL, none died or suffered recurrence of VTE or major bleeding complications during a 3-month follow-up.<sup>92</sup> Still, the value of cardiac biomarkers or echocardiography to exclude RV dysfunction before early discharge have not been thoroughly investigated, and they are not routinely recommended.<sup>40</sup>



**Figure 152.5** High risk pulmonary embolism with refractory shock and the patient on extracorporeal membrane oxygenation. (A) CAT-8 Indigo Penumbra suction thrombectomy system. (B) Pulmonary arteriogram showing complete left pulmonary artery occlusion. (C) Suction thrombectomy using the CAT-8 catheter and the separator wire. (D) Widely open left lower lobe pulmonary arterial segments.



**Figure 152.6** Intermediate high risk pulmonary embolism with increasing oxygen requirement, in a young patient, following brain abscess evacuation. (A) Pulmonary angiogram showing bilateral thrombus (R>L) (arrow points to the occluded right main pulmonary artery). (B) Angiovac (AngioDynamics, Latham, NY) aspiration from a jugular approach. (C) Extracted thromboembolic material. Cardiopulmonary parameters subsequently normalized. (Figure obtained with permission from Avgerinos ED, Chaer RA. Catheter-directed interventions for pulmonary embolism. *J Vasc Surg*. 2015;61:559–565.)

Randomized studies and meta-analyses have set the following features as mandatory for consideration of early discharge<sup>93–96</sup>:

- Low-risk PE as defined by the original or simplified PESI score
- Normal pulse and blood pressure
- No oxygen requirements
- No risk factors for bleeding including thrombocytopenia ( $<70,000/\text{mm}^3$ )
- No serious comorbid conditions (e.g., coronary artery disease, heart failure, chronic pulmonary disease, renal or liver failure)
- Mental capacity to understand the risk and the benefits
- Patient not living alone and having access to telephone and ability to return to hospital promptly if there is clinical deterioration
- Absence of major symptomatic DVT.

## Treatment Strategies

Hemodynamic status remains the most important short-term prognostic factor for patients with acute PE, so patients need to be practically divided to stable and unstable, the unstable ones requiring emergent revascularization and systemic thrombolysis being their first alternative. The stable ones should be further divided to those who are at low and those who are at intermediate risk for a PE complication. Among the intermediate-risk patients, the clinician needs to further identify those who are most likely to decompensate and may benefit from a more aggressive treatment. Current guidelines are summarized in Table 152.4.<sup>6,39,40</sup>

Due to lack of appropriate high-quality evidence, these guidelines lack strong recommendations for all but the lowest-risk PE patients. Many times, treating physicians will face dilemmas to what approach will best balance the benefits of intervention against potential risks of cardiopulmonary failure or death. This need has been addressed by the creation of Pulmonary Embolism Response Teams (PERTs). A PERT brings together multiple specialists to rapidly evaluate intermediate- and high-risk patients with PE, formulate a treatment plan, and mobilize the necessary resources to provide the highest level of care. The PERT is staffed by select experts from cardiovascular medicine, vascular and cardiac surgery, interventional cardiology, radiology, echocardiography, emergency medicine, hematology, pulmonary, and critical care medicine, all of whom have a particular interest and competency in treating PE.<sup>77,97</sup>

An algorithm combining the recommended therapeutic strategies, the PERT Consortium guide<sup>76</sup> and our institutional experience on acute PE is suggested in the Chapter Algorithms.

## Special Populations

### Incidental Subsegmental Pulmonary Embolism

The clinical relevance of incidentally diagnosing subsegmental (asymptomatic) PE in a chest CT is uncertain, and the optimal therapy is controversial.<sup>40,98</sup> As a general rule, patients with risk factors for recurrent or progressive VTE, who are hospitalized

or have reduced mobility for another reason, have active cancer or a low cardiopulmonary reserve or marked symptoms, favor anticoagulant therapy; a high risk of bleeding favors no anticoagulant therapy.

### Thrombus in Transit

Floating right heart thrombus, also known as “thrombus in transit,” is a rare but potentially fatal condition of varying etiology, most commonly clots transiting toward the pulmonary vasculature from peripheral venous circulation. It is encountered in approximately 4% of all PEs according to ICOPER<sup>99</sup>; it usually coincides with massive PE, and the mortality rate can be as high as 40%.<sup>97</sup> There are no distinct guidelines established for the management of free-floating thrombus, and the results of anticoagulation only, systemic thrombolysis, or suction or surgical thrombectomy are variable.<sup>95,100</sup> Surgical thrombectomy should be preferred if there is a patent foramen ovale.

### Pregnancy

PE is the leading cause of pregnancy-related maternal death in developed countries. The risk of PE is higher in the postpartum period, particularly after a caesarean section. Since pregnant women frequently complain of shortness of breath, this symptom should be interpreted with caution.<sup>6</sup> Data on the validity of clinical prediction rules for PE in pregnancy are lacking, but a retrospective series of pregnant women who were referred for CT angiography showed that no patient with an original Wells score of less than 6 points had a PE.<sup>101</sup> The usefulness of D-dimer is controversial, and although D-dimers physiologically increase throughout pregnancy, the usual cutoff values are used to rule out PE.<sup>6</sup> With a positive D-dimer, lower extremity duplex ultrasound can rule in DVT and anticoagulation initiated to avoid a CT scan. However, if duplex ultrasound is negative, a CT angiogram will be necessary. The radiation delivered is well below the threshold for fetal injury.<sup>102</sup> Nevertheless, lung scintigraphy, when available, may be preferred over CT, mainly to avoid radiation to the female breast and its potential effect on breast cancer.<sup>103</sup>

Adjusted dose of LMWH is the anticoagulant of choice in pregnancy. For high-risk PEs that will require thrombolysis, published data on 28 pregnant women treated with 100 mg of rtPA suggest that the risk of complications for the mother may be similar to that in the nonpregnant population.<sup>104</sup> Catheter interventions have a promising role, but evidence is still scarce.<sup>105,106</sup> Thromolytic treatment should not be used peripartum, except for critical cases; surgical or catheter mechanical thrombectomy may have better results.

### Cancer

Venous thromboembolism is four and six times more prevalent in cancer patients and in those undergoing chemotherapy, respectively.<sup>107</sup> Cancer is a risk factor for adverse outcomes in acute PE; patients are at a higher risk for bleeding, shock and death, or recurrent PE.<sup>108,109</sup> For most cancer patients with DVT, first-line therapy should be weight-based LMWH monotherapy for at least 3 to 6 months or as long as the cancer or its treatment

**TABLE 152.4**

Selected Societal Guidelines, Levels of Evidence, and Strength of Recommendation on the Early Management of Acute Pulmonary Embolism

	American Heart Association (2011)	European Cardiology Society (2019)	American College of Chest Physicians (2016)
	I = Benefit >> Risk IIa = Benefit > Risk IIb = Benefit ≥ Risk III = Benefit ≤ Risk	I = Benefit >> Risk IIA = Benefit > Risk IIB = Benefit ≥ Risk III = Benefit ≤ Risk	1 = Strong recommendation 2 = Weak recommendation
	A = Multiple RCTs or MA B = One RCT or non-RCTs C = Expert consensus	A = Multiple RCTs or MA B = One RCT or non-RCTs C = Expert consensus	A = High-quality evidence B = Moderate-quality evidence C = Low-quality evidence
LMWH, IV or SC UFH, or SC fondaparinux (if no contraindication to anticoagulation)	IA	IA (LMWH or fondaparinux preferred over UFH)	—
IVC filters are not recommended if patients are treated with anticoagulation	IIIC	IIIA	1B
IVC filters may be considered for patients with very poor cardiopulmonary reserve	IIbC	—	—
Set-up of a multidisciplinary team (PERT) for the management of high- and selected intermediate-risk PE should be considered, depending on the resources and expertise	—	IIaC	—
<b>High Risk PE (hypotension &lt;90 mm Hg)</b>			
IV anticoagulation with UFH	—	IC	—
Systemic thrombolysis if low bleeding risk	IIaB	IB	2B
Surgical pulmonary embolectomy if high bleeding risk or if systemic thrombolysis failed	IIaC	IC	—
Catheter-directed treatment if high bleeding risk or if systemic thrombolysis failed	IIaC	IIaC	2C
ECMO if refractory circulatory collapse	—	IIbC	—
<b>Non-High Risk PE (normotension)</b>			
LMWH or fondaparinux (IA) are recommended for most patients	—	IA	—
In parallel to parenteral anticoagulation, VKA should be initiated (IB)	—	IB	—
As alternative to parenteral anticoagulation with a VKA, rivaroxaban, apixaban, edoxaban or dabigatran, except for renal impairment, pregnancy or antiphospholipid syndrome	—	IA	—
For most patients, systemic thrombolysis is not recommended	—	IIIB	1B
Systemic thrombolysis should be considered for intermediate high risk PE <sup>a</sup> with signs of hemodynamic or respiratory deterioration	IIbC	IB	2C
Surgical pulmonary embolectomy may be considered for intermediate high risk PE <sup>a</sup> with signs of hemodynamic or respiratory deterioration	IIbC	IIaC	—
Catheter-directed treatment may be considered for intermediate high risk PE <sup>a</sup> with signs of hemodynamic or respiratory deterioration	IIbC	IIaC	2C
Early discharge and home treatment may be considered for low-risk PE if proper outpatient care and anticoagulation can be provided	—	IIaA	2B

<sup>a</sup>Intermediate high risk is defined differently by each society but generally entails combination of imaging signs of RV dysfunctions with positive biomarkers or worsening clinical signs.

is ongoing.<sup>6,39,40</sup> Emerging evidence indicates the safety and efficacy of novel oral anticoagulants; edoxaban, apixaban and rivaroxaban can be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.<sup>110–112</sup> Long-term anticoagulation should be considered for cancer patients given the high recurrence risk. It is recommended to wait 6 months after cure or complete remission before stopping therapy, but consideration should be given to stopping therapy earlier in patients with a high bleeding risk, if the PE occurred post-surgery or in those with lower risk of recurrence.<sup>109</sup>

### *Nonthrombotic Pulmonary Embolism*

Nonthrombotic PE refers to the pulmonary arterial embolization of cell clusters (e.g., adipocytes, amniotic or tumor cells), bacteria or fungi, gas, or foreign materials.<sup>6</sup> Although clinical symptoms are similar to those of thrombotic PE, diagnosis can be a challenge and relies on a high index of suspicion and typical imaging findings.

Fat embolism is a rare entity, usually occurring after long bone fracture or orthopedic surgery and is classically described as triad of pulmonary (respiratory distress), central nervous system (altered mental status) and skin manifestations (petechial rash).<sup>113</sup> Treatment mainly includes supportive measures, although the use of steroids has been controversial.<sup>6</sup>

Amniotic fluid embolism is a rare but catastrophic condition. It involves a complex sequence of events triggered by entrance into the maternal circulation of material from the fetal compartment, resulting in an abnormal activation of proinflammatory mediators and a subsequent systemic inflammatory response. The typical presentation of amniotic fluid embolism includes a triad of sudden hypoxia and hypotension, followed in many cases by coagulopathy, all occurring in relation to labor and delivery. It should be considered in the differential diagnosis in any pregnant or immediately postpartum woman who suffers sudden cardiovascular collapse or cardiac arrest, seizures, severe respiratory difficulty, or hypoxia, particularly if such events are followed by a coagulopathy that cannot be otherwise explained.<sup>114</sup> Analysis of the national U.S. registry reveals that 70% of cases of amniotic fluid embolism occur during labor, 11% after a vaginal delivery, and 19% during a cesarean delivery.<sup>114</sup> Management is mainly supportive.

Tumor cell embolization is rarely diagnosed before death. Carcinoma of the prostate gland, digestive system, liver, and breast are the most commonly implicated. Tumor cell macroembolism is indistinguishable from the thrombotic PE. Treatment should target the underlying malignant disease.<sup>6</sup>

Septic embolism to the pulmonary circulation is a rare event commonly associated with right-sided endocarditis and manifests as sepsis with respiratory distress. Risk factors include intravenous drug abuse, infected indwelling catheters or pacemaker wires, and septic thrombophlebitis from the tonsils and the jugular, dental, and pelvic regions.<sup>6,115</sup> Eradication of the responsible bacterial or fungal microorganism and its source is the cornerstone of treatment.

Air embolism is an iatrogenic complication, with the lethal volume estimated between 100 and 500 mL. Supportive measures include high oxygen concentrations, volume expansion, aspiration with a central catheter, and patient placement in the

left lateral decubitus position to prevent RV outflow obstruction by airlock.<sup>6</sup>

Pulmonary embolization of foreign materials has increased proportionally to the increase of venous endovascular interventions. Filter, stent, wire, or catheter particles have all been reported to have embolized in the pulmonary circulation. Retrieval when possible to prevent thrombosis and sepsis is recommended.<sup>8</sup>

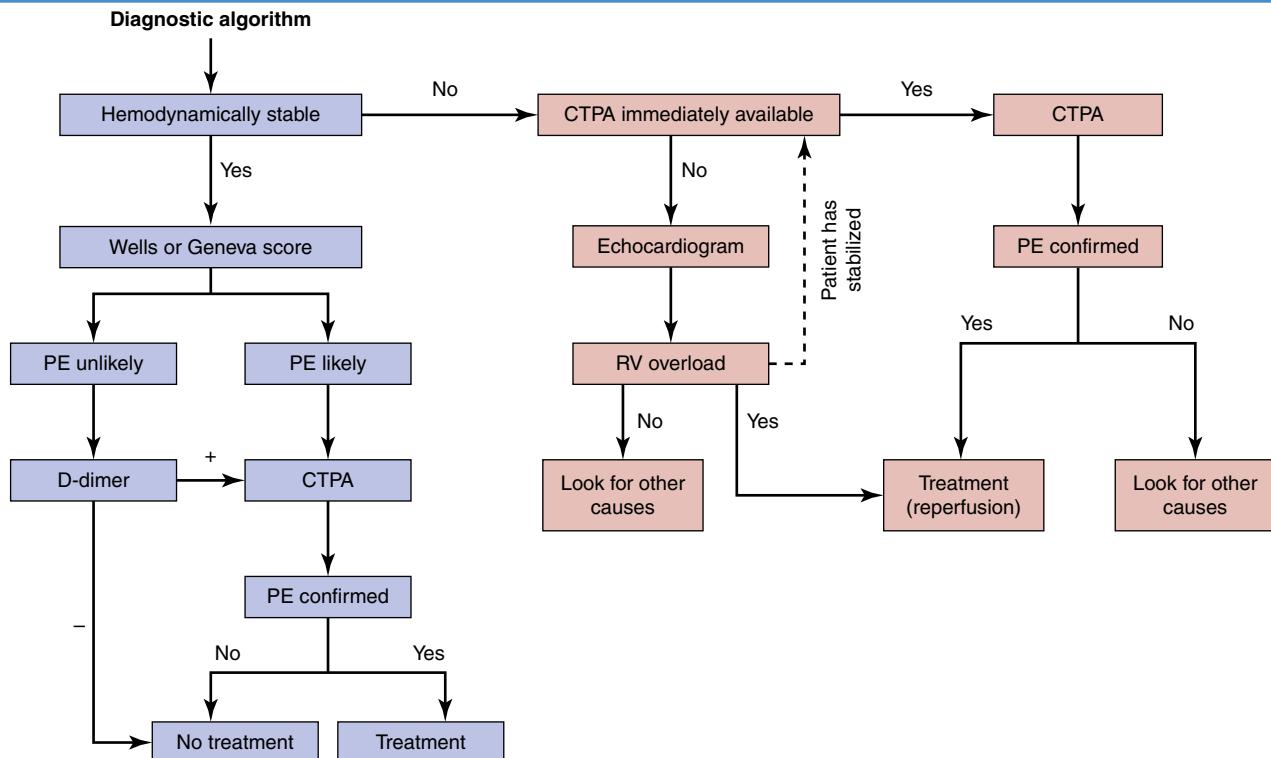
## PROGNOSIS

The prognosis of acute PE varies widely, depending on the severity of pulmonary arterial obstruction and its impact on the RV function. RV failure is the most common cause of death in acute PE. As discussed earlier, RV strain is associated with an adverse in-hospital outcome, not only in hypotensive but in hemodynamically stable patients too. PE without RV dysfunction has a less than 2% death rate. RV dysfunction shifts mortality rates to 3% to 15% for normotensive and greater than 15% for those patients who are hypotensive.<sup>45,46,116</sup> Anticoagulation, contemporary supportive treatment, and thrombolytic therapies continuously decrease these rates.<sup>117,118</sup> Among survivors, later mortality is unlikely to be related to PE, and it is most frequently attributed to other cardiovascular risk factors or underlying malignancies.<sup>119,120</sup> However, PE recurrence or CTEPH should be anticipated.

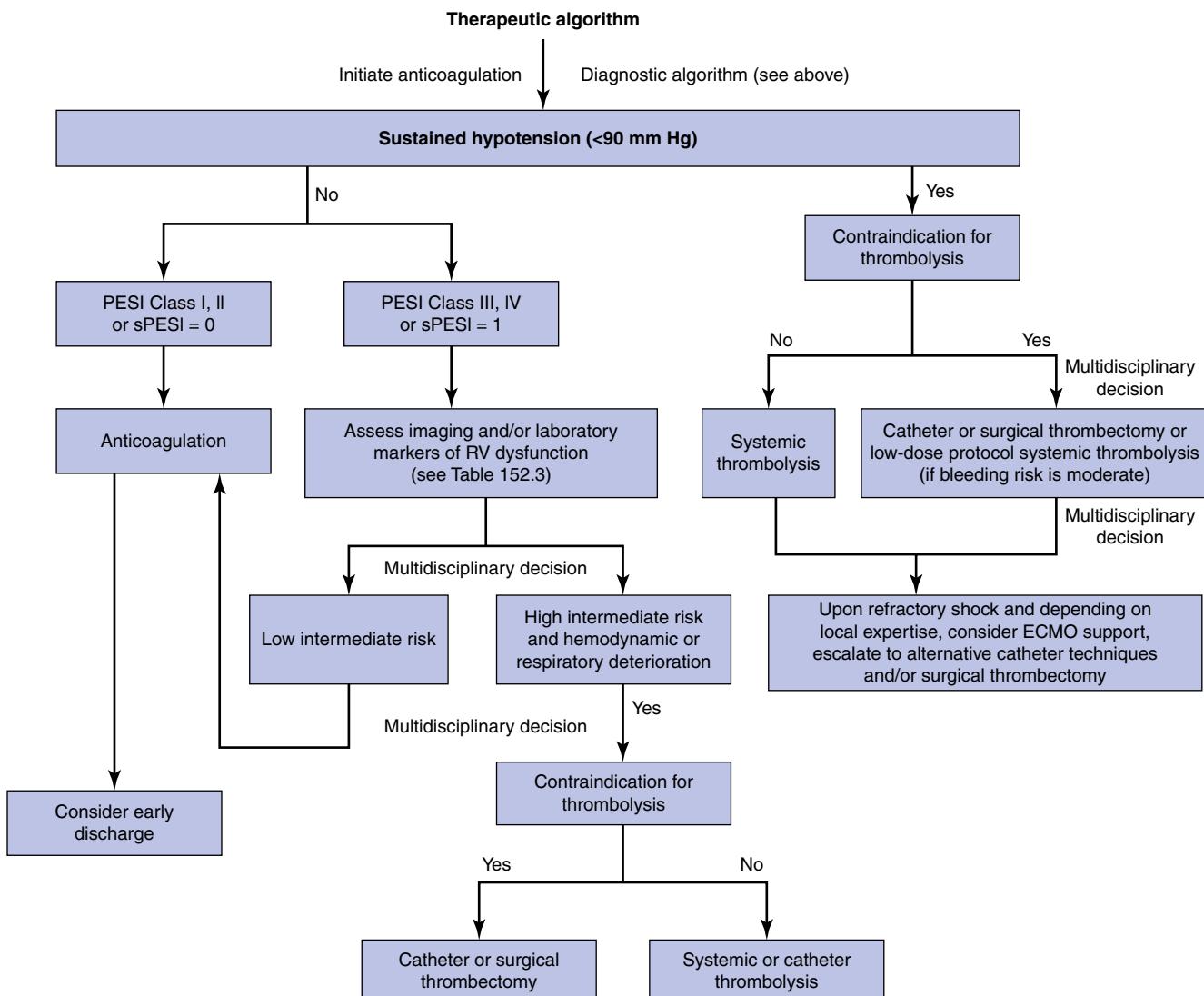
PE recurrence is not infrequent; for this reason, certain patient cohorts (e.g., cancer or unprovoked PE) are candidates for indefinite anticoagulant treatment after an initial episode. Recurrence while on anticoagulation is commonly the result of subtherapeutic anticoagulation. As a general rule, anticoagulants are discontinued when the perceived risk of anticoagulation-related bleeding and the inconvenience of remaining on treatment outweigh the risk of recurrent PE. Late recurrence has been reported to be 13% at 1 year, 23% at 5 years, and 30% at 10 years.<sup>121,122</sup> Interestingly, a recent large prospective study showed similar recurrence rates in patients with symptomatic subsegmental versus more proximal PE; however, the topic remains controversial.<sup>123,124</sup>

CTEPH is usually the result of at least one or multiple recurrent PEs, even if many times they may go unnoticed. Residual accumulating thrombus in the pulmonary arterial tree is remodeled into connective and elastic tissue, leading to vessel narrowing and remodeling. This will subsequently progress to small-vessel arteriolar vasculopathy.<sup>39,125</sup> Pulmonary hypertension results when the capacitance of the remaining healthy vascular beds cannot absorb the cardiac output. It is defined as mean pulmonary artery pressure greater than 25 mm Hg that persists 6 months after the PE event, and, although it may be subclinical for a long period, it may eventually manifest as dyspnea, fatigue, and exercise intolerance. It is estimated to occur in 2% to 4% of patients after acute PE, usually within 2 years.<sup>126,127</sup> There is controversial evidence that thrombolysis may potentially decrease the clinical occurrence of CTEPH because it seems to alter exercise tolerance and quality of life.<sup>54–59</sup> It is recommended that patients 6 weeks after an acute PE should be screened with an echocardiogram for persistent pulmonary hypertension that may predict the development of CTEPH.<sup>39</sup>

# CHAPTER ALGORITHMS



Diagnostic Algorithm. CTPA, computed tomography pulmonary arteriography; PE, pulmonary embolism; RV, right ventricular.



Suggested Algorithm for the Management of Acute Pulmonary Embolism. ECMO, extracorporeal membrane oxygenation; PESI, Pulmonary Embolism Severity Index; sPESI, Simplified Pulmonary Embolism Severity Index.

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# Vena Cava Interruption

MARC A. PASSMAN

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## SUPERIOR VENA CAVA FILTERS 2029

Numerous techniques of vena cava interruption have been described in the past for the prevention of PE, including femoral vein and IVC ligation, and partial interruption of the IVC by means of plastic clips, plication, or mechanical staplers.<sup>1–4</sup> These later measures were developed to compartmentalize the vena cava to allow blood flow but trap large emboli, and they were the mainstay of treatment through the 1950s and 1960s. Despite these measures, there were high rates of IVC occlusion, significant lower extremity venous-related problems, and little improvement in outcome of patients with PE. With the development of techniques to allow transvenous delivery of intravascular vena cava devices, the Mobin-Uddin umbrella filter was introduced in 1967. Structured as a silicone membrane with a hole to allow blood flow, it was associated with a high rate of vena cava thrombosis. In 1973 the original stainless steel Greenfield filter was introduced, followed by titanium Greenfield filter in 1989 and lower profile stainless steel Greenfield filter in 1995, and, as the most extensively studied filter, is the filter design with which current filters are compared. Over the past few decades, several additional filter designs have been developed that have favorable properties, including ease of deployment, clot-trapping effectiveness, preservation of IVC flow, designs that allow filter retrieval or conversion of filter to a non-filtering device. This chapter reviews IVC filter design features, current available IVC filter types, clinical indications

and guidelines for use, anatomic considerations, and techniques for placement and retrieval.

## **FILTER DESIGN**

### **Design Considerations**

The functional goal of filters is to prevent PE by trapping venous thromboemboli in the vena cava. There are several features that are preferred for optimal function and minimal compromise, including the use of non-thrombogenic, biocompatible, non-ferromagnetic, durable implantable material. Filtering efficiency should be high without impedance of flow, and there should be a single trapping level and conical design, which provides the highest filtering-to-flow volume ratio. Ideally, the filter should have a self-centering mechanism with secure fixation to the vena cava wall, a filter hook length and angle sufficient to prevent migration when the filter is in place, and the ability to be retrieved when no longer needed without limitation of the time frame for incorporation. The optimal filter should be highly visible on imaging with ease of percutaneous delivery through a low-profile system and a simple release mechanism. Repositioning and retrievability should also be possible, and the potential for complications should be negligible. The financial cost of filter delivery should be low.

Vena cava filter design categories include the following:

1. *Permanent filter.* Placed with the intention of providing permanent, lifelong filtration, permanent filters have design characteristics that maximize secure fixation.
2. *Optional (retrievable) filter.* May have some similar design features and can function as permanent filters, optional or retrievable filters have the added feature of removal capability. Optional filters adhere to the wall of the vena cava with hooks, barbs, or radial force (or any combination of the three) but can be retrieved by image-guided catheter techniques within a device-specific time interval.
3. *Temporary filter.* These filters are not designed for permanent placement and do not have any means of fixation to the vena cava wall. Rather, temporary filters are attached to a wire or catheter that traverses the venous system and protrudes from the skin to facilitate subsequent removal.
4. *Convertible filter.* Functioning initially as a permanent filter with elements allowing attachment to the vena cava wall, convertible filters are altered structurally to allow for conversion to a non-filtration state after implantation.<sup>5</sup>

## Filter Types

Understanding individual filter structural designs, advantages, and limitations is important before placement to ensure proper filter selection. For the purpose of this chapter, only US Food and Drug Administration (FDA)-approved permanent and optional/retrievable filter designs are discussed (Table 153.1 and Fig. 153.1).

Conical filter design is optimal and permits progressive central filling while allowing circumferential blood flow peripherally, which helps to maintain vena cava patency. For example, the conical geometry of the Greenfield filter makes it possible for thrombi to fill and occlude 70% of the filter cone, a volume of thrombus of approximately 4 cm<sup>3</sup> (34.3% of the total volume), while reducing the cross-sectional area by less than 50%. If the cone is filled to 80% of total volume, the reduction in cross-sectional area is 64%, at which point venous flow begins to decrease and venous pressure proximal to the filter begins to increase<sup>6</sup> (Fig. 153.2). Although other filter designs have double trapping levels or double basket designs and have higher capacity to capture smaller emboli, flow dynamics are reduced compared with single trapping conical designs and may be associated with higher vena cava occlusion rates.

Although rapid and stable incorporation may be desirable for permanent filter design to maintain position and prevent migration, retrievable filter designs need to have sufficient incorporation to prevent migration but not so much that retrieval cannot be accomplished. Altering the filter hook contact point to allow retrievability may have the disadvantage of an increased tendency for filter leg penetration or filter migration. This has also resulted in different filter hook length and angle configurations. Although some filters (such as Greenfield filter) incorporate recurved configuration to create a contact angle of 80 degrees, allowing better hook incorporation without full penetration into the vena cava, other filters (such as Celect Platinum, Denali, OptionElite, ALN Optional filters) use

different hook configuration to prevent excessive incorporation and facilitate retrievability. Filter designs such as VenaTech LP and OptEase do not depend on filter legs for fixation, thereby minimizing potential for penetration. Similarly, although some filters do not have self-centering features, others such as Denali and Celect Platinum have included independent self-centering mechanisms to minimize potential tilt. To improve self-centering of the filter, some designs such as VenaTech LP and Optease have increased contact points with the vena cava wall, which prevents tilt but may lead to increased incorporation and a possible tendency for vena cava occlusion. While these additional filter features may allow for better centering to better optimize flow dynamic, they do not offer any additional filtering capacity and can potentially lead to filter centering strut penetration of the vena cava wall.

Newer filter technology has led to availability of convertible filter designs which function as a filter upon deployment but are altered structurally to allow for conversion to a non-filtration state after implantation. Filters such as VenaTech Convertible requires removal of the filtration portion through a separate percutaneous procedure. Filters such as Sentry have a dissolvable filament that allows spontaneous bioconversion with retraction of the filter arms to the IVC wall around 60 days thereby restoring an open unobstructed IVC lumen.

A temporary filter (Mermaid Angel catheter) is also now clinically available and is designed to remain attached to a central venous catheter, allowing placement and removal at the bedside in critical care patients who may need transient protection during critical illness. The conical, self-expanding, nitinol filter has wide proximal openings that allow the capture of clots in the distal end of the filter. The distal end of the filter is free floating on the central venous catheter so that the filter can expand to the diameter of the vena cava. The filter is permanently attached to the multi-lumen catheter to ensure secure positioning, while simultaneously providing access to the central venous system for administration of medications, fluids, or blood products; blood sampling; and monitoring of central venous pressure. Attachment to the catheter facilitates retraction of the filter bedside when filtration is no longer needed.

## Filter-Related Complications

Because of difficulties comparing data on different filters, several guidelines outlining reporting standards for filter devices have been published.<sup>7–10</sup> Potential vena cava filter-related complications include the following definitions:

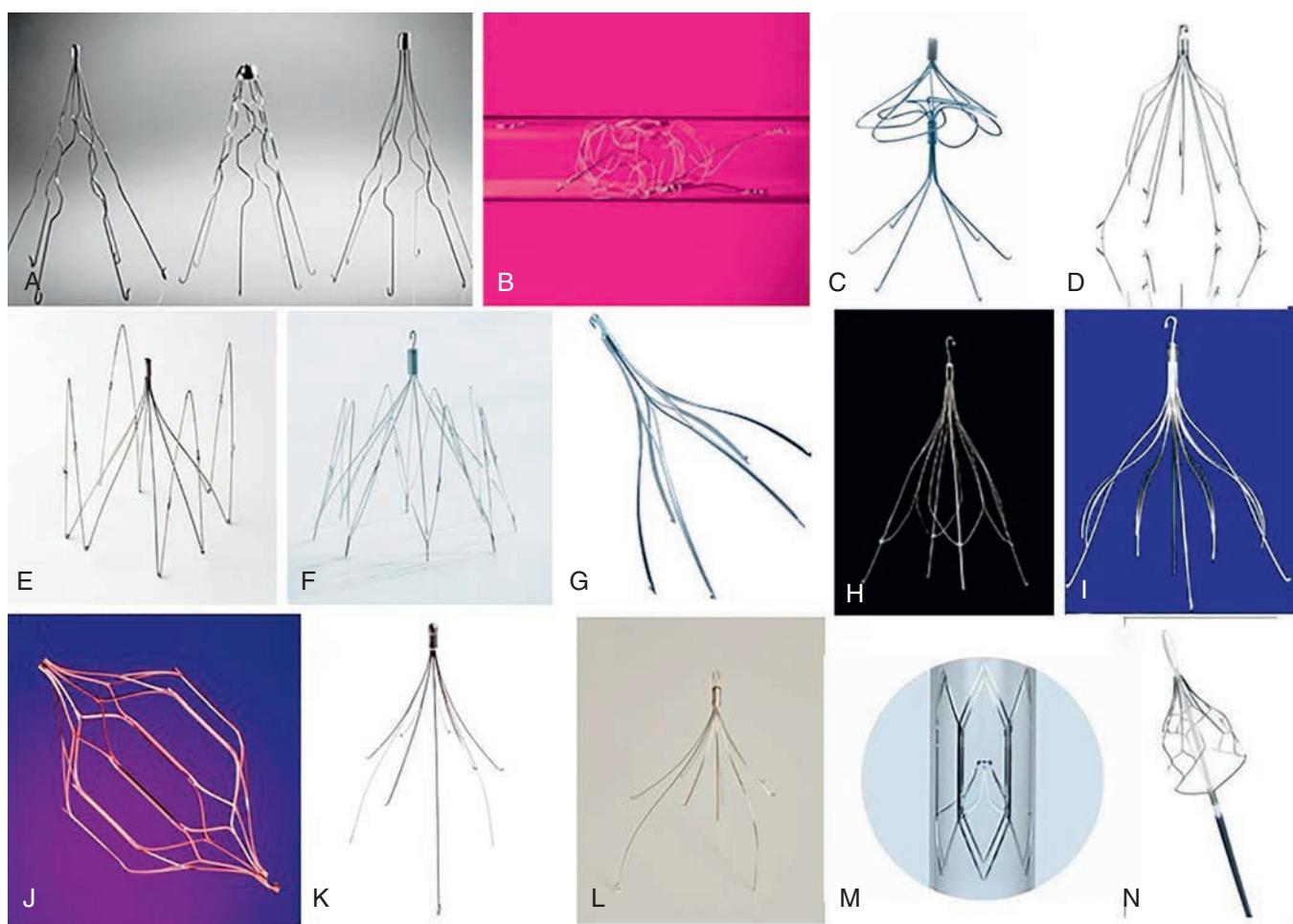
1. *Filter migration or embolization.* Movement of the filter from its deployment position by >2 cm in either caudal or cephalad direction.
2. *Thrombotic occlusion.* Occlusion of the vena cava at the level of the IVC filter, can be primary, caused by the presence of the filter, or secondary after capture of thromboembolic debris.
3. *Filter tilt.* Tilting of the filter compared to the IVC axis by >15 degrees, which can decrease effective filtration and protection from PE.

**TABLE 153.1**

Comparison of Design Features for Current US Food and Drug Administration-Approved and Commercially Available Vena Cava Filter Devices (2020)

Filter Device	Manufacturer	Material	Design	Approach	Delivery Catheter Size: Inner Diameter (Fr)	Maximum Caval Diameter (mm)	Maximum Deployed Length (mm)	FDA-Approved Use
Stainless steel Greenfield filter	Boston Scientific, Natick, MA	Stainless steel	Conical Single trapping	Femoral/jugular	12	28	49	Permanent
Titanium Greenfield filter	Boston Scientific, Natick, MA	Titanium	Conical Single trapping	Femoral/jugular	12	28	47	Permanent
Simon nitinol filter	Bard Peripheral Vascular, Tempe, AZ	Nitinol	Conical Bilevel	Femoral/jugular/antecubital	7	28	38	Permanent
Denali	Bard Peripheral Vascular, Tempe, AZ	Nitinol	Conical Bilevel	Femoral/jugular	8.4	28	50	Optional
VenaTech LP filter	B. Braun/VenaTech, Bethlehem, PA	Cobalt Chromium	Conical Single trapping	Femoral/jugular	7	28	43	Permanent
VenaTech Convertible	B. Braun/VenaTech, Bethlehem, PA	Cobalt Chromium	Conical Single trapping	Femoral/jugular	12.9	28	—	Convertible
TrapEase filter	Cordis Endovascular, Miami, FL	Nitinol	Double basket	Femoral/jugular/antecubital	6	30	50	Permanent
OptEase filter	Cordis Endovascular, Miami, FL	Nitinol	Double basket	Femoral/jugular/antecubital	6	30	54	Optional
Bird's nest filter	Cook Inc., Bloomington, IN	Stainless steel	Variable	Femoral/jugular	12	40	80	Permanent
Günther Tulip filter	Cook Inc., Bloomington, IN	Conichrome	Conical Single trapping	Femoral/jugular	Femoral 8.5 Jugular 7	30	50	Optional
Select Platinum	Cook Inc., Bloomington, IN	Conichrome	Conical Single trapping	Femoral/jugular	7	30	51	Optional
ALN Optional Filter	ALN, Bormes Les Mimosas, France	Stainless steel	Conical	Femoral/jugular/brachial	7	28	55	Optional
Option, Option Elite	Argon Medical Devices, Inc., Plano, TX	Nitinol	Conical	Femoral/jugular/antecubital/popliteal	6.5	30	56.5	Optional
Sentry	Boston Scientific, Natick, MA	Nitinol frame, Bioabsorbable filament	Conical	Femoral/jugular	7	16–28	57.7	Convertible
Angel Catheter	Mermaid Medical	Nitinol	Conical	Femoral	8	15–30	50	Temporary

FDA, U.S. Food and Drug Administration.



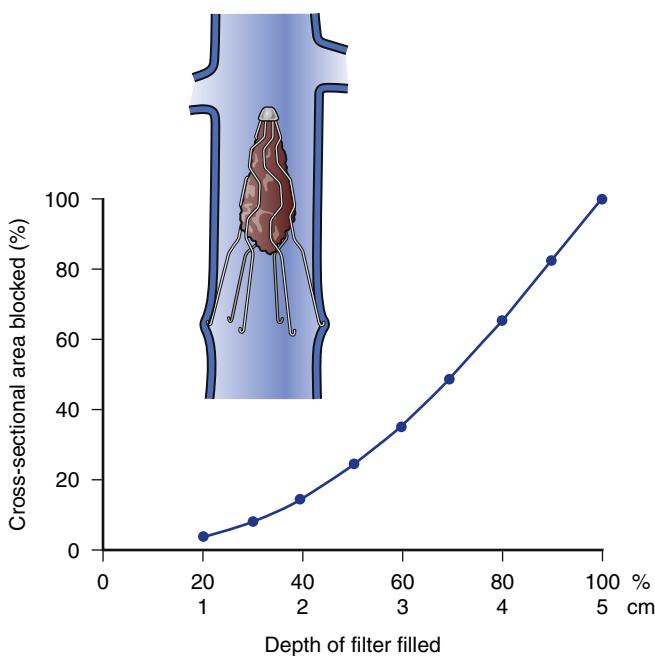
**Figure 153.1** Current US Food and Drug Administration-Approved Filter Designs. (A) Boston Scientific titanium Greenfield filter, original stainless steel Greenfield filter, and low profile stainless steel Greenfield filter (from left to right); (B) Cook Gianturco-Roehm bird's nest filter; (C) Bard Simon nitinol filter; (D) Bard Denali filter; (E) B Braun VenaTech LP filter; (F) B Braun VenaTech convertible filter; (G) Argon OptionElite filter; (H) Cook Günther Tulip filter; (I) Cook Celect Platinum filter; (J) Cordis OptEase filter; (K) ALN Optional filter; (L) ALN Optional filter with hook; (M) Boston Scientific Sentry; and (N) Mermaid Medical Angel catheter.

4. *Filter perforation.* Extension of the filter strut or anchor >3 mm beyond the adventitial layer of the vena cava wall.
5. *Filter fracture.* Loss of structural integrity of the filter leading to separation of filter leg components.

Overall reported complications for vena cava filters include pulmonary embolism (PE) (2%–5%), fatal PE (0.7%), death linked to filter insertion (0.12%), venous access site thrombosis (2%–28%), filter migration (3%–69%), vena cava penetration (9%–24%), vena cava obstruction (6%–30%), venous insufficiency (5%–59%), filter fracture (1%), and guide wire entrapment (1%).<sup>11,12</sup> Penetration of the IVC wall by filters is also being noted with increasing frequency. In a systematic review, overall frequency was 19%, with 8% exhibiting symptoms usually due to organ/structure involvement. Although asymptomatic filter penetration is often noted incidentally on imaging, endovascular retrieval or surgery is usually required for symptomatic patients.<sup>13</sup> Table 153.2 summarizes data on different filter types. Overall, most of the available filters are approximately equivalent in prevention of PE, but there is some variation in complication rates.<sup>14–16</sup>

## Permanent Versus Optional Filter

Although it remains unclear whether filters actually improve survival, they do provide protection against PE. Because the risk for PE in patients with proven VTE and contraindications to anticoagulation is high, potential complications of filters must be balanced against the risk of no filter. Randomized evidence on permanent filters is limited. In the PREPIC (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) trial, 400 patients with proximal DVT with or without PE were randomized in a 2 by 2 factorial study design to filter placement versus no filter and unfractionated heparin versus enoxaparin. There was a significantly lower incidence of PE with filter protection during the first 12 days (1.1% vs. 4.8%), but the filter group had a significantly increased incidence of recurrent DVT at 2 years (20.8% vs. 11.6%).<sup>17</sup> Eight-year follow-up data from the PREPIC trial confirmed the previous findings of cumulative recurrent PE (6.2% vs. 15.1%, filter vs. no filter, respectively) but increased recurrent DVT (35.7% vs. 27.5%) and no difference in post-thrombotic



**Figure 153.2** Relationship between the percentage and depth of thrombus trapped within the filter and the percentage of cross-section occluded.

venous insufficiency or survival.<sup>18</sup> The authors concluded that although permanent filter use may be beneficial in patients at high risk for PE, systematic use in the general population with VTE is not recommended. Unfortunately, no firm conclusions regarding filter efficacy in the prevention of PE can be drawn from the PREPIC trial given that the study design varies significantly from the wider application in current clinical practice (i.e., patients with documented VTE in whom anticoagulation has failed or cannot be administered).

Given the paucity of randomized data, determining the best permanent versus optional filter design is difficult. Some studies have used meta-analysis of data to compare the different filter designs and document the efficacy of filters in the prevention of PE and complication rates.<sup>19–21</sup> In the randomized open label, blinded end point PREPIC-2 trial for hospitalized patients with acute PE, the use of retrievable vena cava filters plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent PE at 3 months. Although PREPIC-2 did not support the use of retrievable filter in patients with acute PE who can be anticoagulated, the role of retrievable filters in patients who cannot be anticoagulated, those with DVT but no PE, or for other selected relative indications remains unclear based on current evidence.<sup>22</sup>

**TABLE 153.2**

Comparison of Vena Cava Filter Types for the Prevention of Pulmonary Embolism and Complication Rates Based on Systematic Reviews of Vena Cava Filter Studies

Filter Device	COMPLICATION RATES						
	PE: Overall (%)	PE: Fatal (%)	Insertion Site Thrombosis (%)	Vena Cava Thrombosis (%)	Filter Migration (%)	Tilt >15 degrees	Filter leg penetration (%)
Stainless steel Greenfield	3.5	1.3	8.6	3.5	2.0	a	2–15
Titanium Greenfield	3.4	1.8	13.1	4.4	7.5–15	a	13–50
Percutaneous stainless steel Greenfield	2.7	0.3	4.3	3	2.6	a	1.0
Simon nitinol	3.3	1.8	11.5	5.2	0–5	a	25–95
Bird's nest	3.4	1.5	7.4	2.8	1.1	a	85
VenaTech LP or LGM	3.6	0.9	15.3	9.5	6–18.4	a	a
TrapEase	0.9	a	0.4	2	0.9		
OptEase	1.6	a	0.8	3.7	0.3	5.6	1.9
G2	3.4	a	—	3.7	4.5		44
Recovery G2	1.0	a	10.4	1.0	0.8	15.5	15.1
Günther Tulip	0.9	0.4	a	2.3	0.7	5.9	22–78
Celect	1.1	a	1.2	0.6	0.6	12.1	22–93
ALN Optional	0.7	a	14.0	1.8	0.5	a	3.4
Rex Option	4.0	a	18.0	1.0	2.0	a	2.9–10
Denali	a	a	a	a	a	a	2.5

<sup>a</sup>Limited or insufficient systematically reviewed published data to report.

PE, pulmonary embolism.

Data from Hann CL, Streiff MB. The role of vena cava filters in the management of venous thromboembolism. *Blood Rev.* 2005;19:179–202; Angel LF, Tapson V, Galgon RE, et al. Systematic review of the use of retrievable inferior vena cava filters. *JVIR.* 2011;22(11):1522–1530; Andreoli JM, Lewandowski RJ, Vogelzang RL, et al. Comparison of complication rates associated with permanent and retrievable inferior vena cava filters: a review of the MAUDE database. *Vasc Interv Radiology.* 2014;25:1181–1185; Deso SE, Idakoji IA, Kuo WT. Evidence-based evaluation inferior vena cava filter complications based on filter type. *Semin Intervent Radiol.* 2016;33:93–100.

Despite lack of clear supporting evidence, filter use expanded significantly in the United States over the past few decades, but has seemingly peaked with most volume trends now in the downward direction.<sup>23–26</sup> This increase in filter utilization seemed to parallel availability of optional filters and their expanded use for VTE prophylaxis. With the expanding use of optional vena cava filters, there has been a growing body of literature and reports to the FDA Manufacturer and User Facility Device Experience (MAUDE) database that led FDA to issue a communication of risk of adverse events with long-term use on August 9, 2010: “Since 2005, the FDA has received 921 device adverse event reports involving IVC filters, of which 328 involved device migration, 146 involved embolizations (detachment of device components), 70 involved perforation of the IVC, and 56 involved filter fracture.”<sup>27</sup> The FDA raised concern that some of these events may be related to retrievable filters being left in place for an extended time, beyond the time when risk of PE has subsided. As a result, the FDA recommended that “implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as possible when protection from PE is no longer needed.” In an external follow-up study of the MAUDE database of 1606 reported adverse events involving 1057 filters, 86.8% involved retrievable filters vs. 13.2% for permanent filters, although this data source is limited by self-reporting mechanisms and may underestimate true filter complication rates.<sup>28</sup> The FDA updated the original 2010 safety communication on May 6, 2014, reiterating the importance of filter removal as soon as protection from PE is no longer needed and when the risk/benefit profile favors removal based on the patient’s overall health status.<sup>27</sup> In addition, the FDA is now requiring collection of clinical data for currently marketed IVC filters in the United States to address further safety questions for both permanent and retrievable filter designs either by manufacturers conducting postmarket studies (522 studies) or through manufacturers’ participation in the ongoing PRESERVE (PREdicting the Safety and Effectiveness of Inferior VEna Cava Filters) study, which began enrolling in 2015.<sup>29</sup>

Complicating the decision to use retrievable filters is poorly defined timing of possible retrieval. For example, based on FDA indications for use (IFU), retrieval of Günther Tulip filters is recommended within 20 days, OptEase filters within 14 days, and the Celect filter within 52 weeks, while more recently approved filters like Denali, OptionElite, and ALN Optional do not have clearly specified time windows for retrieval. Further confusing best timing are case reports suggesting that potential retrieval at extended periods is possible for all filters but can be more problematic with a higher failure to retrieve rates.<sup>30–33</sup> Regardless, the longer a filter is in place, the less successful retrieval will be, as shown in a recent systematic review documenting technically successful retrieval rates of 99% at 1 month and 94% at 3 months, falling to 37% at 12 months.<sup>34</sup> Until further data are available, the optimal period for retrieval of currently available optional filters probably falls within a few months of placement, after which the technical success of retrieval will diminish.

Data on the efficacy and safety of retrievable filters are derived from smaller series with insufficient long-term data in comparison to other permanent filter designs to warrant permanent implantation. With the lack of extended outcome data for optional filters, the decision to use a retrievable filter instead of a permanent filter should be based on the intent to discontinue filtration. To determine optimal timing for filter retrieval based on a mathematical model, the FDA published a quantitative decision analysis weighing risk of PE versus risk of IVC filters over time showing a risk–benefit profile cross point favoring removal of IVC filter between 29 and 54 days.<sup>35</sup> Factored into this decision of permanent vs. optional filter should be the anticipated required duration of protection from VTE vs. the risk associated with anticoagulation compared to increased filter dwell time. In patients with proven VTE, anticoagulation should be resumed as soon as possible when the risk has diminished. For patients in whom filters are placed for prophylaxis of VTE, anticoagulation should be restarted in accordance with published VTE prophylaxis guidelines. When the risk of resuming anticoagulation is extended, permanent filtration may be preferable. Optional/retrievable filters should not be used as a replacement for a permanent filter if permanent PE prevention is needed. Optional filters are preferred in the following clinical scenarios: (1) indications for permanent filters are not present; (2) the risk of clinically significant PE is acceptably low; (3) return to high risk for VTE is not anticipated; (4) life expectancy is long enough that the benefit of filter removal will be realized; and (5) the filter can be removed safely or converted.<sup>5</sup>

## CLINICAL DECISION MAKING

### Guidelines

Indications for the use of vena cava filters are shown in [Box 153.1](#), and supported by the evidence-based guidelines from the 2012 and 2016 American College of Chest Physicians (ACCP).<sup>36,37</sup> Without anticoagulation, the risk of PE developing in patients with VTE is high, and it may be fatal in as many as 25% of patients (see [Ch. 152](#), Pulmonary Embolism: Presentation, Natural History, and Treatment). In general, both 2012 and 2016 ACCP guidelines, and 2019 American Society of Hematology guidelines<sup>38</sup> recommend against IVC filter use for prophylaxis, although the strength of this recommendation varies based on low certainty in the evidence of effects. Resumption of anticoagulation as soon as possible is recommended because, although vena cava filters are effective in preventing PE, they are not for prevention of DVT.

Expanded relative indications based on inconclusive evidence have included poor compliance with anticoagulation; free-floating ilio caval thrombus; renal cell carcinoma with renal vein extension; placement in conjunction with venous thrombolysis or thromboembolectomy; presence of DVT and limited cardiopulmonary reserve or chronic obstructive pulmonary disease; recurrent PE complicated by pulmonary hypertension; proven DVT in an oncology, burn, or

BOX 153.1	<b>Evidence-Based Guidelines, Relative Expanded Indications, and Contraindications to Vena Cava Filter Placement</b>
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#### Evidence-Based Guidelines

- Documented VTE with contraindication to anticoagulation
- Documented VTE with complications of anticoagulation
- Recurrent PE despite therapeutic anticoagulation
- Documented VTE with inability to achieve therapeutic anticoagulation

#### Relative Expanded Indications

- Poor compliance with anticoagulation
- Free-floating ilio caval thrombus
- Renal cell carcinoma with renal vein extension
- Venous thrombolysis/thromboembolectomy
- Documented VTE and limited cardiopulmonary reserve
- Documented VTE with high risk for anticoagulation complications
- Recurrent PE complicated by pulmonary hypertension
- Documented VTE – cancer patient
- Documented VTE – burn patient
- Documented VTE – pregnancy
- VTE prophylaxis – high-risk surgical patients
- VTE prophylaxis – trauma patients
- VTE prophylaxis – high-risk medical condition

#### Contraindications

- Chronically occluded vena cava
- Vena cava anomalies
- Inability to access the vena cava
- Vena cava compression
- No location in the vena cava available for placement

PE, pulmonary embolism; VTE, venous thromboembolism.

pregnant patient; and venous prophylaxis in high-risk surgical, medical, or trauma patients, as shown in **Box 153.2**.

Recent multi-societal clinical practice guidelines in 2020 review the most updated evidence and provides more current recommendations for the use of IVC filters in a range of clinical scenarios.<sup>39</sup> These multispecialty guidelines are summarized in **Box 153.3**. As outlined in the 2019 American College of Radiology Appropriateness Criteria for Management of Venous Thromboembolism – IVC filters, evidence-based guidelines are applied to specific clinical conditions and after an extensive analysis of current medical literature from peer-reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation, GRADE), the appropriateness of IVC filters for these specific clinical scenarios has been rated.<sup>40</sup> The appropriate use criteria for IVC filters is shown in **Table 153.3**.

### Specific Patient Groups

#### Trauma Patients

The risk of VTE in major trauma patients without prophylaxis may be as high as 50% and incidence of PE as high as 30%.<sup>41,42</sup> General guideline recommendation for trauma

BOX 153.2	<b>Relative Recommendations for Vena Cava Filter Use as Venous Thromboembolism Prophylaxis, Including High-Risk Patient Factors and/or High-Risk Situation Combined with an Increased Bleeding Risk</b>
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#### Prophylaxis in High-Risk Patients

- Critically ill
- Previous DVT
- Family history of DVT
- Morbid obesity
- Malignancy
- Known hypercoagulable state
- Prolonged immobility

#### Prophylaxis in Trauma

- Multiple traumatic injuries
- Spinal cord injury
- Closed head injury
- Complex pelvic fractures
- Multiple long-bone fractures

#### Increased Bleeding Risk

- Major operation
- Intracranial hemorrhage
- Solid intra-abdominal organ injury
- Pelvic or retroperitoneal hematoma
- Ocular injury
- Medical problems (cirrhosis, end-stage renal disease, peptic ulcer disease, medication, coagulation disorder)

DVT, deep venous thrombosis.

patients with at least one risk factor is to receive some form of thromboprophylaxis, preferably with an anticoagulant if there is no contraindication of bleeding.<sup>43</sup> For patients who cannot receive anticoagulation, mechanical thromboprophylaxis is recommended. However, societal guidelines have varied in their recommendations for trauma patients: The 2002 Eastern Association for the Surgery of Trauma (EAST) guidelines include a recommendation that IVC filters be considered for high-risk trauma patients with long-term anticipated immobility who cannot receive thromboprophylaxis<sup>44</sup>; The 2019 American College of Radiology Appropriateness criteria and 2020 Society of Interventional Radiology, while recommending against routine use of prophylactic filters, have allowed consideration for selective prophylactic IVC filter placement in certain high-risk trauma patients.<sup>39,40,45</sup>

Due to the risk of bleeding in severely injured trauma patients, standard pharmacologic thromboprophylaxis may not be possible. Prophylactic filter placement has been recommended by some for use in trauma patients who were considered at very high risk for VTE, with most series reporting a decreased incidence of all PE and fatal PE with the use of vena cava filters in appropriately selected high-risk patients.<sup>46,47</sup> Level II and III data would indicate that the risk to benefit ratio of prophylactic filter placement may be favorable in selected high-risk trauma patients. In a retrospective review of 9721 patients, high-risk categories included head injury plus spinal cord injury, head injury plus long-bone fracture, severe pelvic fracture plus long-bone

**BOX 153.3****Summary of Evidence-Based Recommendations on the Use of Inferior Vena Cava (IVC) Filters in the Treatment of Patients with or at Substantial Risk of Venous Thromboembolic Disease****Acute VTE**

- In patients with acute PE with a contraindication to anticoagulation therapy, suggest an IVC filter be considered based on various clinical risk factors.
- In patients with acute DVT without PE and with a contraindication to anticoagulation therapy, suggest that an IVC filter be considered based on various clinical risk factors.

**Anticoagulation for VTE**

- In patients undergoing anticoagulation for acute VTE (DVT, PE) in whom a contraindication to anticoagulation develops, suggest that an IVC filter be considered in the setting of ongoing significant clinical risk for PE.
- In patients undergoing extended anticoagulation for VTE (DVT, PE), who have completed the acute phase of treatment and in whom a contraindication to anticoagulation develops, suggest that an IVC filter not be placed, with rare exceptions.

**Recurrent VTE**

- In patients who are receiving therapeutic anticoagulation for VTE (DVT, PE) who experience a recurrent VTE, suggest that a filter not be placed, with few exceptions. Reasons for anticoagulation failure should always be addressed.

**Routine IVC Filter Placement**

- In patients with acute VTE (DVT, PE) who are being treated with therapeutic anticoagulation, recommend against routine placement of an IVC filter.

**PE and DVT with Advanced Therapies**

- In patients with acute PE who are undergoing advanced therapies, suggest considering the placement of IVC filters only in select patients.
- In patients with DVT who are undergoing advanced therapies, suggest considering the placement of IVC filters only in select patients.

Adapted from: Kaufman JA, Barnes GD, Chaer RA, et al. Society of Interventional Radiology Clinical Practice Guideline for Inferior Vena Cava Filters in the Treatment of Patients with Venous Thromboembolic Disease. Developed in collaboration with the American College of Cardiology, American College of Chest Physicians, American College of Surgeons Committee on Trauma, American Heart Association, Society for Vascular Surgery, and Society for Vascular Medicine. *J Vasc Interv Radiol.* 2020; 31:1529–1544.

fracture, and multiple long-bone fractures.<sup>48</sup> A meta-analysis demonstrated a 0.2% incidence of PE with filters as opposed to 1.5% in controls without a filter and 5.8% in historic controls.<sup>42</sup> In a comparison of 40 critically injured patients who received a filter and 80 matched historic controls, PE occurred in 3% versus 18%, respectively.<sup>49</sup> At a 5-year follow-up of 132 trauma patients receiving prophylactic filters, Rogers and coauthors reported a 2.3% incidence of PE after filter placement and a mortality of 4.4% with one fatal PE episode.<sup>50</sup>

Analysis of the results of filter placement in trauma patients is limited mainly by the lack of adequate control groups. Several reports and a meta-analysis of prospective studies found no difference in rates of PE in patients with and without prophylactic filters.<sup>51</sup> In a review of a trauma quality collaborative registry, use of IVC filter placement had no effect on reduction of trauma patient mortality and were associated with an increase in DVT events.<sup>52</sup> A recent multicenter randomized controlled trial in trauma patients with a contraindication to

**VTE Prophylaxis – Trauma, Major Surgery**

- In trauma patients without known acute VTE, recommend against the routine placement of IVC filters for primary VTE prophylaxis.
- In patients without known acute VTE who are undergoing major surgery, suggest against routine placement of IVC filters.

**Indwelling IVC Filters – Anticoagulation, Mitigated PE Risk**

- In patients who have indwelling IVC filters with no other indication for anticoagulation, unable to recommend for or against anticoagulation.
- In patients with indwelling retrievable/convertible IVC filters whose risk of PE has been mitigated or who are no longer at risk for PE, suggest filters be routinely removed/converted unless risk outweighs benefit.
- In patients with indwelling permanent IVC filters whose risk of PE has been mitigated or who are no longer at risk for PE, suggest against routine removal of filters.

**Planned Filter Removal**

- In patients in whom IVC filter removal is planned, suggest against routine preprocedural imaging of the filter and the use of laboratory studies except in select situations.

**Complications Indwelling IVC Filters**

- In patients with complications attributed to indwelling IVC filters, suggest filter removal be considered after weighing filter- versus procedure-related risks and the likelihood that filter removal will alleviate the complications.

**Filter Removal without Standard Snare Techniques**

- In patients undergoing filter retrieval whose filter could not be removed by using standard techniques, suggest attempted removal with advanced techniques, if appropriate and if the expertise is available.

pharmacoprophylaxis showed no mortality benefit or reduction in symptomatic PE in those receiving a prophylactic IVC filter within 72 h of presentation compared with a control group.<sup>53</sup> However, trauma patients who survived at least 7 days but were unable to be converted to prophylactic anticoagulation by day 7 had a 14.7% incidence of PE in the control group compared to no PEs in those receiving filters. This randomized Level I study suggests that not all trauma patients with an initial contraindication to pharmacologic VTE prophylaxis should receive prophylactic IVC filters, but that there may be a subset of trauma patients who cannot be anticoagulated for an extended period who may benefit from prophylactic filter placement. Until further high quality Level I evidence is available, IVC filter use in trauma patients should be reserved only for documented VTE when anticoagulation cannot be used or as prophylaxis in selective high-risk trauma patients with contraindications to anticoagulation where the risk of VTE outweighs the risk of the filter.

**TABLE 153.3**

Summary of American College of Radiology Appropriate Use Criteria for Inferior Vena Cava (IVC) Filters in the Treatment of Patients with or at Risk for Venous Thromboembolic Disease Across Specific Clinical Variant Scenarios

Procedure	Appropriateness Category
<b>Variant 1: Acute venous thromboembolism (proximal deep vein thrombosis of the leg or pulmonary embolism) with no contraindication to anticoagulation</b>	
Anticoagulation	Usually appropriate
Retrievable IVC filter	May be appropriate
Permanent IVC filter	Usually not appropriate
<b>Variant 2: Acute venous thromboembolism (proximal deep vein thrombosis of the leg or pulmonary embolism) with contraindication to anticoagulation, major complication of anticoagulation, or failure of anticoagulation</b>	
Retrievable IVC filter	Usually appropriate
Permanent IVC filter	May be appropriate
Observation	Usually not appropriate
<b>Variant 3: Isolated acute distal deep vein thrombosis of the leg</b>	
Observation with serial imaging	Usually appropriate
Anticoagulation	May be appropriate
Retrievable IVC filter	Usually not appropriate
Permanent IVC filter	Usually not appropriate
<b>Variant 4: Chronic venous thromboembolism (e.g., chronic thromboembolic pulmonary hypertension)</b>	
Anticoagulation	Usually appropriate
Pulmonary thromboendarterectomy	Usually appropriate
Balloon pulmonary angioplasty	May be appropriate
Permanent IVC filter	May be appropriate
Retrievable IVC filter	May be appropriate

Adapted from: ACR Appropriateness Criteria Radiologic Management of Venous Thromboembolism-Inferior Vena Cava Filters. *J Am Coll Radiol.* 2019;16:S214–S226.

### Bariatric Patients

Obesity is a strong independent risk factor for the development of VTE. PE is considered the most important cause of perioperative mortality in bariatric surgical patients, with an incidence of 1% to 3%, but the incidence has been reported to be as high as 17%, especially in super-obese patients (body mass index = 55 kg/m<sup>2</sup>).<sup>54,55</sup> Combined with the added risk associated with surgery, the potential risk for VTE is increased. Furthermore, several studies suggest that the risk for PE after bariatric surgery extends to the period after hospital discharge.<sup>56–57</sup>

Difficulty in proper dosing of anticoagulation thrombo prophylaxis in obese patients increases susceptibility to venous thromboembolic-related morbidity and mortality, making optimal pharmaco-prophylaxis difficult. Several authors have compared various thromboprophylactic regimens, but no conclusive results on the safest and most effective form of anticoagulation were reached.<sup>58–62</sup>

In light of these limitations of anticoagulation, placement of IVC filters for VTE prophylaxis has been used in bariatric surgical patients. In a study of 5554 bariatric operations by Hamad and Bergqvist, risk factors for postoperative VTE, including body mass index greater than 60, truncal obesity, and hypoventilation syndrome, were identified and recommended as indications for prophylactic filters.<sup>63</sup> A comparison of the

incidence of VTE in 248 high-risk bariatric patients receiving vena cava filters and 2852 low-risk patients who did not receive filters showed that the incidence of PE was not significantly different.<sup>64</sup> The use of prophylactic IVC filters reduced the risk for PE in high-risk obese patients, a group known to have a much greater incidence of morbidity and mortality, to a rate comparable to the baseline of low-risk. With optional/retrievable filters, there is the potential for using vena cava filters as a bridge during the highest risk period with subsequent removal. Among 59 patients undergoing bariatric surgery who met high-risk criteria in which retrievable filters were placed immediately before surgery, and removal was attempted 4 weeks postoperatively, there was one postoperative PE (1.7%) and no fatal PE or deaths.<sup>65</sup>

However, evidence from these studies favoring prophylactic vena cava filters in high-risk bariatric patients is significantly limited by small study sample size, lack of prospective data, no adequate control populations, and variable approaches to VTE prophylaxis. In a recent systematic review of IVC filter use for prevention of VTE in obese patients undergoing bariatric surgery, published data reporting safety and efficacy was noted to be heterogeneous and there was no clear evidence to suggest the potential benefit of IVC filters outweighing risk in this population.<sup>66</sup> Given the relative infrequency of fatal PE

after bariatric surgery, much larger trials are required before the indications for and efficacy of vena cava filter placement in the bariatric surgery population can be better defined.

### *Orthopedic Patients*

Patients undergoing major orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, and traumatic lower extremity fracture repair, have a significantly increased risk for VTE. Several studies support the efficacy of filter placement for the prevention of VTE in selected orthopedic patients.<sup>67,68</sup> Optional filters may be more appropriate in these high-risk orthopedic patients because they provide temporary protection at the time of increased risk and are intended to be retrieved when the risk for VTE has diminished.<sup>69</sup> Although the use of retrievable filters has the advantage of bridging high-risk orthopedic patients during the period of most increased risk, in the absence of randomized studies their use should be limited at this time. Based on current evidence-based guidelines, use of either permanent or optional vena cava filters in high-risk orthopedic patients should be reserved for those with documented VTE and a contraindication to or complication of anticoagulation.

### *Cancer Patients*

Malignancy is an independent risk factor for the development of VTE, with a reported incidence of 7% to 50% and a risk for PE twofold to fourfold higher in patients with malignancy than without.<sup>70</sup> Although some authors have suggested that primary filter placement in patients with malignant disease may be beneficial, others have favored anticoagulation.<sup>71–77</sup> Lin and associates suggested that vena cava filters may be a reasonable alternative to long-term anticoagulation in a subgroup of patients at high risk for recurrence, provided that their quality of life is reasonable and a decrease in the risk for fatal PE is justified.<sup>78</sup>

The financial cost of filter placement in cancer patients may be less than anticoagulation therapy because of the added costs of treating bleeding complications of anticoagulation therapy.<sup>79</sup> In a series of 30 patients with malignancy who had filters placed, 76% were alive at 1 month, 56% at 3 months, and 40% at 6 months.<sup>80</sup> In comparing the complication rates and cost, vena cava filter placement was favored if reasonable survival was expected. In a Markov model to compare the cost-effectiveness of filters versus anticoagulation,<sup>81</sup> vena cava filters were not cost-effective in patients with brain tumors, but when the model was applied to the anticipated 5-year survival for a breast cancer population, vena cava filter placement appeared to be more cost-effective than did anticoagulation alone. From the available data, it appears that filter placement is most cost-effective in cancer patients with documented VTE, good functional status, and anticipated survival.

However, a problem with filters as primary therapy for cancer patients is the finding of increased VTE events – PE, recurrent DVT, or vena cava thrombosis. The rate of recurrent VTE events after filter placement in cancer patients varies from 4% to 62%.<sup>82–84</sup> In a review of 166 cancer patients with VTE, although technical complications of filter placement were low, serious life-threatening or limb-threatening thromboembolic complications developed in 17% of patients, and survival

was poor in all patients regardless of treatment, thus leading to support for a conservative approach of routine anticoagulation therapy with selective filter placement.<sup>85</sup> In a large registry study, 19.6% of patients with cancer with acute VTE received IVC filters, but only 21% of them had a contraindication to anticoagulation. The filter recipients had no reduction in 30-day mortality or recurrent PE at 180 days but had an increased risk of DVT at 180 days.<sup>86</sup>

Based on current evidence, the current recommendation is that IVC filters should be reserved for cancer patients with documented VTE, contraindications to or complications of anticoagulation, and longer anticipated survival. IVC filters should be discouraged in patients with advanced malignant disease and a poor prognosis.

### *High-Risk General Surgical Patients*

The incidence of DVT in high-risk general surgical patients not receiving prophylaxis varies between 15% and 30%, with rates of fatal PE between 0.2% and 0.9%.<sup>87–91</sup> While there are some perceived advantages of IVC filters in high-risk surgical patients in avoiding the bleeding risk associated with thromboprophylaxis and extending VTE prophylaxis past discharge, overall use of prophylactic vena cava filters for high-risk general surgery patients is not well defined.<sup>92</sup>

### *Pregnant Patients*

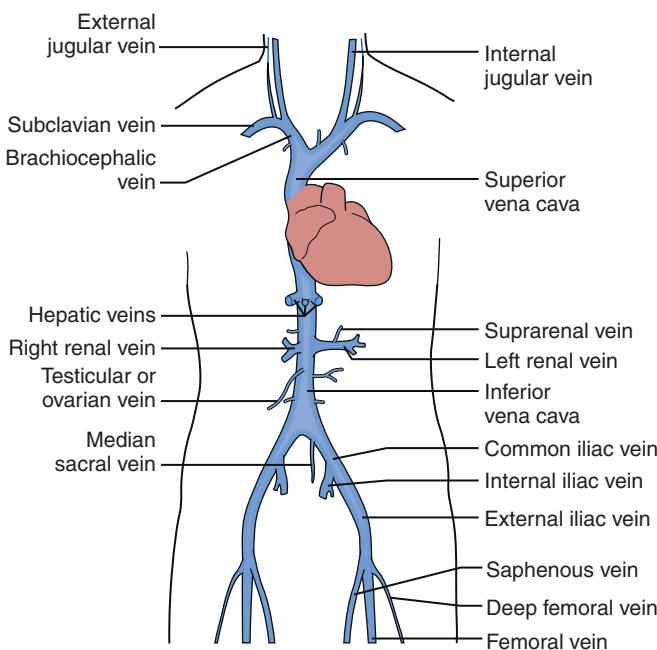
Indications for IVC filters during pregnancy follow the standard indications for non-pregnant patients, i.e. documented VTE and complications of or contraindications to anticoagulation. Anticoagulation may have to be halted in the immediate peripartum period in patients with high bleeding risk. In special circumstances such as a recent proximal DVT, especially in the setting of a significant PE, an optional IVC filter may be temporarily placed and then retrieved shortly after birth when anticoagulation can be resumed. A systematic review found that IVC filters can be used effectively to prevent PE in pregnant patients and decrease maternal mortality.<sup>93</sup>

What differs for vena cava filter placement in pregnancy is the recommendation for suprarenal positioning because of compression of the infrarenal portion of the vena cava by an enlarging pregnant uterus, especially in the third trimester. Use of jugular access may also be preferred to avoid catheterization of the vena cava adjacent to the gravid uterus. Use of optional filters seems to be an attractive alternative for providing VTE prophylaxis to high-risk patients with proven DVT, particularly those with a short-term contraindication to anticoagulation, although suprarenal insertion of optional filters can be problematic during pregnancy because of higher potential for possible migration than with permanent filters.

## ***INFERIOR VENA CAVA PLACEMENT AND RETRIEVAL***

### *Anatomic Considerations*

The normal IVC is located on the right side and is composed of four main segments in the craniocaudal direction: the hepatic, suprarenal, renal, and infrarenal segments (Fig. 153.3).



**Figure 153.3** Normal inferior vena cava anatomy.

The renal veins drain into the IVC at the L1 to L2 vertebral level, with the right renal vein shorter and more caudal and the left renal vein longer, more cephalic, and crossing over the aorta. The left gonadal vein typically drains into the left renal vein, whereas the right gonadal vein is more variable and sometimes drains into the right renal vein, directly into the IVC, or at the confluence of the IVC and the right renal vein. At this level the IVC runs posterior to the head of the pancreas and ascends posterior to the liver as the infrahepatic portion. The left, middle, and right hepatic veins and often a separate branch from the caudate lobe join the infrahepatic vena cava before it passes behind the right crus of the diaphragm to enter the right atrium.

There are some anatomic variations of the IVC that reflect incomplete involution or persistence of the cardinal veins during embryologic development (see Ch. 2, Embryology and Developmental Anatomy).<sup>94–96</sup> These variations are important to identify before filter placement because their presence and location may affect filter placement.

1. *Renal vein anomalies.* Multiple bilateral renal veins and retroaortic or circumaortic left renal vein anomalies are the most common and may be present in 5% to 7% of the population. Although a retroaortic renal vein will not affect filter placement, circumaortic renal veins may have a large confluence with the IVC or may have separate drainage. Although the tip of the filter should be positioned inferior to the lowest portion of any circumaortic vein, it is critical to identify any additional renal veins to avoid inadvertent tilting caused by entrapment of one of the filter legs.

2. *IVC transposition.* Transposition of the vena cava occurs in 0.2% to 0.5%. The left-sided IVC usually drains into the left renal vein, which crosses to the right and continues cephalad in the normal position. Filters can still be positioned in a transposed vena cava, but anatomic landmarks,

especially the location of the right renal veins, need to be accurately defined, and suprarenal vena cava placement may be preferred.

3. *IVC duplication.* Vena cava duplication is present in 0.2% to 0.3%. The right-sided IVC typically drains the right iliac vein and right renal vein, whereas the left-sided IVC, which is usually smaller in diameter, drains the left iliac veins and joins the left renal vein, where it crosses over into the right-sided vena cava. Demonstration of this anomaly is important because placement of a filter in the right IVC only may not provide adequate prevention of PE in a patient with a left-sided DVT. For duplicated vena cava anomalies, placement of a filter in each vena cava or in the suprarenal vena cava after the left renal vein crosses over is required.<sup>97</sup>
4. *IVC agenesis.* Absence of the infrarenal segment of the IVC is an extremely rare anomaly, but hepatic segmental anomalies occur when the right subcardinal vein fails to anastomose with the hepatic sinusoids and is referred to as an abnormal IVC with azygous drainage or infrahepatic interruption of the IVC with azygous continuation. In this anomaly the infrarenal IVC is normal, whereas the renal segment drains into the azygous system and right atrium through the superior vena cava. Cardiovascular defects, such as dextrocardia, atrial septal defect, and pulmonary artery stenosis, and visceral anomalies, such as polysplenia/asplenia and renal defects, are associated with this anomaly.<sup>98,99</sup> Filter placement in an enlarged azygous vein pathway in patients with this congenital anatomic variation of the IVC has also been described.<sup>100</sup>

## Technical Considerations

The reported technical success rate is usually 98% to 100% with low complication potential. Overall, acute procedure-related complications of venographic-guided filter placement include malpositioning (1.3%), hematoma (0.6%), air embolism (0.2%), arterial puncture (0.04%), arteriovenous fistula (0.02%), and pneumothorax (0.02%).<sup>101</sup> Fatal complications are rare and occur in 0.13% of insertions. Although a higher procedural mortality rate has been noted to be associated with the bird's nest filter (0.34%) than with the titanium Greenfield filter (0.15%), stainless steel Greenfield filter (0.11%), and Vena-Tech filter (0.07%), with scant reports for the other filters, most of these fatal events are more likely due to patient comorbid factors and not necessarily filter-related problems.<sup>102,103</sup>

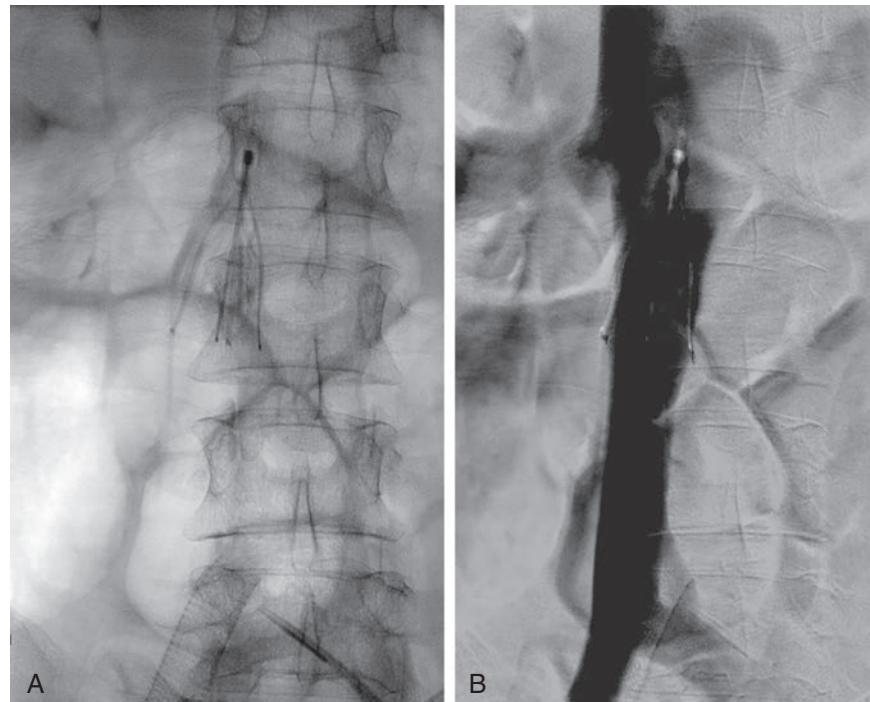
Suprarenal filter placement may be required if thrombus is present in the IVC; for malpositioning of an infrarenal filter, a duplicate IVC, and ovarian vein thrombosis; or when a filter is needed during pregnancy. In a series of 22 suprarenal filters, renal insufficiency occurred in 6%, recurrent PE in 6%, filter migration in 28%, filter fracture in 6%, and filter penetration in 6%.<sup>104</sup> In a series of 148 suprarenal filters, recurrent PE occurred in 8%, caval occlusion in 8%, filter penetration in 7%, and migration in 15%.<sup>105</sup> Although data are limited, suprarenal filter placement can be performed but should be reserved for selected patients in whom the risk for PE outweighs the potential development of these filter complications.

Bedside placement of IVC filters under either transabdominal duplex ultrasound or intravascular ultrasound guidance has been shown to be safe, effective, and reliable.<sup>106–111</sup> In a collective reported experience, 498 patients were initially imaged by transabdominal duplex ultrasound, and technical feasibility was determined in 435 patients (87.3%).<sup>112–114</sup> The procedural technical success rate for filter placement with transabdominal duplex ultrasound guidance when IVC visualization was adequate was 97.7% ( $n = 425$  patients). If visualization with transabdominal duplex ultrasound was determined to be inadequate, bedside imaging with intravascular ultrasound was then performed. Of 53 patients imaged with intravascular ultrasound, technical feasibility was determined to 96.2% ( $n = 51$  patients), and the procedural technical success rate for placement under intravascular ultrasound guidance was 96.1% ( $n = 49$  patients). The potential for malpositioned IVC filters as a result of suboptimal imaging remains a risk with bedside insertion, but this risk is low, approximately 2% to 3%. In a series of 396 bedside filter placements using IVUS in critically ill patients over a 5-year period, IVUS guidance continued to be a safe and effective option in a high-risk population, with noted time-dependent improvement in outcome measures.<sup>115</sup> Although malpositioned filters have traditionally been managed by either observation or insertion of a second filter, percutaneous retrieval and repositioning techniques have been described, even for “nonretrievable” filters, thus allowing an effective rescue technique without significant additional morbidity or mortality.<sup>116</sup>

#### Venographically-Guided Filter Placement

Use of fluoroscopy either in an operating room setting with a mobile C-arm fluoroscope or in an endovascular or radiology suite with fixed-arm imaging is the standard approach for

most filter placements. Depending on the clinical situation and the filter type used, femoral, jugular, or antecubital percutaneous access is obtained. Although some techniques described included placement of filters based on bony landmarks alone, this approach should be discouraged because there is some variability in renal vein positioning and potential venous anomalies that need to be better defined before filter delivery. Guide wire and catheter access into the vena cava is obtained for initial nonselective venography. Venographic images of the IVC are obtained for confirmation of venous landmarks, correlation with bony vertebral levels, and exclusion of the presence of thrombus at the intended deployment level. Correlation of bony landmarks with venography showed that the lowest renal vein corresponded to the L1 vertebral body in 17.3%, the L1 to L2 disk space in 36.5%, the L2 vertebral body in 34.6%, the L2 to L3 disk space in 7.7%, and the L3 vertebral body in 3.8%. Similarly, the common iliac vein confluence corresponded to the L5 to S1 disk space in 3.8%, the L5 vertebral body in 80.8%, the L4 to L5 disk space in 11.5%, and the L4 vertebral body in 3.8%.<sup>117</sup> Although guidance by nonselective venography is usually adequate for defining the iliac confluence and renal vein levels before filter deployment, additional selective venography may be an important consideration if these important venous landmarks cannot be defined. With the addition of selective venography, detection of aberrant anatomy or some abnormal finding that leads to a change in the intended location for filter deployment occurred in 11% to 30% of patients in some series.<sup>118–120</sup> Additional large venous branches in the infrarenal portion of the IVC are also identified to avoid deployment of a filter leg into the branch and prevent tilting of the filter. Based on venographic guidance, the filter is then ideally positioned with the tip at the lowest most renal vein and the base above the iliac confluence (Fig. 153.4).



**Figure 153.4** Infrarenal vena cava placement showing the anatomic relationship with lumbar vertebral bodies (A) and straight alignment with the tip of the filter at the lowest most renal vein (B).

If suprarenal filter placement is required, venographic imaging of the suprarenal vena cava is required to confirm the level of the renal veins for the distal landmark and the position of the hepatic vein confluence. Usually this will align with the T11 to L1 vertebral body levels. The suprarenal vena cava is generally larger than the IVC, and accurate diameter measurements should be made to confirm a diameter smaller than 28 mm. For suprarenal filter positioning, it is important to align the filter leg attachment point just above the most cephalic renal vein to avoid deployment of the filter hook into a renal vein, which may cause the filter to tilt. Although the level of the tip of the filter is less important, if possible it is best for it to be below the hepatic vein confluence to avoid potential hepatic vein thrombosis (Fig. 153.5).

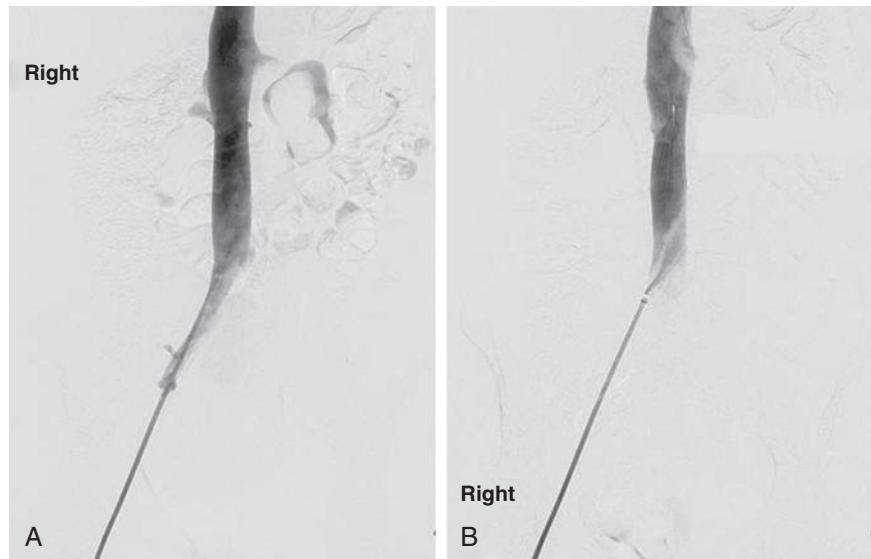
### *Transabdominal Duplex Ultrasound-Guided Filter Placement*

Transabdominal duplex ultrasound is performed to determine whether visualization of the IVC at the renal vein level is adequate in both the transverse and longitudinal axis views.<sup>121</sup> Identification of the right renal vein is important because it is usually the lowest most renal vein. In the longitudinal axis, the level of the right renal artery serves as an indirect landmark for the right renal vein. Percutaneous venous access is obtained and

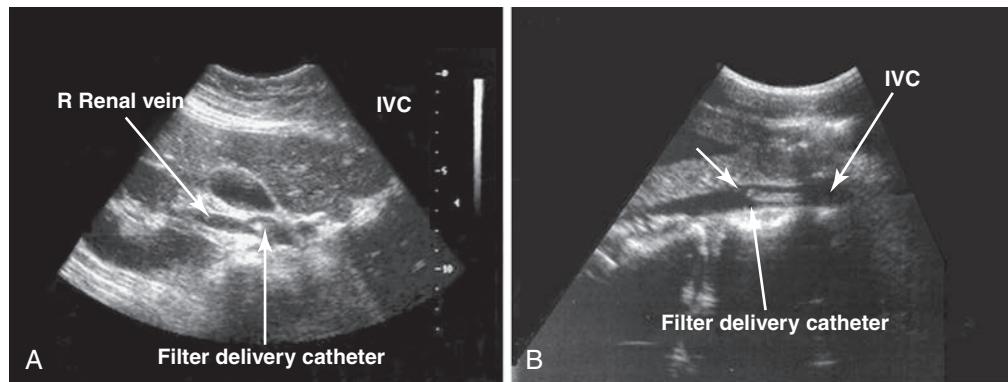
a guide wire is passed into the IVC under duplex ultrasound visualization. The introducer sheath is inserted to a level just past the renal vein confluence under duplex ultrasound guidance. For over-the-wire filter systems, the guide wire needs to be removed to be able to differentiate the end of the filter delivery catheter. The right renal vein–IVC junction is visualized transversely, and the filter delivery catheter is advanced inside the sheath to the renal vein level (Fig. 153.6). With the filter delivery catheter in the correct position, the sheath is slowly pulled back to expose the filter delivery catheter tip at the renal vein level. The filter delivery catheter can be moved back and forth to confirm its position, and when the tip of the filter delivery catheter disappears and reappears in this view, the intended deployment position has been reached. In the longitudinal view the tip of the filter delivery catheter should be easily visualized and in proper alignment. Under direct visualization with duplex ultrasound in the longitudinal view, the filter is deployed. Post-deployment duplex ultrasound imaging confirms full expansion and proper position of the filter in the IVC (Fig. 153.7).

### *Intravascular Ultrasound-Guided Filter Placement*

After adequate local anesthesia, percutaneous femoral venous access is obtained. Depending on the intravascular ultrasound system used, usually an 8-Fr sheath is needed. Although smaller

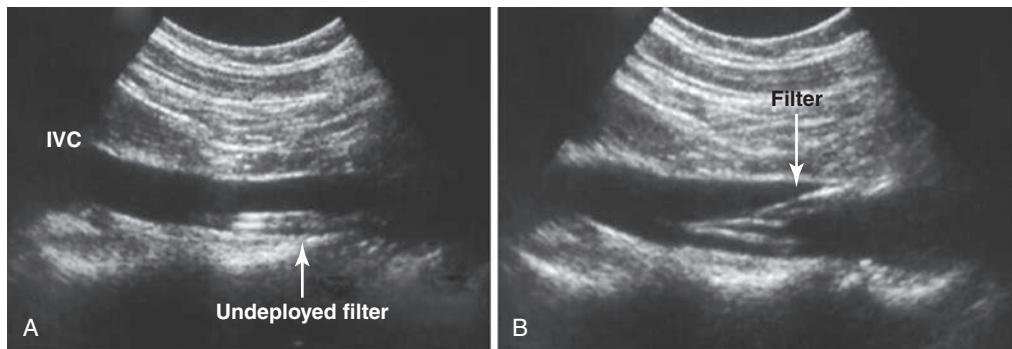


**Figure 153.5** Suprarenal vena cava filter placement in a patient with a tortuous and enlarged infrarenal segment (A). Note the base of the filter just above the renal vein origins, the tip below the hepatic vein confluence, and the filter in straight axial alignment in the suprarenal segment of the vena cava (B).

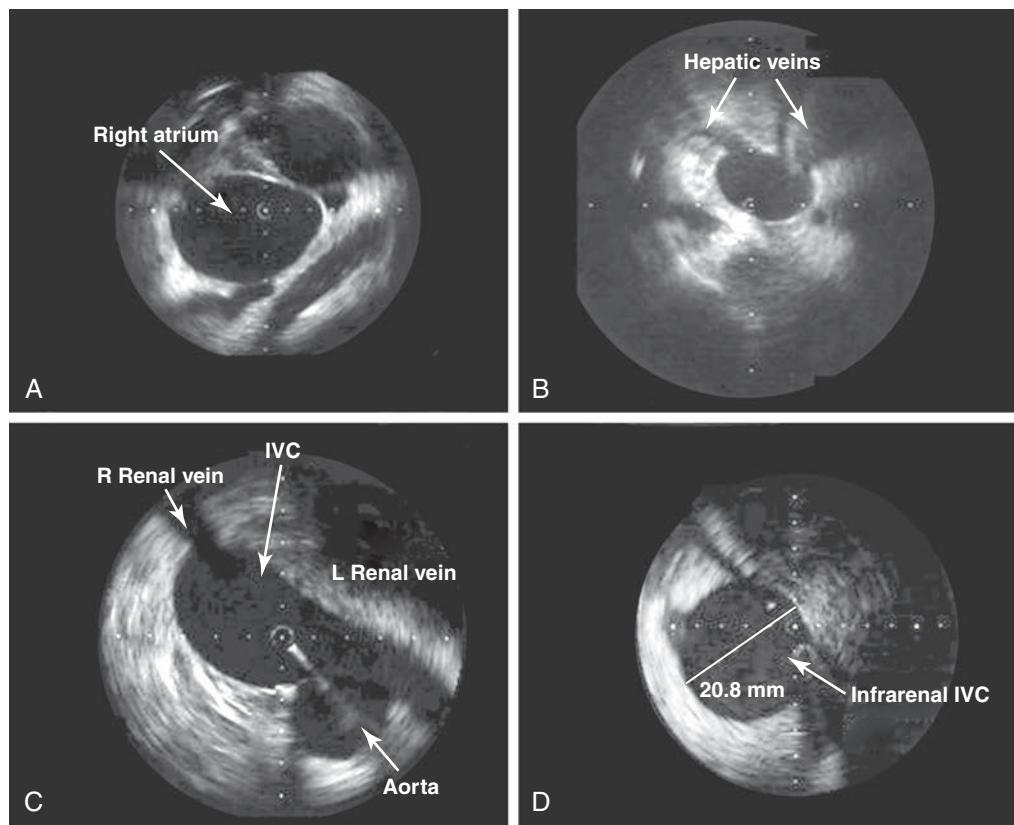


**Figure 153.6** Visualization of the tip of the filter delivery catheter at the right renal vein–inferior vena cava (IVC) junction in the transverse (A) and longitudinal planes (B) during bedside placement of the filter under transabdominal duplex ultrasound guidance. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg*. 2005;42:1027–1032.)

**Figure 153.7** Confirmation of proper filter deployment in the inferior vena cava (IVC) after bedside placement under transabdominal duplex ultrasound guidance, both undeployed (A) and after deployment (B). (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg*. 2005;42:1027–1032.)

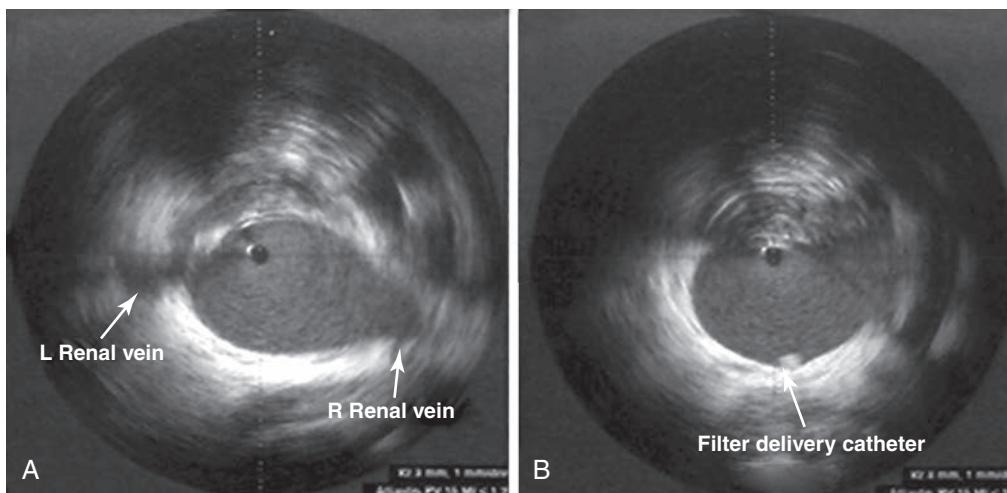


**Figure 153.8** Preprocedure imaging of the inferior vena cava (IVC) with intravascular ultrasound to identify venous anatomic landmarks at the right atrium (A), hepatic veins (B), renal veins (C), and infrarenal IVC above the iliac vein confluence (D). (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg*. 2005;42:1027–1032.)



profile intravascular ultrasound probes can be used, the image size produced with the increased-megahertz probe is generally too large for adequate visualization of adjacent anatomic landmarks. The intravascular ultrasound probe is inserted into the sheath over the guide wire and directed into the IVC to the level of the right atrium of the heart. Using a pull-back technique, the venous anatomic landmarks are sequentially identified, including the right atrium, hepatic veins, renal veins, and confluence of the iliac veins (Fig. 153.8). If the location of the iliac vein confluence is unclear, additional contralateral femoral venous access is obtained for passage of a second guide wire to allow precise identification of this confluence at the level where this second contralateral wire is visualized in the IVC. The intravascular ultrasound probe is directed just below the level of the lowest most renal vein, and IVC diameter measurements are made before proceeding with deployment of the IVC filter.

A single venous access technique can be used if the filter delivery kit sheath exceeds 8 Fr. Sheath exchange is performed over the guide wire, and the sheath is advanced to the predetermined level of the renal veins. The intravascular ultrasound probe is used to precisely direct the end of the sheath to the level of the lowest most renal vein. For filter systems with predetermined marks (such as the Günther Tulip and Celect filters), the filter delivery catheter is advanced to the mark by aligning the tip of the filter with the end of the sheath, and then the sheath is withdrawn in a “pin-pull” fashion to allow deployment of the filter at the infrarenal level.<sup>122</sup> For filter systems without predetermined marks (such as the Greenfield filter), the sheath is first pulled back over the intravascular probe a distance equivalent to the length that the filter delivery catheter extends beyond the sheath (for the Greenfield filter, this distance is approximately 7 cm) so that when the



**Figure 153.9** Visualization of the tip of the filter delivery catheter just below the right renal vein (A) at the level of the infrarenal inferior vena cava (B) during bedside placement of the filter under intravascular ultrasound guidance using a dual venous access technique. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg*. 2005;42:1027–1032.)

filter delivery catheter is loaded into the sheath, the tip of the filter will precisely align with the lowest most renal vein on deployment.

If filter placement is not feasible with the single-puncture technique or for lower profile filter systems, a dual venous access technique is required.<sup>123–127</sup> The intravascular ultrasound probe is left at a position just below the renal veins. Separate percutaneous access is obtained, preferably in the contralateral femoral vein, which allows confirmation of the iliac confluence and avoids double large sheaths in the same femoral vein. If contralateral venous thrombosis is present, the ipsilateral femoral vein adjacent to the intravascular ultrasound probe can be used, but the potential for access site thrombosis is increased. With real-time intravascular ultrasound imaging, the filter delivery catheter is directed to the level of the renal veins through the additional femoral access (Fig. 153.9). Once position of the filter delivery catheter tip is confirmed, the intravascular ultrasound probe is pulled back and the filter is deployed. The intravascular ultrasound probe can be carefully advanced to confirm apposition of the filter legs to the IVC wall, but care should be taken when advancing the filter tip to avoid dislodgement. Post-procedure plain abdominal radiographs are obtained to verify filter position and alignment.

### Filter Retrieval

Retrieval should be timed for a period when the risk for PE is low, when anticoagulation can be restarted if continued VTE treatment or prevention is required, and when retrieval can be performed safely with low complication potential. Active protocols that follow patients after filter placement and determine optimal timing of retrieval are more successful than passive protocols in terms of limiting lost to follow-up and improved filter retrieval rates, and include patient education, electronic patient tracking systems, utilization of quality care filter retrieval programs, multidisciplinary teams, and dedicated filter retrieval clinics.<sup>128–137</sup>

At the time of retrieval, the integrity of the filter should be radiographically confirmed to make sure that there are no filter-related problems that would make retrieval not possible. Venography should be performed first to determine whether

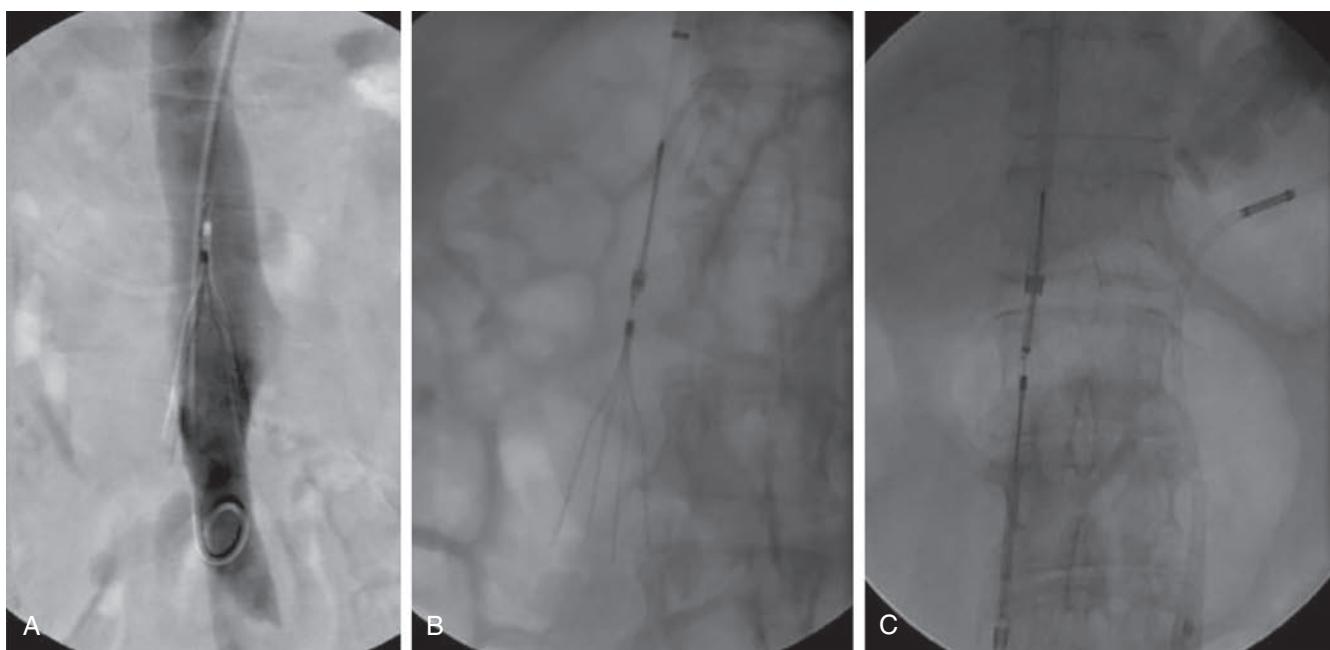
thrombus is present within the filter, in which case the filter should be left in place. Most retrieval options use catheter snare techniques, but depending on the type of optional filter used, different approaches may be required (Fig. 153.10). For the Cordis OptEase filter, percutaneous femoral access is obtained and a snare is used on the caudal hook to recapture the filter into a 10-Fr sheath. For the Cook Günther Tulip and Celect filters, percutaneous jugular access is obtained and a snare is used on the cephalic hook to recapture it into an 11-Fr sheath. For the Bard Denali filter, ALN Optional filter, and Option-Elite filter, which incorporates a hook at the apex of the filter, retrieval options using snare techniques via jugular access are also performed.

Independent of filter type, during the retrieval process difficulty releasing the filter from the IVC attachment may occur, and retrieval should be aborted if the filter does not release with modest tension. Pre-retrieval CT has shown that characteristics such as filter tip embedding, increased tilt angle, high grade filter leg perforation and longer dwell time are associated with complicated filters.<sup>138</sup> For malpositioned or difficult-to-retrieve filters, additional advanced techniques using various loop wire/catheter techniques to free up filter hook, balloon angioplasty of attachment points, bronchoscopic forceps to break up any fibrous adhesions and directly grab filter hook, and laser sheath-assisted photothermal ablation of tissue encasing filter struts have also been described and shown to be safe and effective for refractory filters<sup>139–144</sup> (Fig 153.11).

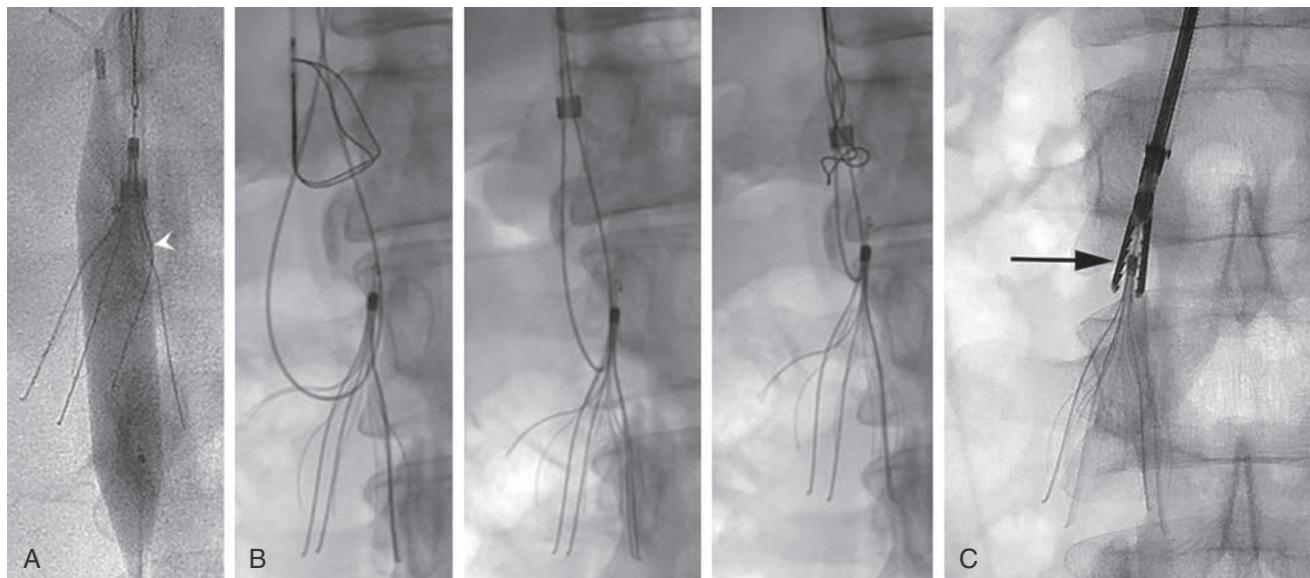
### Convertible and Temporary Filter Placement

More recent availability of convertible and temporary IVC filters may offer additional options in patients with transient VTE risk.<sup>145–150</sup> Placement, conversion and removal techniques for these devices are extensions of those described above for traditional filter designs.

VenaTech Convertible Filter placement requires access either from right femoral vein or right jugular vein to avoid tortuosity of left iliac or jugular access. A pre-deployment cavogram is performed to confirm patency, identify any venous anomalies, and mark the level of renal veins. The filter dilator/sheath is positioned slightly past the intended



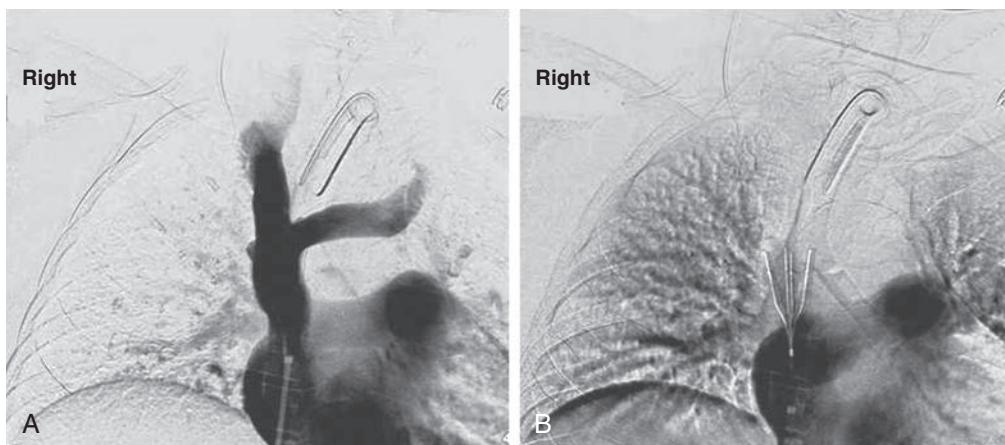
**Figure 153.10** Pre-retrieval venogram showing minimal filter tilt and no thrombus within the filter (A). Successful catheter snare capture of the apical filter hook (B) and retrieval of the filter via the sheath (C).



**Figure 153.11** Advanced filter retrieval techniques using balloon displacement (A), catheter loop wire snaring of proximal filter (B), and bronchoscopic forceps (C). (Reprinted with permission from Desai KR, Pandhi M, Seedial S, et al. Retrievable IVC filters: comprehensive review of device-related complications and advanced retrieval techniques. *RadioGraphics*. 2017;37:1236–1245; and Kuyumcu G, Walker TG. Inferior vena cava filter retrievals, standard and novel techniques. *Cardiovasc Diagn Ther*. 2016; 6(6):642–650.)

filter deployment site, the filter cartridge is loaded allowing advancement of the filter using a pusher to the end of the sheath under fluoroscopy, then the filter position is adjusted so the tip will be at the lowest renal vein, with deployment performed by withdrawing the sheath as the pusher is stabilized. Final filter position is confirmed with venography. Once filtration is no longer clinically indicated, the VenaTech Convertible Filter can be converted to an open configuration percutaneously by unlocking the mechanism that secures the filter head to the filtering legs. Right jugular vein access is

obtained and repeat cavogram is performed to make sure the filter is clear of thrombus. Using an intravascular snare, the hook of the filter cone is secured and the snare catheter advanced down over the hook. The snare catheter is straightened with slight upward tension, and while maintaining traction, the filter head is released and removed, thereby allowing the filter legs to open and retract to the vena cava wall. If there is incomplete opening of the filter legs due to fibrin strands, additional catheter manipulation or balloon angioplasty may be required to completely open all filter legs.



**Figure 153.12** Venogram of the superior vena cava (A) followed by superior vena cava filter placement with the filter base just distal to the confluence of the brachiocephalic veins and the tip at the junction of the right atrium (B).

The Sentry filter when deployed has a nitinol frame that expands to appose the IVC wall leading to incorporation of a portion of the filter into the intima, and a bioabsorbable filament that will hydrolyze after 60 days thereby releasing the filter arms from the filtering cone. The Sentry filter comes preloaded in a bidirectional cartridge, which can be inserted through a 7-Fr sheath for deployment in the infrarenal position by means of a femoral or jugular approach by pinning the filter with a pusher while sheath is withdrawn. However, because of the bioconversion mechanism, additional subsequent conversion procedure is not needed.

As a temporary filter, the Mermaid Angel catheter is a retrievable vena cava filter permanently attached to a central venous access catheter. The catheter is designed to constrain the IVC filter component in an unexpanded state for delivery to the IVC and to function as the sheath for retrieval of the IVC filter. Placement is via standard femoral vein access. The catheter is inserted up to its hub which will align the filter portion in the IVC. The coaxial locking hub is then pulled back to deploy the filter portion. Position can be confirmed with plain abdominal radiography confirming the tip of the filter at L2 level. The catheter has markers that can be used if pullback is needed. The catheter has the dual function of central venous access and filtration. Because the filter remains attached to the catheter, bedside retrieval is facilitated allowing recapture of the filter portion prior to removal.

## SUPERIOR VENA CAVA FILTERS

Upper extremity DVT is becoming increasingly common, especially with the expanding use of central venous access, pacemakers, and implantable defibrillators. Other contributing factors, including thoracic outlet-related venous occlusion, malignancy, congestive heart failure, sepsis, and thrombophilia, have also been implicated (see Ch. 150, Acute Upper Extremity and Catheter-Related Venous Thrombosis). The risk for PE with upper extremity DVT is approximately 5% to 10% in most series, but risk as high as 28% and several cases of fatal PE have been reported.<sup>151–155</sup> Although standard treatment of upper extremity DVT is anticoagulation, when anticoagulation is contraindicated or complications of anticoagulation develop,

superior vena cava placement may be an option in selected cases, with experimental data on the use of filters in the superior vena cava based on animal models, case reports, and case series growing.<sup>156–158</sup> Because of superior vena cava anatomic constraints, conical filters with filter leg hook attachment points are preferred over more rigid filter designs. Although use of permanent Greenfield filters for superior vena cava placement has mostly been described, there have been some reports of optional filter use and retrieval.<sup>159–161</sup> Until a specifically designed filter for superior vena cava use is available, current IVC filters may continue to be adapted to this use.

Superior vena cava filter placement can be performed via jugular or femoral percutaneous venous access. For proper filter orientation, a jugular set is used for femoral insertion and a femoral set for jugular insertion. If inferior and superior vena cava filters are being placed simultaneously, the sequence of filter placement is dependent on the site of venous access, with the most distal filter requiring placement first. Any previously placed central venous catheters need to be removed or retracted before placement to avoid entrapment. Detailed venography is performed to define the anatomic landmarks of the superior vena cava. A duplicated superior vena cava occurs in approximately 0.1% to 0.3% of the population and can be a potential bypass for emboli if not identified.<sup>162</sup> Thrombus or occlusion of the superior vena cava and azygos or hemiazygos enlarged collaterals needs to be assessed if present. The intended filter position for filter leg attachment is just at the confluence of the innominate veins and is defined by venography (Fig. 153.12). The filter length deployed must be taken into consideration to avoid extended protrusion into the right atrium. Superior vena cava measurements are based on preprocedure computed tomography, venography, or intravascular ultrasound, and filter placement in a superior vena cava with a diameter greater than 28 mm is not recommended. With correct positioning and sizing, the filter delivery catheter is passed through the sheath and the filter deployed.

In the largest experience of superior vena cava filter placement for upper extremity DVT including 72 patients, with a mean follow-up of 22 months, complication occurred in 1.3% and included filter malpositioning without migration, but no PE.<sup>163</sup> Although mortality in this series was 47%, causes of

death were unrelated to filter placement and were more reflective of the serious illness in this patient population. Others have documented complications, including superior vena cava perforation, cardiac tamponade, dislodgement by central line placement, guide wire entrapment, superior vena cava thrombosis, pneumothorax, and erosion into the thoracic aorta.<sup>164</sup> Based on the limited available evidence, superior vena cava filter placement is a safe and effective alternative for prevention of PE in selected patients with upper extremity DVT when anticoagulation is not possible.

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# Varicose Veins: Surgical Treatment

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In the past, venous disease received relatively little attention in the public arena and in vascular training programs, despite the fact that it is more prevalent in the United States than coronary artery disease, peripheral arterial disease, congestive heart failure, and stroke combined.<sup>1</sup> The latter half of the 20th century saw dramatic advances in diagnostic testing; however, surgical treatment of varicose veins benefited from only modest refinements. The 21st century launched a resurgence of interest and innovation in venous disease. Increased awareness of thrombotic and venous reflux disease has been coupled with advances in the diagnosis and treatment of acute deep venous thrombosis (DVT) (see Chs 146–152), and endovenous ablation (EVA) techniques for the treatment of chronic venous disease have

proved appealing to patients and physicians alike (see Ch. 155, Varicose Veins: Endovenous Ablation and Sclerotherapy). Although sclerotherapy and EVA occupy preeminent roles in the contemporary management of superficial venous disease, surgical approaches remain relevant when applied appropriately. In addition to treatment of the great saphenous vein (GSV) and tributary varicosities, this chapter emphasizes management of the small saphenous vein (SSV) and other veins of the popliteal fossa; these veins are important contributors to chronic venous insufficiency (CVI), and they are particularly well suited for treatment with open surgical techniques. In a guidelines publication, Gloviczki et al.<sup>2</sup> recommended specific diagnostic and treatment steps for varicose veins, with the strength of

**TABLE 154.1** Varicose Vein Guidelines

Number	Guideline	Strength of Recommendation	Quality of Evidence
9.1	We suggest compression therapy using moderate pressure (20–30 mm Hg) for patients with symptomatic varicose veins.	2	C
9.2	We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation.	1	B
9.3	We recommend compression as the primary therapeutic modality for healing venous ulcers.	1	B
11.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery.	1	B
10.1	For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	2	B
10.3	For treatment of small saphenous incompetence, we recommend high ligation of the vein at the knee crease, about 3 to 5 cm distal to the saphenopopliteal junction, with selective invagination of the incompetent portion of the vein.	1	B
10.7	We recommend ambulatory phlebectomy for treatment of varicose veins performed with saphenous vein ablation, either during the same procedure or at a later stage. If general anesthesia is required for phlebectomy, we suggest concomitant saphenous ablation.	1	B
10.5	We suggest that preservation of the saphenous vein using the ambulatory conservative hemodynamic treatment of varicose veins (CHIVA) technique be used only selectively in patients with varicose veins and only when performed by trained venous interventionists.	2	B
10.6	We suggest that preservation of the saphenous vein using the ASVAL under local anesthesia procedure be used only selectively in patients with varicose veins.	2	C

ASVAL, ambulatory selective varices ablation; CHIVA, Cure Conservatrice et Hémodynamique de l'Insuffisance veineuse en Ambulatoire.

Modified from Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(Suppl):2S–48S.

recommendation and quality of supporting evidence. Recommendations specific to the open treatment of axial reflux and tributaries are reported in Table 154.1.

## DECISION MAKING

### Pathophysiology and Natural History

Varicose veins are defined as “subcutaneous veins in the lower extremities which are dilated to  $\geq 3$  mm in diameter in the upright position”.<sup>3</sup> They can occur in the axial superficial veins (GSV and SSV) and/or in any of their tributaries. Current thinking is that they represent primary venous disease and occur as a result of structural weakening of the vein wall, which can be focal or diffuse. This weakening is most likely the result of underlying morphologic or biochemical abnormalities. Valvular incompetence in the superficial veins is usually present, which may represent an inciting factor or a secondary result of vein wall dilation. Varicose veins can also occur as a result of secondary venous disease (post-thrombotic).<sup>3,4</sup>

Varicose veins constitute a progressive disease; remission does not occur except after pregnancy. Venous disease produces symptoms which frequently prompt the patient to seek medical care. Symptoms and signs include lower extremity pain and swelling, particularly after prolonged standing, and a feeling of heaviness in the lower extremities. The most frequent complications are superficial thrombophlebitis, bleeding from

thin-walled varices, eczema, and skin ulceration. Depending on his or her age, general health condition, and symptomatology, a patient with varicose veins may be offered one or more of the following: no treatment, conservative management with compression, venotonic medications, sclerotherapy, or surgical treatment (open or endovascular). CVI is common in western societies and affects approximately one-third of the adult population. Fortunately, only a small proportion of these patients develop the most severe form of venous insufficiency – namely venous ulcers. Though affecting only a small fraction of the population with venous insufficiency, venous ulcers are reported to occur in up to 4% of people older than 65 years.<sup>5,6</sup> Even though nonoperative management of venous disease – including compression, elevation, and skin care – is beneficial,<sup>7</sup> such therapy does not correct the underlying pathology, allows recurrence of symptoms if patients are unable to comply with the elevation and compression regimen, and is associated with a high incidence of recurrent ulceration.

### Treatment Options

Invasive treatment of superficial venous incompetence can be accomplished by techniques that remove, ablate, or ligate the refluxing venous segment. Current options for eliminating this target reflux include high ligation, ligation and stripping (L&S), EVA, sclerotherapy, chemical ablation (glue), and ambulatory phlebectomy. Each of these techniques has a role in

the treatment of patients with symptomatic varicose veins. Vascular surgeons should be comfortable in applying these procedures in a thoughtful manner based on the patient's individual needs. As requested by insurers, a trial of compression treatment is generally employed with compression hose (20–30 mm Hg) for patients in CEAP classification C2 to C4 to determine whether the patient's symptoms are relieved. For patients with an ulcer (C6), compression therapy with 30–40 mm Hg garments is recommended.

## Patient Risk Assessment

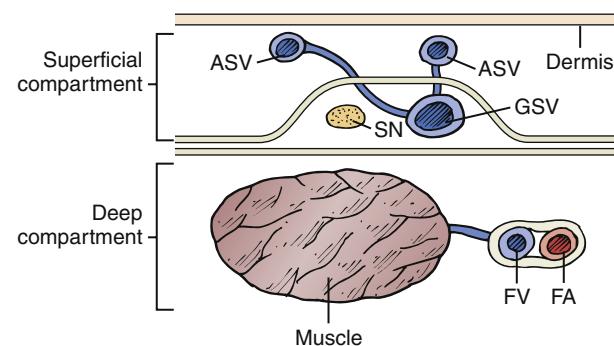
When considering any intervention, the patient's medical status and venous anatomy should be considered. Because venous insufficiency results in chronic discomfort and stasis changes that may be ameliorated by compression garments, skin care, and lifestyle changes, venous surgery must always be considered somewhat elective; accordingly, prudent consideration of medical factors is indicated. Patients who are fit, with longer life expectancies, have reduced risk for complications from the procedure as well as a longer period during which the benefits may accrue. The advent of less invasive treatment by EVA has expanded the range of ages being treated; indeed, patients over 70 years of age are now routinely treated safely.<sup>8</sup> Patients with severe comorbid conditions are typically managed with conservative measures. In recognition of the shorter recovery time and reduced pain and morbidity, the Varicose Vein Guidelines (VVGL) recommend endovenous thermal ablation over open treatment of saphenous incompetence (see Table 154.1, VVGL 11.2), for most patients.

## Anatomic Considerations

The lower extremity venous system is unique in its need to overcome gravity while returning blood toward the heart. The calf muscle pump and vein valve system normally accomplish this task efficiently. The thin vein valves float open in the venous stream during prograde flow. During calf muscle relaxation, retrograde flow and higher supravalvular pressure cause the valve cusps to oppose, so that reflux is prevented. These valves can be disrupted by thrombotic events (secondary), can be congenitally absent or atretic, or can become dysfunctional over time (primary). The anatomic classification of CVI is important because it links the location of CVI with its subsequent clinical management.

### Great Saphenous Vein

The GSV arises anterior to the medial malleolus and courses obliquely and posteriorly as it crosses the anteromedial surface of the calf. At or below the knee joint, the posterior arch vein joins. A solitary vein is found in the calf in two-thirds of cases, whereas a duplicated system is present in the remainder. The GSV at the calf level is usually anterior-dominant. As the main saphenous trunk continues in a slightly more superficial plane around the knee joint, an anterior accessory vein often merges. The GSV then courses cephalad on top of the deep fascia and deep to the superficial fascia (Fig. 154.1). The GSV may run



**Figure 154.1** The saphenous compartment is bounded by deep and superficial layers of fascia. Tributaries to the saphenous vein pierce the superficial fascia, and it is they that become varicose. ASV, accessory saphenous vein; FA, femoral artery; FV, femoral vein; GSV, great saphenous vein; SN, saphenous nerve.

within this envelope for the entire length of the thigh or may enter at some distance above the knee. If the GSV is “duplicated,” both veins run in this fascial envelope; there may be anterior and posterior accessory veins that enter the fascial envelope to join the GSV, but they exist primarily in the extra-fascial plane. Three anatomic variants have been characterized and are demonstrated in Figure 154.2. Kupinski reported on duplex ultrasound (DUS) evaluation of the GSV in nearly 1500 limbs.<sup>9</sup> At the thigh level in 60% of the limbs the GSV had a single medial-dominant system, whereas a branching double system was observed in nearly 20%, a complete double system in 10%, a closed-loop system in 10%, and a lateral-dominant system in 8%.

### Small Saphenous Vein

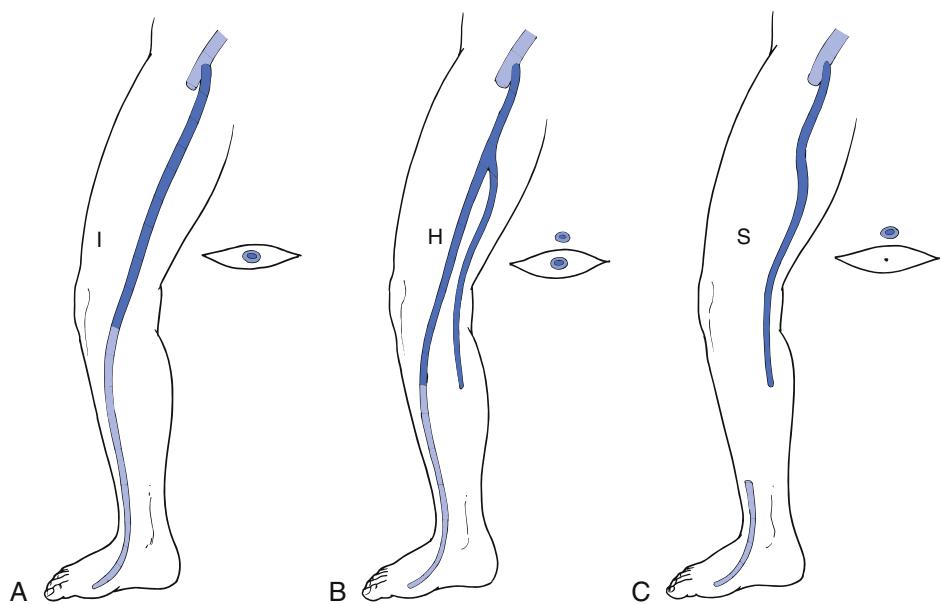
The confluence of the SSV with the popliteal vein has long been recognized as variable (Fig. 154.3). Approximately 33% of SSVs terminate at a (high) above-knee popliteal vein site; a low termination site is unusual (<10%).<sup>10–12</sup> We have observed that DUS examination of the SSV allows exact localization of the saphenopopliteal junction for appropriate placement of the skin incision.

### Gastrocnemius Veins

The gastrocnemius veins arise from both the medial and lateral heads of the gastrocnemius muscle and may join the popliteal vein directly or merge with the SSV to form a common trunk before joining the popliteal vein.<sup>13</sup> Hobbs and Vandendriessche reported a 20% incidence of incompetence of the gastrocnemius veins,<sup>13</sup> a proportion similar to that described by Gillet and colleagues in 180 operations for SSV reflux.<sup>14</sup> If the SSV is ligated distal to its junction with a common trunk and an incompetent gastrocnemius vein, persistent reflux will occur.

### Intersaphenous Vein

The second important non-SSV vein of the popliteal fossa, the intersaphenous (formerly named Giacomini) vein, has been classically described as coursing up the posterior medial aspect of the thigh.<sup>15</sup> The intersaphenous vein usually arises off the SSV either



**Figure 154.2** Anatomic types of the great saphenous vein (GSV) with respect to the fascial envelope. (A) *I* type. The GSV is present within the fascial envelope along its entire length. (B) *H* type. There is a subcutaneous collateral running parallel and superficial to the main saphenous trunk (left). (C) *S* type. The caudal portion of the GSV in the thigh is atretic, and the extrafascial tributary is dominant.

as a branch or as a trunical continuation of the SSV, and courses along a subfascial plane to join the GSV more frequently (64%) than the deep venous system (45%).<sup>15</sup> Reflux is less frequent in the intersaphenous vein than in either saphenous vein. The proportion of limbs with intersaphenous vein incompetence, however, is greatly increased when incompetence of the SSV is found alone (odds ratio of 11.94) or combined with GSV incompetence (odds ratio of 11.7),<sup>15</sup> and this vein may facilitate reflux between the GSV and SSV.<sup>16</sup> In our series a dominant and incompetent intersaphenous vein that formed a common trunk with the SSV was observed in 8.5% of limbs undergoing surgery for SSV reflux. Delis' DUS study of 818 limbs also showed a low 3% incidence of popliteal area veins,<sup>17</sup> the third non-SSV vein of the popliteal fossa. By contrast, Dodd's classic study of 444 operations in the popliteal fossa showed popliteal area veins in 177 cases (40%), and in 60% they were branches of the SSV (50%) or gastrocnemius veins.<sup>18</sup> They directly entered the popliteal vein in 37% of cases.

### Neurovascular Relationships in the Popliteal Fossa

Surgical exploration of the popliteal fossa can be associated with postoperative neurologic disability and, rarely, disastrous complications. Two motor nerves, the tibial and occasionally a low-lying sciatic nerve, can be juxtaposed near the SSV and its termination with the popliteal vein. The tendon-like appearance of both motor nerves may falsely encourage the surgeon to perform a less delicate dissection or to retract more vigorously in a deeper plane than would be carried out when a nerve is clearly identified. The sensory sural nerve courses superficial to the SSV or may intertwine with it, and this nerve can also be damaged by retraction or dissection.

### Perforating Veins

Perforating veins connect the superficial venous system to the deep venous system and are discussed in detail in Chapter 158, Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence.

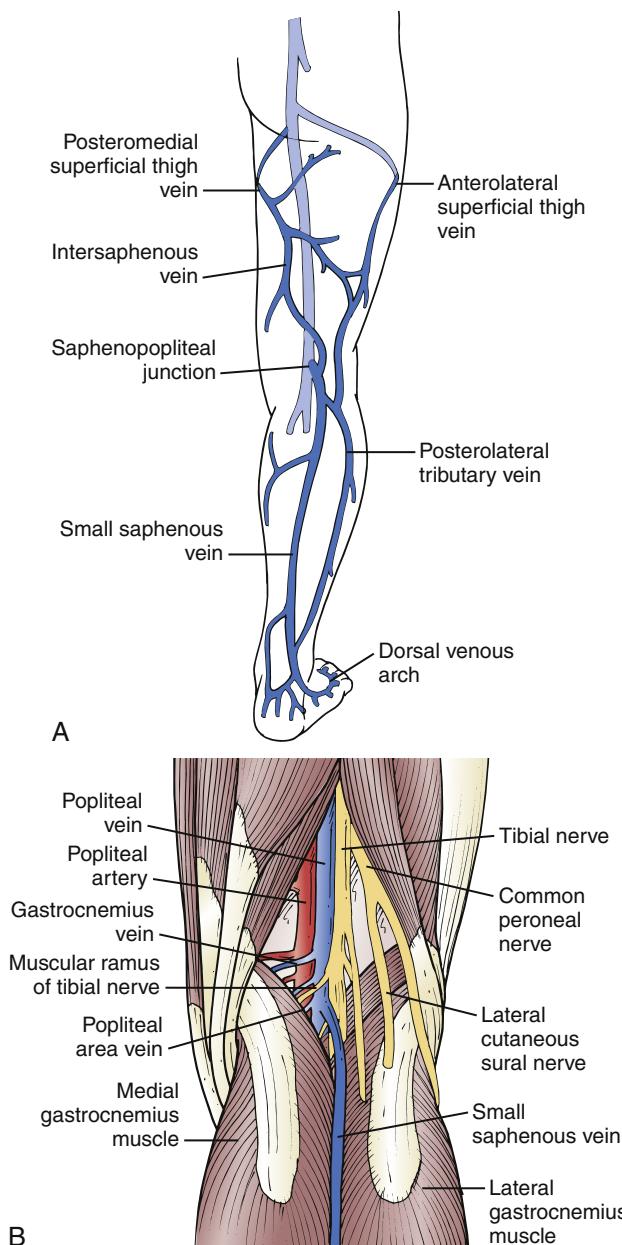
## SURGICAL TECHNIQUES

Surgery for superficial varicose veins should be individualized according to the patient's preoperative evaluation. A combination of ligation, axial stripping, and stab phlebectomy may be applied as needed to the GSV, SSV, tributary veins, and perforating veins. Technical considerations for each of these techniques are summarized in the following sections.

After preoperative evaluation elucidates the necessary scope of surgery, a decision is made regarding the appropriate method of anesthesia and site of service. Any of the surgical procedures can be performed under general or regional anesthesia in an operating theater. This level of care may be appropriate for patients undergoing multiple incisions, requiring extended procedure times or those with medical or anxiety issues requiring monitoring by an anesthesiologist. However, tumescent local anesthetic techniques, with or without sedation, allow essentially any of these vein operations to be performed in an office procedure room. Ultimately the decision is influenced primarily by local resources, physician experience, and patient expectations. Preoperative marking of the patient in the standing position is important whenever stab phlebectomy or direct perforator ligation is contemplated. Such marking is essential because visualization of varicose tributaries may be impossible once the patient is prepared and the leg elevated.

### High Ligation of the Great Saphenous Vein

The GSV is most easily approached through an oblique incision parallel to the groin crease. DUS-guided marking of the saphenofemoral junction allows for precise incision placement minimizing incision size and subcutaneous dissection. The incision starts over the femoral artery and extends medially, the thicker the subcutaneous layer the longer the incision will need to be. As the subcutaneous tissue is split, the main trunk of the GSV is identified. A self-retaining retractor is helpful, and the



**Figure 154.3** (A) The small saphenous vein dominates the posterolateral superficial venous drainage and originates in the dorsal venous arch. At the posterolateral aspect of the ankle, it is intimately associated with the sural nerve. Note the important posterolateral tributary vein and the posterior thigh vein, which ascend and connect the small sphenous venous system with the GSV. The anterolateral superficial thigh vein and the posterolateral tributary vein can be very important in congenital venous anomalies, such as Klippel–Trénaunay syndrome. (B) The most common neurovascular configuration of the popliteal fossa, although the site of anastomosis is highly variable.

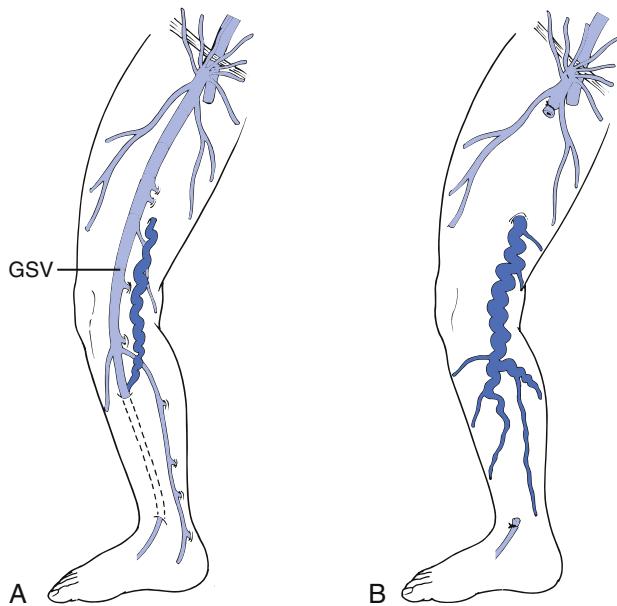
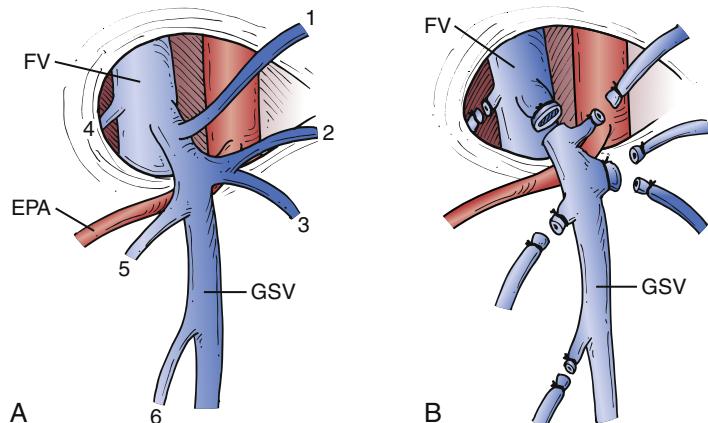
plane over the sphenous vein is extended toward the sphenofemoral junction. This anterior plane is generally free of encumbrances, except that care should be taken to ligate a small branch of the femoral artery, which frequently crosses anterior to the sphenofemoral junction and can cause troublesome bleeding. Each of the tributaries is divided and ligated because the sphenofemoral junction must be clearly identified. Failure to clearly define the sphenofemoral junction has resulted in disastrous injuries to the femoral vein or artery.<sup>19,20</sup>

There are six main tributaries joining the GSV near its termination (Fig. 154.4). However, the number and position of these tributaries vary greatly; therefore, it is necessary to dissect the femoral vein 2 cm above and below the confluence to be sure that no additional tributaries join the femoral vein directly. Lateral and medial accessory sphenous veins may enter the main trunk between 2 and 20 cm below the confluence. When stripping is planned, these distal tributaries are avulsed, but if ligation alone is planned, the dissection should be extended caudal for approximately 10 cm to ensure division of these hidden tributaries. High ligation of the GSV is performed close to the femoral vein. Double ligation is generally performed on the proximal stump with the second ligation being a suture ligature. Care should be taken to avoid narrowing the femoral vein. Equally important is to avoid leaving a long stump with a risk for thrombus formation and potential embolism. Alternatively, the GSV may be divided close to its termination and the femoral side closed with a two-layered monofilament suture. Whichever method is used to secure the GSV stump, we recommend involution of the cut end of the GSV to prevent exposure of the endothelium to the subcutaneous tissue, which may reduce neovascularization. The incision is closed in layers by approximating the subcutaneous tissue with absorbable suture and the skin with absorbable subcuticular sutures. The requirement for sufficient exposure of the sphenous vein and its tributaries should be tempered by data suggesting that extensive dissection results in upregulation of vascular growth factors that lead to neovascularization, which in turn is believed to cause recurrent varicose veins.<sup>21</sup> Although ligation of all SFJ tributaries has for decades been a hallmark of a well-executed High Ligation (HL), this premise has been brought into question by Ganesini.<sup>22</sup> He reported on a series of 867 patients who underwent GSV HL with or without ligation of SFJ tributaries. At 5-year DUS follow-up, tributary ligation resulted in a higher recurrence rate (7.4% vs. 1.1%), more frequent direct stump connections (3.7% vs. 0.2%), and more newly developed pelvic shunts (3% vs. 0.5%). These data suggest that there may be merit to a targeted approach wherein refluxing SFJ tributaries should be ligated at the time of HL, however sparing normal tributaries may yield long-term benefits.

### Great Sphenous Vein Stripping

GSV stripping is the central component of the classic operation for varicose veins. Recurrence rates are markedly reduced when the GSV is stripped as opposed to when high ligation is performed alone<sup>23,24</sup>; therefore, stripping is usually performed in conjunction with ligation. During preoperative marking for L&S of the GSV, the surgeon should review the extent and distribution of reflux disease. The GSV in the thigh is incompetent in only about two thirds of patients undergoing surgery for symptomatic varicose veins or CVI.<sup>25,26</sup> In addition, unless the below-knee sphenous vein is obviously incompetent and varicose, there is no need to remove it. When whole leg GSV reflux was treated with AK GSV L+S or ablation and the calf treated with tributary phlebectomy alone, Hong reported that at 1-year DUS follow-up 49% of the patients resolved the

**Figure 154.4** (A) The most common arrangement of tributary veins at the saphenofemoral junction. The external pudendal artery (EPA) usually runs between the great saphenous vein (GSV) and the femoral vein (FV), but it may pass above the GSV and is then more susceptible to injury during dissection. 1, Inferior epigastric vein; 2, superficial circumflex iliac vein; 3, lateral accessory saphenous vein; 4, deep external pudendal vein; 5, superficial external pudendal vein; 6, medial accessory saphenous vein. (B) All vessels must be individually divided and ligated to prevent recurrence. If no stripping of the GSV is to be performed, the proximal 5 to 10 cm of the GSV should be resected.



**Figure 154.5** Stripping of a competent great saphenous vein (GSV) serving as runoff for a varicose collateral vein (A) results in postoperative worsening of the collateral varicosity because of resistance to outflow (B).

below-knee (BK) reflux. He further noted that preoperative vein diameter and reflux time did not predict postoperative resolution of reflux. Furthermore he showed marked clinical improvements (VCSS and AVVSS) at 6 and 12 months which was not affected by the postoperative BK GSV competence.<sup>27</sup> Similarly, when H- or S-type anatomy is defined (see Fig. 154.2), it is not necessary to treat normal or atretic segments of the GSV; in fact, such treatment may worsen the clinical situation by removing competent drainage paths (Fig. 154.5). This targeted approach to stripping leaves normal distal veins, avoids injury to the saphenous nerve, and results in less postoperative pain and bruising without compromising the goals of surgery.<sup>27–29</sup> Incompetent accessory saphenous veins should be addressed during the initial surgery. It is likely that the high recurrence rates noted for vein stripping in the past have resulted in part from unrecognized accessory veins. The availability of

DUS and awareness of the issue may result in improved efficacy in the future; thus preoperative duplex marking is essential in modern-day operations on the great or small saphenous vein.

After flush ligation is performed, a transverse venotomy is created and a stripper is passed distally. Wire strippers or disposable plastic strippers are commonly used. In most cases the presence of reflux allows easy passage of the stripper to the level of the knee. A second small incision is made over the palpable stripper near the knee. The caudal incision is made transversely, and the subcutaneous tissues are dissected to allow recovery of the saphenous vein. This top-down passage of the stripper facilitates identification of the saphenous vein at the knee, allows for a small lower incision, and avoids the potential for the stripper passed from below to enter the femoral vein through a thigh perforator and cause the femoral vein to be mistaken for the saphenous vein. The GSV should be stripped in a downward direction, which results in improved avulsion of tributaries and diminished injuries to the saphenous nerve.<sup>30</sup> To avulse the vein with the endoluminal stripper, one must affix the catheter to the most cephalad portion of the vein. This may be accomplished by attaching the classic stripper head (Fig. 154.6) to the top of the disposable stripper after first placing a silk ligature around the vein and the stripper just below the head. Using the smallest head size minimizes tissue injury and bruising, whereas a larger head size will improve the chance of recovering the entire vein and the tributary segments. A long trailing silk suture is attached at the stripper head and drawn through the tunnel with the vein. After the tributaries have been avulsed and the caudal GSV has been divided and ligated, the vein and stripper are drawn back up to the groin incision, thereby minimizing the size of the distal incision.

Although many variations of this technique have been described, the most common alternative approach involves invagination of the GSV into itself. This technique may be performed with a disposable plastic Codman vein stripper without attaching a stripper head but instead intussuscepting the vein, as shown in Figure 154.7.<sup>31</sup> Alternatively, a reusable metal cannula may be used in a similar fashion.<sup>32</sup> This technique minimizes the diameter of the tunnel created by vein removal in an effort to diminish local trauma to soft tissues and nerves. However, the saphenous vein is susceptible to tearing at the

sites of tributary confluence; thus the technique could result in incomplete stripping of the target vein. Consequently, when the vein is removed, it should be unfurled and compared with the planned treatment length. When the vein is torn during stripping, the caudal end typically remains in place at the lower

incision. In this case, if a trailing heavy silk suture has been affixed to the stripper (see Fig. 154.7), a second inversion technique can be performed in the opposite direction (Fig. 154.8) (see Table 154.1, VVGL 10.1).

## Adjunctive Considerations for Stripping Procedures

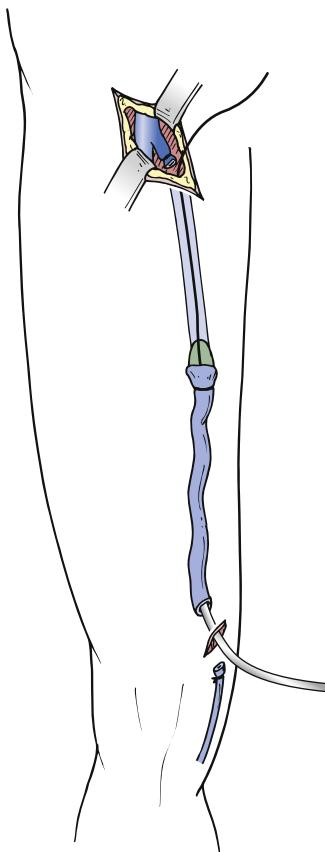
Saphenous vein stripping is commonly perceived as a painful and morbid procedure by patients and referring physicians alike. The memory of large incisions, extensive bruising, significant pain, and prolonged disability from antiquated techniques is a major concern of patients and referring physicians. However, these undesirable effects can be ameliorated by using relatively simple adjunctive techniques.

### Ultrasound Guidance

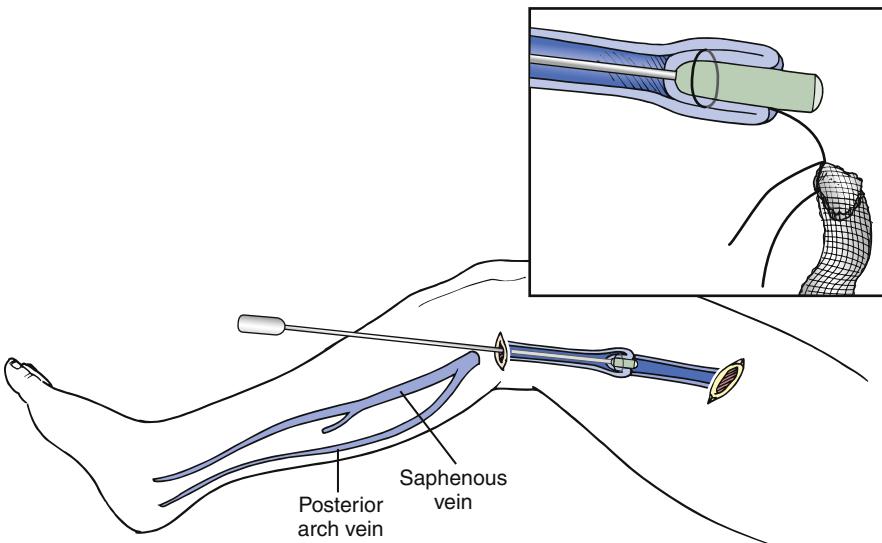
DUS should be used to mark the saphenofemoral or saphenopopliteal junction, as well as the course and distal location of the saphenous vein at the knee. This allows precise placement of the skin incision and permits very small incisions with limited subcutaneous dissection. Incompetent accessory veins should also be marked.

### Tumescent Anesthesia

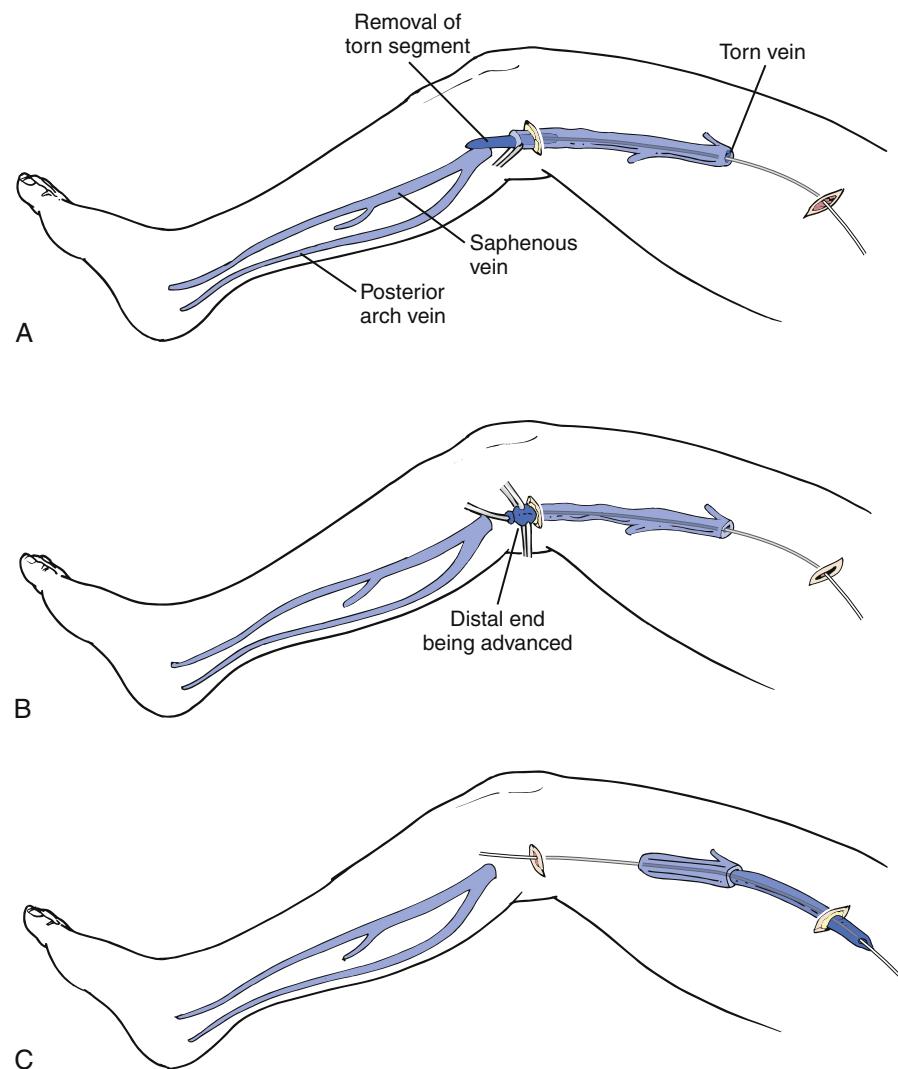
The GSV in the thigh lies within a fascial envelope for most of its length, allowing a modest infusion of tumescent anesthesia (200–500 mL) to fully surround the saphenous vein. We use a combination of 40 mL of 1% lidocaine with epinephrine, 10 mL of sodium bicarbonate, and 450 mL of normal saline in the tumescent mixture, which is administered under duplex scanning using an infusion pump. This technique provides excellent anesthesia and allows vein stripping to be performed under straight local anesthesia in the office. In addition, the vasoconstriction from the epinephrine and the direct compressive effects of the instilled volume result in rapid hemostasis from the avulsed tributaries and a marked decrease in postoperative ecchymosis and pain.



**Figure 154.6** The intraluminal stripper is passed distally, the vein fixed by ligature proximally, and the stripping head secured. Stripping distally minimizes lymphatic and tributary damage and avoids avulsion of the saphenous nerve branch. When the stripper head reaches the distal incision, the distal vein fixed to the stripping device by ligature can be recovered through the proximal incision, thereby minimizing surgical trauma at the lower incision.



**Figure 154.7** The endoluminal device, commonly a disposable plastic stripper, can be introduced from above downward and the vein ligated around the stripper proximally. As distal traction is applied, the vein is then inverted into itself and removed distally in the region of the knee. Roll gauze moistened with epinephrine may be attached to the stripper and drawn temporarily into the tunnel to enhance hemostasis.



**Figure 154.8** Steps in removal of a residual venous segment after proximal vein tearing. (A) Removal of the torn segment. (B) Attachment of the distal segment of vein to the intraluminal stripper and initiation of reverse invagination as the vein is removed from below upward. (C) Removal of the remaining venous segment.

### Minimize Accumulated Blood in the Stripping Tunnel

If blood is left in place in the stripping tunnel, a firm palpable cord, sometimes called pseudothrombophlebitis, results. This will eventually reabsorb but contributes to the early discomfort traditionally associated with vein-stripping procedures. In addition to the use of tumescent anesthesia, we recommend that stripping be performed as the last step of the procedure if concurrent tributary varices and/or perforator disease are to be addressed at the same setting. In this way the leg can be immediately wrapped in a compressive dressing and elevated after the vein stripping is performed. A full leg compression wrap with eccentric padding over the area of stripping, employing >20 mm Hg is recommended, there however is no consensus on the appropriate length of time to utilize this postoperative compression.<sup>33</sup> If the vein is to be removed from the knee incision, the groin incision can be closed with the stripper head in place, leaving only the distal incision at the knee to close after stripping. Alternatively, one may tie a length of roller gauze soaked in lidocaine with epinephrine to the end of the stripper (see Fig. 154.7). This provides direct compression, absorption

of blood in the tunnel, and application of epinephrine to the avulsed tributary sites.<sup>31,34</sup> The gauze is then removed before closure.

### Leg Elevation Before and During Stripping

Elevation of the leg reduces venous bleeding and ecchymosis associated with stripping. The leg should be elevated before the stripping is performed. Postoperatively, the patient should ambulate as soon as possible, although vigorous post-operative exercise or extended periods of leg dependency are to be avoided. Most varicose vein surgery is currently performed either on an outpatient basis or as an office-based procedure. While recovery and return to full activity varies widely between patients and regions, most patients can attend to their activities of daily living with minimal assist within a few days.

### Proximal Tourniquet

This technique is usually reserved for patients with massive varices in the calf or thigh, as is common in Klippel–Trénaunay syndrome, to prevent major hematomas. Esmarch compression of the limb is followed by placement of a proximal

sterile pneumatic tourniquet, which is inflated to 200 mm Hg. The tourniquet is deflated once the GSV is stripped and its tributaries removed.

## Surgery on the Small Saphenous Vein and Veins of the Popliteal Fossa

SSV disease is often neglected or incompletely treated by surgeons. This problem may be explained by: (1) a paucity of studies emphasizing a significant role for SSV incompetence in CVI; (2) the lower proportion of limbs with SSV compared with GSV incompetence; (3) technical considerations, such as the need to reposition the patient if both GSV surgery and SSV surgery are being performed in the same treatment session; and (4) the intimate and variable neurovascular relationships of the SSV, which can present significant potential for morbidity. However, the few papers that have addressed the role of the SSV in CVI have described a strong association of SSV reflux with: (1) posterior calf varicosities,<sup>35</sup> particularly in individuals with recurrent varicosities after superficial venous surgery; (2) isolated lateral malleolar ulcers<sup>36</sup>; and (3) ulcer recurrence after perforating surgery.<sup>37</sup>

A survey conducted among members of the Vascular Surgical Society of Great Britain and Ireland, which was motivated by the poor outcomes and high litigation rates associated with SSV surgery, characterized surgeons' attitudes toward SSV surgery.<sup>38</sup> Although nearly 90% of surgeons carried out preoperative duplex imaging, only 50% added preoperative skin marking of the saphenopopliteal junction. In an effort to avoid damage to neurovascular structures and DVT, few surgeons (10%) exposed the popliteal vein during this procedure, which would make identification and treatment of gastrocnemius or popliteal area veins less difficult.

An understanding of the relationship of the SSV to other veins of the popliteal fossa – the gastrocnemius veins, the intersaphenous vein, and popliteal area veins – is important to achieve optimal results with SSV surgery. If these veins are ignored, they can be a factor in the persistence of reflux.<sup>13,16</sup> These veins are particularly well suited to open surgery as opposed to EVA or sclerotherapy, particularly when they enter the popliteal vein directly.<sup>39</sup>

## Operative Technique for Small Saphenous Vein Procedures

After the induction of general, regional, or local anesthesia, patients are positioned prone with care taken to pad bony areas and breasts. To provide laxity of the neurovascular structures in the popliteal fossa, the limb is slightly flexed at the knee. Preoperative marking guided by DUS allows a small transverse skin incision to be made just distal to the saphenopopliteal junction. The length of the incision is dictated by the thickness of the subcutaneous tissue (shorter incision for thinner legs). The fascia is opened transversely and the SSV is identified. The SSV is traced distally between the fascia and calf muscles. Because of sustained venous hypertension, the SSV can resemble an artery (popliteal), so Doppler may be used to provide the surgeon

with assurance that the structure is indeed venous. The SSV is then divided between two right-angle clamps. Care is taken to dissect in the perivenous plane, and any nerve structure – usually sural – is carefully dissected from the SSV. Gentle retraction is used to avoid injury to the tibial nerve and to visualize the saphenopopliteal junction. The stump of the SSV is ligated with a 3-0 monofilament transfixion suture. If present, the common trunk of the SSV with either the gastrocnemius or intersaphenous veins is ligated proximally just above the popliteal vein.

If preoperative DUS identifies incompetence of individual gastrocnemius, intersaphenous, or popliteal area veins, exposure is extended and they are ligated as well. The distal SSV is dissected to a point beneath the fascia, and a segment is excised. We do not usually strip the SSV because of the risk of injury to the sural nerve, which is generally adherent to the SSV in its distal third. The popliteal wound is closed in layers with attention to approximating the fascia to avoid unsightly hernias. The short skin incision is approximated with running 5-0 subcuticular suture. The preoperatively marked posterior calf varicosities are removed by stab phlebectomy. Particular attention is paid to ligating any incompetent gastrocnemius perforating veins that connect with the SSV branches (see Table 154.1, VVGL 10.3).

## Excision of Local Varicosities (Ambulatory Phlebectomy)

Ligation and/or stripping of the GSV or SSV directly reduces axial reflux and therefore results in the preponderance of hemodynamic benefit in most vein operations. However, if left uninterrupted, the remaining superficial varicosities will drain via alternative pathways and may remain both symptomatic and cosmetically displeasing. In the past, these tributary varices were commonly dealt with by making large incisions leaving dramatic transverse scars. Refinements in technique have improved cosmetic results with effective elimination of tributary varices through small (1–3 mm) stab incisions.<sup>40,41</sup> Effective use of these minimally invasive techniques requires planning, experience, and patience. It is common for procedures to require in excess of 20 phlebectomies. Preoperative marking while standing is important in ambulatory phlebectomy, as these target veins are difficult to see when the patient is reclining.

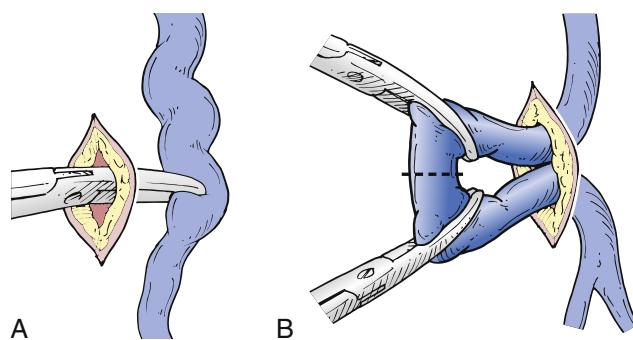
Although local, regional, and general anesthesia are all options, ambulatory phlebectomy, especially performed in isolation, is well suited to local infiltration anesthesia. This can be accomplished by superficial subdermal infiltration around the vessel of interest or by large-volume tumescent techniques. At the end of the infiltration the skin appears pale because of the epinephrine-induced vasoconstriction. However, direct visualization of varicosities during phlebectomy is generally not a problem. Inclusion of epinephrine in the anesthetic may be contraindicated in patients with diabetes, glaucoma, coronary heart disease, cardiac dysrhythmias, hypertension, hyperthyroidism, and peripheral arterial disease. In such cases, epinephrine may be omitted from the anesthetic mix, which results in somewhat more bleeding, which can generally be controlled by

a few minutes of digital compression. The patient is positioned to optimize surgical exposure. Phlebectomy is best performed on a horizontal plane, and because many patients are treated under a local anesthetic, it is often possible to have them rotate the extremity during the procedure to maximize exposure.

Mueller is credited with popularizing and refining the technique of stab avulsion.<sup>41</sup> He considered a 2-mm incision to be large. Although the process of removing the vein often stretches the small skin incision, the combination of postoperative compression and the intrinsic elasticity of the skin allows retraction to the original small incision size. The skin incision is most commonly made with a #11 blade, but 18-gauge needles and blood lancets have been used effectively. The incisions are typically oriented longitudinally except in the groin, knee, and ankle, where a transverse orientation aligns with the lines of Langer.

Three types of instruments are recommended for vein retrieval: hooks, iris forceps, and fine-pointed clamps. The small dermal varicosities are hooked and avulsed. Larger veins are grasped and brought up through the incision (Fig. 154.9). The vein loop is cleared of fat, doubly clamped, and divided. By applying in-line traction, varicosities can be teased out and several centimeters removed from each end. Rolling of the vein onto the clamp prevents the vein from avulsing prematurely. The varicose segments should be removed in their entirety, and if the vein breaks during the process, it may be reobtained through a new incision. These varicosities are typically tributaries of the axial veins which should be addressed if incompetent, thus ligation is optional. However, when the tributaries are particularly large or pressurized, ligation with undyed absorbable ties is recommended. Perforating veins associated with clusters of varices should also be ligated. The skin incisions are small enough that Steri-Strip closure is usually sufficient. Should an individual incision be larger than usual, a single interrupted absorbable subcuticular or nylon skin closure will suffice (see Table 154.1, VVGL 10.7).

When the axial reflux is to be addressed with endovenous ablation in the presence of significant tributary varicosities, one must determine whether the tributaries should be addressed at the same setting as the ablation or in a staged fashion. Proponents of a staged approach generally cite the possibility that GSV or SSV ablation alone may provide adequate clinical improvement to meet the patient's expectations, thus avoiding a second procedure all together, or possibly allowing a more limited phlebectomy. Also, the elimination of axial reflux may de-pressure the tributaries allowing them to shrink to a size more appropriate for sclerotherapy. Since extensive phlebectomy is generally more time consuming than an ablation, the cadence of the procedures may be improved with staged procedures. Lastly, performance of phlebectomy concomitant with GSV EVA has been shown to increase the risk of EHIT (OR = 4.5;  $P = 0.02$ ).<sup>42</sup> Advocates of combined/complete correction of superficial disease cite the greater hemodynamic impact of a more complete surgery, the inevitable progression of chronic venous disease, and the convenience to patients of a single treatment session. Hager et al. in 2017 published an evidence summary which reported on eight clinical comparative studies comparing the benefits of staged vs. combined approaches and found



**Figure 154.9** Ambulatory Phlebectomy. (A) A 2- to 3-mm stab incision oriented transversely at the groin, knee, or ankle or longitudinally along Langer's lines elsewhere in the leg provides access for phlebectomy. (B) The target varicosity is drawn through the incision, divided, dissected, and avulsed.

better short-term and better to equivalent long-term patient outcomes with a combined approach.<sup>43</sup> More recently, data from the Vascular Quality Initiative (VQI) registry reporting on 3375 C2 patients found that patients undergoing ablation alone (1376 patients) had a more modest improvement in median VCSS than patients undergoing ablation plus phlebectomy ( $n = 1999$ ), VCSS 3 vs. 5, ( $P < 0.001$ ).<sup>44</sup>

### Transilluminated Powered Phlebectomy

Transilluminated powered phlebectomy, or TriVex, uses tumescent dissection, transillumination, and powered phlebectomy to accomplish extensive ambulatory phlebectomy. Because of the tumescent anesthesia, this technique can be carried out without general or regional anesthesia. The device used to transilluminate the veins and perform the phlebectomy is similar to devices used to remove subcutaneous fat. It is inserted into the subcutaneous tissue through a small incision and moved forward and backward over as much area as possible to disrupt and remove the varicosities.

The technique has the proposed advantages of decreasing the number of incisions and reducing operative time. Aremu and colleagues' randomized controlled trial (RCT) of 141 patients and 188 limbs compared TriVex with conventional stab phlebectomy.<sup>45</sup> The TriVex group had fivefold fewer incisions (5 vs. 29), whereas postoperative pain and other patient-reported measures were comparable. There was a nonsignificant trend toward a shorter operative time with the TriVex group. A subsequent RCT of similar design carried out in Australia showed that fewer incisions were required but reduced operative time was not seen.<sup>46</sup> In contrast to the Aremu study, early postoperative bruising, pain, and quality of life were worse in the TriVex group. Finally, a meta-analysis conducted by Luebke and associates of five RCTs noted that the reduced operating time for TriVex applied only for large and extensive varicosities – and at the expense of more hematoma formation and a higher mean pain score than with standard hook phlebectomy.<sup>47</sup> A report utilizing the second generation device had similar results. They asked their patients "If needed, would you be ready to have this operation again?" The answer was no in 40% of the time.<sup>48</sup> This technique continues to be rarely employed in current practice.

## Saphenous-Sparing Operations

Routine use of DUS to map flow in the great and small saphenous veins, as well as in associated varicosities, has led to the development of hemodynamic-based “saphenous-sparing operations.” These procedures challenge the hypothesis, initially promulgated by Trendelenburg, that an incompetent saphenous vein is the cause of varicosities. This thesis holds that reflux from the deep to the superficial system at the saphenofemoral or saphenopopliteal “connections” produces incompetence in the saphenous trunk, which descends distally, then outward to form superficial varicosities. The detailed duplex studies of Labropoulos and others challenged this theory and supported an “ascending” cause of varicose veins, which is initiated in the “distal superficial venous network.” Proponents of this theory remove only refluxing segments, concentrating on the varicosities of the peripheral venous network rather than the saphenous vein, thus sparing it. Two groups of procedures accomplish this approach: the Cure Conservatrice et Hémodynamique de l’Insuffisance veineuse en Ambulatoire (CHIVA)<sup>48–51</sup> and ambulatory selective varices ablation (ASVAL)<sup>52</sup> techniques.

### *Conservatrice et Hémodynamique de l’Insuffisance veineuse en Ambulatoire (CHIVA)*

A detailed preoperative duplex ultrasound determines where reflux starts, the entry point, and where it reenters, with the goal of promoting normal superficial-to-deep flow through reentry perforating veins during muscular diastole. Determination of the competence of the terminal and preterminal valves of the saphenous guides the decision of whether it should be ligated. The tributaries are assessed for competence (flow into saphenous) or incompetence (flow into tributaries and associated varicosities). Incompetent tributaries are ligated and the varicosities removed. Francheschi classified several types of communications between the superficial and deep system, which dictate the required surgical steps: type I, with reentry by a venovenous shunt at the saphenous trunk; type II, with no reflux from the deep system but with reflux from the superficial venous network, not surrounded by the superficial fascia or through a communicating superficial vein; type III, with reentry on an extrasaphenous superficial perforator; and type IV, with reflux from the pelvic circulation. Carandina and associates compared CHIVA with standard high-ligation and stripping (HLS) in an RCT of 150 patients.<sup>53</sup> Outcome measures at 10 years were: recurrence of varicose veins (VVs) by objective clinical and duplex criteria; clinical outcome (Hobbs score); and patient-reported subjective symptoms. Although there was no difference in the Hobbs score between the two groups, recurrence of VVs at 10 years was lower in the CHIVA group (18%) than in the HLS group (35%) ( $P < 0.04$ ).

The definitive large RCT on CHIVA conducted by Parés and colleagues<sup>54</sup> compared CHIVA with two control groups: HLS with or without duplex guided marking. The primary outcome was recurrence of VVs as observed by independent physicians. In this RCT, “cure” of VVs was twice as frequent in the CHIVA group as in the two HLS groups, whereas the

OR favoring the CHIVA group was 2.64 (95% CI, 1.76–3.97;  $P < 0.001$ ) over the HLS clinical and 2.01 over the HLS duplex group. Several criticisms have been leveled at the study: (1) the study had a high incidence of patients with mild disease, C2; (2) a significant number of patients underwent treatment for cosmetic purposes in the absence of symptoms; and (3) no patient-reported outcome measure was used – an important consideration in mild disease and particularly when cosmesis is the indication. Finally, in a small RCT, Zamboni and associates showed superiority of CHIVA over compression treatment in CEAP C6 patients.<sup>53</sup> This RCT, however, had narrow inclusion/exclusion criteria, no postthrombotic limbs, and no deep venous reflux/obstruction. Time to ulcer healing was shortened, and the 38% recurrence rate in the compression group was reduced to 9% in the CHIVA group. CHIVA has shown excellent results in lowering the recurrence of varicose veins; however, despite increasing facility with intraoperative DUS and minimally invasive techniques, this approach has not found widespread adoption in its pure form (see Table 154.1, VVGL 10.5).

### *Ambulatory Selective Varices Ablation (ASVAL)*

This procedure is performed under local and tumescent anesthesia with removal of the venous varicose reservoir (multiple varicosities) through multiple stab incisions (average, 30), generally using Muller phlebectomy hooks.<sup>52</sup> In Pittaluga and associates’ large contemporaneous and comparative trial, which was conducted in 831 limbs, ASVAL was performed in 303 limbs of 221 patients and HLS in the remainder.<sup>52</sup> They ultimately reported 10-year follow-up on this series of 359 ASVAL procedures, in 360 lower extremities, in 264 patients, aged from 21 to 85 years.<sup>55</sup> The C classification was: C2 in 303 (84.2%), C3 in 24 (6.7%), C4 in 33 (9.2%), and C5–C6 in none. Symptomatic in 63.3% of cases. The GSV presented reflux on ultrasound in all the cases with an average diameter of 6.8 mm (range: 3–15 mm). The average duration of follow-up was 59.8 months. Surgical reintervention was carried out in 24 cases during the follow-up, consisting of a new ASVAL procedure in 15 cases and a stripping or thermal ablation in nine cases. Survival curve analysis showed an absence of saphenous reflux at 24, 60, 84 and 120 months in 71%, 69.7%, 68.5% and 64.4% of the cases, an absence of varicose recurrence in 93.1%, 84.7%, 75.5% and 68.8% of the cases, an absence of surgical reintervention in 96.9%, 90%, 83.6%, and 76.7% of the cases, a functional improvement in 86.7%, 83.8%, 78% and 69.9% of the cases and esthetic improvement in 92.2%, 86%, 77.2%, and 65.7% of the cases. Though time-consuming, ASVAL appears to provide an effective and durable treatment option for patients with mild disease (C2) and minimal symptoms, when performed by surgeons appropriately trained in this technique. (see Table 154.1, VVGL 10.6).

### *Endovenous Ablation*

The evolution of minimally invasive techniques for the treatment of GSV reflux has culminated in the development of EVA. These techniques are discussed in Chapter 155, Varicose Veins: Endovenous Ablation and Sclerotherapy.

## RESULTS

For a century, HLS was the “gold standard” for the treatment of GSV incompetence and tributary avulsion for residual varicose veins. The preponderance of data advocating a surgical approach to CVI is derived from clinical reports of HLS. The role of HLS has diminished greatly with the advent of EVA by either thermal or nonthermal methods, and sclerotherapy has replaced tributary avulsion in many cases. HLS has decreased from 155,000 procedures in 1999 to less than 30,000 in 2016. By contrast, EVA has grown from none in 1999, to 355,000 procedures in 2016. What accounts for this change? Is there valid evidence to show that EVA is superior to HLS? This section reviews the evidence, including from RCTs when available.<sup>56</sup>

### Results of Surgery on the Great Saphenous Vein vs. Nonoperative Treatment

The ESCHAR trial was the first large prospective randomized trial to address this fundamental question. Patients with severe sequelae of CVI (C5–C6) and superficial or mixed deep and superficial venous insufficiency were randomized to medical therapy (elevation, compression, and exercise) either with or without surgical treatment of superficial venous reflux. Although no difference was found in healing rates, a reduction was seen in ulcer recurrence (12% vs. 28% at 12 months;  $P = 0.001$ ) in the surgical group. It is notable that 20% of patients in the surgical arm refused surgery but remained in the surgical arm according to an intention-to-treat analysis plan. This likely resulted in understating the treatment effect of surgery.<sup>57</sup> Michaels and colleagues carried out an RCT that examined the impact of superficial venous surgery on quality of life in 246 patients with uncomplicated varicose veins who were randomized to compression and lifestyle changes versus surgery with HLS and multiple phlebectomies.<sup>58</sup> This well-designed study incorporated clinically relevant changes in health status as determined by the Short Form 36 (SF-36) and the EuroQol 5D (EQ5D). The surgical group showed significant improvement in quality-adjusted life years over the compression group. In addition, the surgical group demonstrated significant anatomic and symptomatic relief. These large RCTs provide a grade A recommendation for surgery in addition to conservative treatment in patients with varicose veins caused by GSV reflux.

### Comparison of Endovenous Ablation vs. Ligation and Stripping of the Great Saphenous Vein

Twelve groups reported RCTs in which EVA was compared with HLS. Several groups provided follow-up reports that supplemented the initial data in meaningful ways. Eight of these reports compared laser treatment with L&S,<sup>59–65</sup> whereas six reported on radiofrequency ablation with L&S.<sup>63,66,67</sup> A single study compared L&S, EVA, and CHIVA.<sup>68</sup> The studies were of modest size, with 28 to 580 limbs being treated. Many of the RCTs were lacking some elements of proper study design:

a priori calculation of sample size, comparability of baseline characteristics between groups, and intention-to-treat analysis. Desirable outcome measures such as quality of life were used in all but one series, whereas all but two provided a disease-specific evaluative score so that preoperative and postoperative values could be compared. Table 154.2 shows the objective endpoints for the comparisons between L&S and EVA. Overall, EVA showed an early postoperative advantage in quality of life; but by 1 month, the disease-specific scores were comparable. “Soft” outcome measures, such as return to normal activities or work and less postoperative pain, also favored EVA. Rasmussen,<sup>59</sup> Perälä,<sup>69</sup> and Darwood<sup>60</sup> found no differences between L&S and EVA in disease-specific scores by 1 month postoperatively. Eight RCTs (Rasmussen,<sup>59,63,65</sup> Kalteis,<sup>61</sup> Carradice,<sup>70</sup> Christenson,<sup>71</sup> Gauw,<sup>62</sup> Rass,<sup>64</sup> Cañas,<sup>68</sup> Liao<sup>72</sup>) showed no difference in quality-of-life measures, whereas two demonstrated an advantage for EVA (Rautio<sup>66</sup> and Lurie<sup>67</sup>). Morbidity is putatively less with EVA because the vein is ablated in place. HLS involves stripping the vein with avulsion of branches and some tract bleeding, which can be mitigated but will never be eliminated. Certainly if thrombophlebitis develops in the ablated GSV, the pain can be as severe as that with stripping. The use of postoperative analgesics is usual with HLS, in contrast to EVA. We have observed that local tumescent anesthesia results in reduced pain and bruising with vein stripping and phlebectomy as well as with EVA. Rasmussen compared L&S and EVA in a randomized trial in which tumescent anesthesia was used in all patients.<sup>59</sup> In this report, 121 patients (137 limbs) were randomized to HLS with local anesthesia or endovenous laser treatment. Both groups had varicosities removed through mini-phlebectomies and received perivenous tumescent solution and intravenous fentanyl. HLS was performed by the perforate-invaginate (PIN) stripping technique. The two treatments were found to be equally effective in eliminating GSV reflux, with no difference in time to resume normal activities or return to work. There was more pain and bruising in the HLS group but no change in pain medication use between the groups. No difference was observed in the venous clinical severity score or in the Aberdeen score between the two groups at any time point. The bodily pain score component of the SF-36 was higher after HLS than after EVA 12 days postoperatively.

Taken as a group, these data demonstrate an early postoperative advantage in pain for the EVA procedures. In 2016 we analyzed the 10 RCTs listed here which were published at that time to investigate the timing and mode of failure (recurrence of varicose veins after surgery: REVAS).<sup>73</sup> We found no difference in the overall incidence of the recurrence of varicose veins after surgery (REVAS) between EVA and HLS, nor was there a difference in the rates of reoperation. In addition, REVAS was progressive over time, with more than a doubling of clinical recurrence in Rasmussen's trial between years 1 and 5.<sup>63</sup> However, there was a different pattern of failure with the techniques. Neovascularization was more common after HLS, whereas recanalization occurred more frequently after EVA. Although there was individual variation as to the site of REVAS within each study, meta-analysis showed that the thigh and calf are comparable as sites of recurrence for EVA.

**TABLE 154.2** Comparison of EVA vs. L&S of GSV (PRTs)

Series	Year	EVA Treatment	Earliest F/U	Latest F/U	Number of Limbs Treated	FAILURE		ADVANTAGE OF EVA		
						L&S	EVA	QoL	Pain/Bruising	Comments
Gauw et al. <sup>62</sup>	2016	Laser	NA	5 years	130	10/60	20/61	Φ	NA	Inc SFJ reflux at 5 years in EVA
Rasmussen et al. <sup>59</sup>	2007	Laser	12 days	6 months	137	2/68	3/69	Φ	⊕	Costs of laser; no change in pain medication
Rasmussen et al. <sup>63</sup>	2013	Laser	NA	3 years	580	22/66	24/73	Φ	NR	3-year F/U data P = NS
Rass et al. <sup>64</sup>	2012	Laser	NA	2 years	346	37/61 (clin) 2/161 (SFJ reflux)	30/185 (clin) 33/185 (SFJ reflux)	Φ	NR	P = 0.15 P < 0.001
Darwood et al. <sup>60</sup>	2008	Laser	12 days	3 months	103	4/32	4/71	Φ	NR	No Δ in return to physical activity or work
Kalteis et al. <sup>61</sup>	2008	Laser	1 week	4 months	100	0/50	0/50	Φ 4 weeks	NR	HL in both groups ↓ Hematoma with EVA ↓ Time to return to work with EVA
Christenson et al. <sup>71</sup>	2010	Laser	12 days	2 years	204	0/100	7/104	Φ		EVA failed in 4 initially. At 1 year, 2 GSVs fully and 3 partially reopened
Carradice et al. <sup>70</sup>	2011	Laser	1 week	12 months	208	10/132	1/137	Φ	NR	Recurrence at 1 year was lower after EVA
Rasmussen et al. <sup>63</sup>	2013	RFA	NA	3 years	580	22/64	17/74	Φ	NR	3-year F/U data P = NS
Rautio et al. <sup>66</sup>	2002	RFA	1 day	8 weeks	28	0/13	0/15	NR	⊕	
Perälä et al. <sup>69</sup>	2005	RFA (F/U)	1 day	3 years		3/13 Recurrent varices	5/15 Recurrent varices	NR	NR	
Lurie et al. <sup>67</sup>	2003	RFA	3 days	4 months	86	0/36	2/44	⊕	NR	↓ Time to return to normal activity and work with EVA
Lurie et al. <sup>75</sup>	2005	RFA (F/U)	1 year	2 years	65	1/36 Recanalized GSV 14% Recurrent VVs	2/44 Recanalized GSV 21% Recurrent VVs	⊕ 1 + 2 years	NR	
Cañas <sup>68</sup>	2021	RFA	1 week	24 months	225	L+S3/75 CHIVA 11/76	5/74		Less bruising in RFA, no change in pain.	VCSS and CIVIQ improved in all groups, no difference between groups.
Liao <sup>72</sup>	2021	RFA	1 week	1 year	200	9/99	2/101		No change in VCSS or CVI questionnaire at 12 months	Both groups used Powered phlebectomy. OR time, LOS, EBL all better with RFA.

EVA, endovenous ablation; F/U, follow-up; GSVs, great saphenous veins; HL, high ligation; L&S, ligation and stripping; NR, not reported; QoL, quality of life; RFA, radiofrequency ablation; VVs, varicose veins. Φ, No difference; ⊕, better with EVA.

Rasmussen also provided 5-year comparative data from a PRT including RFA, laser, HLS, and UGFS and found that UGFS had a much higher composite rate of recanalization, recurrence, and re-operation compared to all of the other treatments (UGFS, 31.5 % vs. all other groups, <7%,  $P < 0.001$ ).<sup>65</sup> Wallace et al. published the 5-year follow-up of 218 patients available for long-term evaluation after enrolling 276 patients in a British PRT of laser vs. HLS. Both groups received phlebectomy at the index procedure. Clinical recurrence was more frequent following surgery than EVLA at 5 years (34.3 vs. 20.9%;  $P = 0.01$ ). Both groups demonstrated sustained significant improvements at 5 years over baseline in VCSS, AVVQ, and EQ-5D. VCSS was better for EVLA than surgery at 5 years ( $P = 0.03$ ). Technical success assessed by DUS remained high at 5 years (85.4% for surgery and 93.2% for EVLA;  $P = 0.07$ ).<sup>74</sup>

## Results of Surgical Treatment of Veins of the Popliteal Fossa

Reported rates of recurrent varicosities and reflux after SSV surgery are often high. In a DUS survey, Tong and colleagues reported a 61% incidence of recurrent SSV reflux.<sup>76</sup> In Creton's review of 125 reoperations for recurrence of SSV reflux, the majority (>60%) were due to inadequate ligation of the proximal SSV: 13.6%, intact SSV trunk; 42.4%, residual long stump of the SSV off the popliteal vein; and 3%, small residual and incompetent small saphenous trunk.<sup>77</sup> A less frequent cause of recurrent reflux in the popliteal fossa was an incompetent popliteal area perforating vein.

Although Tong and colleagues<sup>76</sup> found that SSV reflux was the cause of recurrent varicosities in 43 of 70 limbs (61%), an appreciable incidence of non-SSV incompetence was noted. In fact, Rettori et al. identified incompetence of a gastrocnemius vein as the cause of recurrent popliteal fossa varices in 34% of their cases.<sup>78</sup> The retrospective series of Tong<sup>76</sup> and Creton<sup>77</sup> were based on patients with presumed recurrence of SSV reflux. However, Mitchell and colleagues carried out a prospective study of SSV surgery and found SSV reflux in 33% of patients and gastrocnemius reflux in 17%. These findings underline the importance of defining by perioperative DUS exactly which veins are incompetent in the popliteal fossa as well as their relationship to the SSV. Armed with preoperative DUS findings the surgeon can plan the operative approach accordingly and must be committed to correcting it.

A single RCT investigating surgery versus EVA of the SSV<sup>79</sup> reported on 106 patients. Abolition of SSV reflux was significantly higher after EVA (96.2%) than after surgery (71.7%) ( $P < 0.001$ ). Postoperative pain was significantly lower after EVA ( $P < 0.05$ ), allowing an earlier return to work and normal function ( $P < 0.001$ ). Minor sensory disturbance was significantly lower in the EVA group (7.5%) compared with the surgical group (26.4%) ( $P = 0.009$ ). Both groups demonstrated similar improvements in VCSS and quality of life. These data suggest that the application of EVLA to the SSV is supported by this early literature, however concern about potential thermal injury to the many nerves in the popliteal fossa has limited its application at this point. By combining a thorough preoperative

evaluation with an aggressive surgical approach aimed at eliminating all refluxing segments in the popliteal fossa, we found no sensory or motor nerve injuries, no hematomas or wound infections, no DVT, and no reflux of the SSV, popliteal junction, or other veins of the popliteal fossa in a study of 47 consecutive limbs.<sup>80</sup> Additionally, at a 6-month follow-up, the mean VCSS had decreased significantly to 2.5 from a preoperative value of 7.0, with no cases of recurrent reflux in the popliteal fossa. These data support a continued central role for well-planned and well-executed venous surgery in the treatment of popliteal fossa venous disease.

## MULTIMODALITY AND INDIVIDUALIZED CARE

The many approaches advocated by passionate experts from around the globe serve to emphasize that no single treatment for venous disease is appropriate for all patients or, for that matter, for all venous issues in a single patient. Modern venous specialists have many tools at their disposal, and it is common to employ a combination of EVA, HLS, phlebectomy, sclerotherapy, and stenting. For example, Kalodiki et al. randomized patients with GSV reflux and tributary varicose veins to high ligation plus either phlebectomy or foam sclerotherapy to treat the tributaries. At 3 and 5 years of follow-up, the tributary treatments were equally effective, as demonstrated by VCSS, VSDS, and the SF-36 physical component score.<sup>81</sup> These authors also found that follow-up sclerotherapy was commonly used in both groups, and they suggested routine interval treatments. Yin and colleagues conducted a similar protocol with 163 randomized to HL with stripping or HL with UGFS. Follow-up at 1, 6 and 12 again showed no difference in recurrence, VCSS, AVVQ, or hemodynamics. However the operating time (38 vs. 81 min), recovery time (5.4 vs. 9.6 days), and expense (\$853 vs. \$1575) were all greater in the stripping arm ( $P < 0.01$  for all).<sup>82</sup> The fact that these and other groups continue to incorporate HL in their treatment arms suggests an ongoing belief in the value of this technique among leaders in the field.

In recent years, there has been significant interest in identifying and treating iliac vein stenosis in chronic venous disease patients. While there is clear benefit to iliac vein stenting for venous outflow stenosis (CHP 161), a small retrospective report by Guo found that adding GSV ablation to stenting of nonthrombotic iliac vein compression (NIVCS) in C4–6 patients resulted in improved VCSS, pain score, and ulcer healing (each  $P < 0.05$ ).<sup>83</sup> This study highlights the central importance of correcting lower extremity venous reflux even in the face of venous outflow stenosis. While Guo reported on EVA, it seems likely that HLS would provide similar benefit.

Recurrent reflux in the groin after previous HLS has been reported as up to 40% after 10 years.<sup>84</sup> These long-term failures are commonly attributed to neovascularization or long residual GSV stumps. Operative treatment of symptomatic groin recurrences typically consists of redo surgery with ligation or resection of the refluxing veins in the groin. The results of this procedure vary in the literature, with re-recurrence up to 20%.<sup>85</sup>

Re-do operations at the SFJ should utilize a lateral approach across the femoral artery to avoid dissection through scar. The femoral vein should be exposed to ensure that the junction of the recurrent venous reflux to the deep system is removed. Freis et al. reported a series of 86 re-do procedures in patients whose index operation was a mean of 13.9 years earlier. In addition to utilizing the techniques noted above, they dissected the recurrent varicosities at least 2 cm from the junction with the common femoral vein. Finally, they placed a  $1.5 \times 3$  cm barrier patch of PTFE on the femoral vein covering the SFJ. At 1-year DUS follow-up they had an overall re-recurrence rate of 12%, of which only 2.4% were caused by recurrent neovascularization in the groin bypassing the barrier patch. The remaining 9.6% were caused by different sites of reflux (pelvic veins and perforators).<sup>86</sup> Similar results were reported by Rass and colleagues who instead of using a patch, performed inguinal re-operation for recurrent SFJ incompetence using a combined approach of stump suture technique, removal of neovasculatures, cauterization of free endothelium, and additional tumescent local anesthesia. They reported 83 patients (100 legs) who had f/u > 1 year, median 16.2 months. Duplex-detected reflux in the groin arising from the common femoral vein was identified in 5% with only one leg showing grade 2 neovascularization according to International Union of Phlebology classification. Same site clinical recurrence originating from the SFJ was detected in 3%.<sup>87</sup> These studies demonstrate the excellent results possible with a focused and well executed plan to address recurrent SFJ reflux.

## PATIENT MANAGEMENT AND REIMBURSEMENT CONSIDERATIONS

Most insurers have well-defined criteria for approval of varicose vein treatments, termed medical review criteria, which are used to preauthorize interventional treatments. Policies vary between carriers and regions, but typically insurers require that three conditions be satisfied to authorize treatment for axial reflux: (1) symptomatic varicose veins; (2) duplex evidence of reflux greater than 1 second (some also require a minimum GSV diameter [e.g., >4 mm]); and (3) a trial of conservative care including: compression stockings for 6 weeks to 6 months, exercise, leg elevation, and medications. Other indications for intervention may include the following: a venous ulcer, lipodermatosclerosis, more than one episode of minor hemorrhage from a superficial varicosity, a single significant hemorrhage from a ruptured superficial varicosity, two or more episodes of superficial thrombophlebitis, or persistent superficial thrombophlebitis unresponsive to 4 weeks of conservative therapy.

Insurers usually do not distinguish between authorization for EVA or HLS, nor do they dictate the setting. Reimbursement to the physician, however, can vary greatly depending on the site of service. If the procedure is performed in a hospital or surgical center, the insurer pays a professional fee to the physician as well as a facility fee to the hospital. By contrast, in office-based procedures, the surgeon receives a global reimbursement. This system typically results in higher costs to the

payer and lower margins for the physician for hospital-based venous procedures. These financial realities, the decreased invasiveness of modern venous interventions, the proliferation of vein centers, and the ease of use of the office setting have resulted in a dramatic shift of venous surgery to offices and away from hospitals. Comparing the costs of conventional surgery versus EVA, Lees reported a prospective randomized trial in which 91 patients were randomized to RFA versus L&S in the United Kingdom.<sup>88</sup> Ablation was more expensive (mean hospital cost per patient £1275.90 vs. £559.13 for L&S) in their setting; however, they concluded that in employed patients the quicker return to work (mean 12.2 vs. 19.8 days,  $P = 0.006$ ) justified the additional procedural cost.

Considering outcomes (reintervention on truncal veins, re-treatment of residual varicosities, and QOL over 5 years) in addition to costs, Bootun and colleagues performed a decision model analysis based on data from all treatment modalities employed in the UK over a 5-year period in the National Health Service.<sup>89</sup> They concluded that conservative management had the optimal cost-effectiveness; HLS and EVA were acceptable options at a threshold £20,000/quality adjusted life year, while MOCA and cyanoacrylate were the least cost-effective options.

Financial considerations are subject to constant re-evaluation as insurance rules change and data on the effectiveness of the various modes of therapy is updated. The choice of therapy in each case will be influenced by the clinician's familiarity with various techniques, the data underlying these therapies, and the financial realities of the locality.

## Indications for Ligation and Stripping of the Great Saphenous Vein in the Current Climate Favoring Endovenous Ablation

Listed here are the indications the authors use to identify patients who will receive the most benefit from open surgery on the GSV as opposed to endovenous procedures.

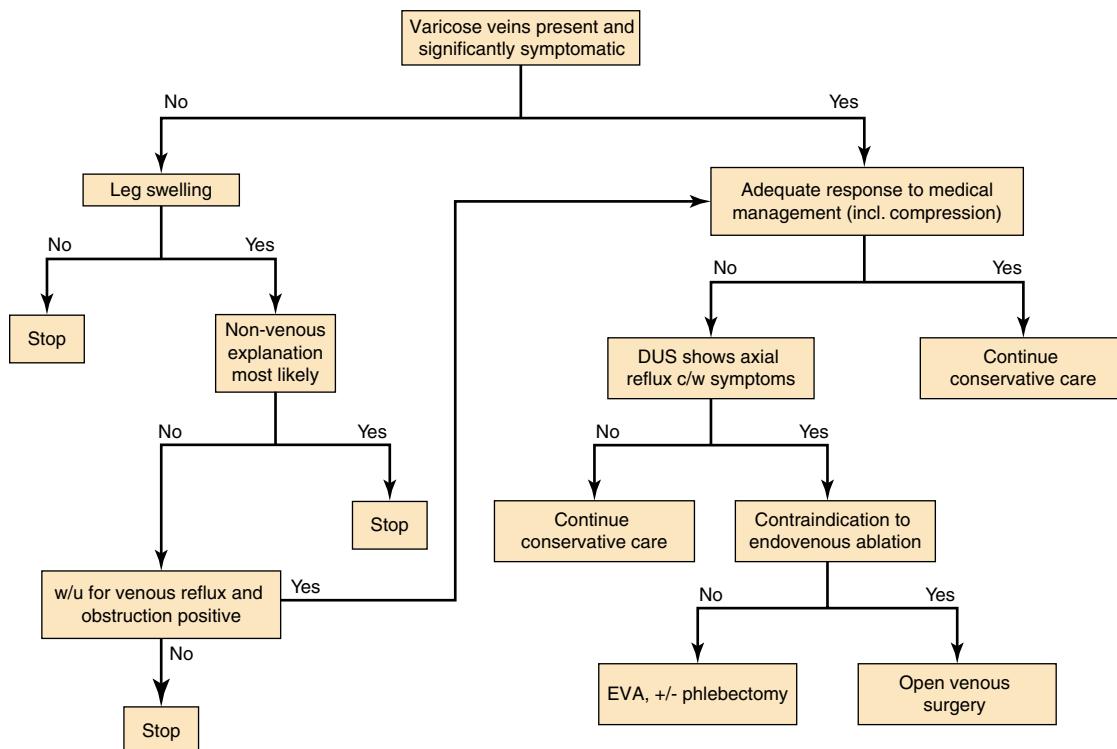
1. Superficial saphenous tributary. The most common indication for HLS of GSV is to treat a superficial saphenous vein or tributary that is closely adherent to the skin. This vein can be an "extrafascial" superficial tributary to the GSV, a separate anterior accessory saphenous vein, or a truly duplicated GSV. The inability to create at least a 1-cm buffer zone between the skin and the vein with tumescent anesthesia during thermal ablation increases the risk for skin burns and is a contraindication to thermal EVA. Nonthermal techniques have eliminated the burn issue, but inflammation and pigmentation remain issues when the treated vein is very superficial. These patients more frequently undergo a stab phlebectomy of this venous segment rather than the classic HLS.
2. GSV dilation or aneurysmal venous segments. Dilation of the proximal GSV to greater than 2.5 to 3 cm or large aneurysmal venous segments along the course of the GSV are also indications for L&S. Despite external compression, copious tumescent solution, and the use of newer endovenous techniques, the proximal GSV may be difficult to

- ablate effectively and may be more prone to thrombotic complications in these circumstances.
3. Chronic thrombophlebitis. The formation of synechiae within the GSV as a sequela of superficial thrombophlebitis may prevent advancement of the radiofrequency ablation catheter or laser sheath. This may occur even if a guide wire crosses the diseased segment. In this situation it is often possible to perform HLS with the flexible Codman stripper or the relatively stiff wire PIN strippers. If this also fails, simple ligation plus segmental excision is performed. In addition, if the vein wall is markedly thickened on DUS, it will not constrict appropriately in response to thermal ablation and would be more effectively treated with HLS.
4. Suppurative thrombophlebitis. Often managed nonoperatively with antibiotics and anticoagulation, open surgical ligation with segmental stripping can provide dramatic benefit in refractory cases. Not only does EVA have no role in the management of suppurative thrombophlebitis, but EVA has been the cause of this vascular infection in at least two reported cases.<sup>90</sup>
5. Excessive tortuosity (same considerations as in no. 3).
6. Acute superficial thrombosis. Acute superficial vein thrombosis with extension to the saphenofemoral junction remains an indication for anticoagulation, GSV ligation, or both to prevent extension to the common femoral vein. EVA is clearly contraindicated in any vein with acute thrombus.
7. Lateral marginal vein (LMV). Commonly seen in Klippel-Trenaunay, these large veins present multiple potential complications including potentially lethal thromboembolic events. While endovenous procedures have an established role in the management of LMVs, open surgery with segmental ligation and resection has been shown to be effective as well. Open surgery is particularly pursued in refractory veins or when phlebitis persists after endovenous procedures. Adjunctive techniques including tourniquet, coil embolization, staged procedures, and cell saver may be employed to reduce the hemodynamic consequences of these procedures.<sup>91</sup>
8. Economic consideration. Capital costs for establishing an endovascular vein ablation program may exceed \$50,000. In addition, there are high per-case consumable costs. Even though venous interventions are considered to provide a solid return on financial investment, the up-front capital costs may prove a significant barrier to entry. In addition, if patients are responsible for the costs of their treatment, they may favor the less costly open procedures.

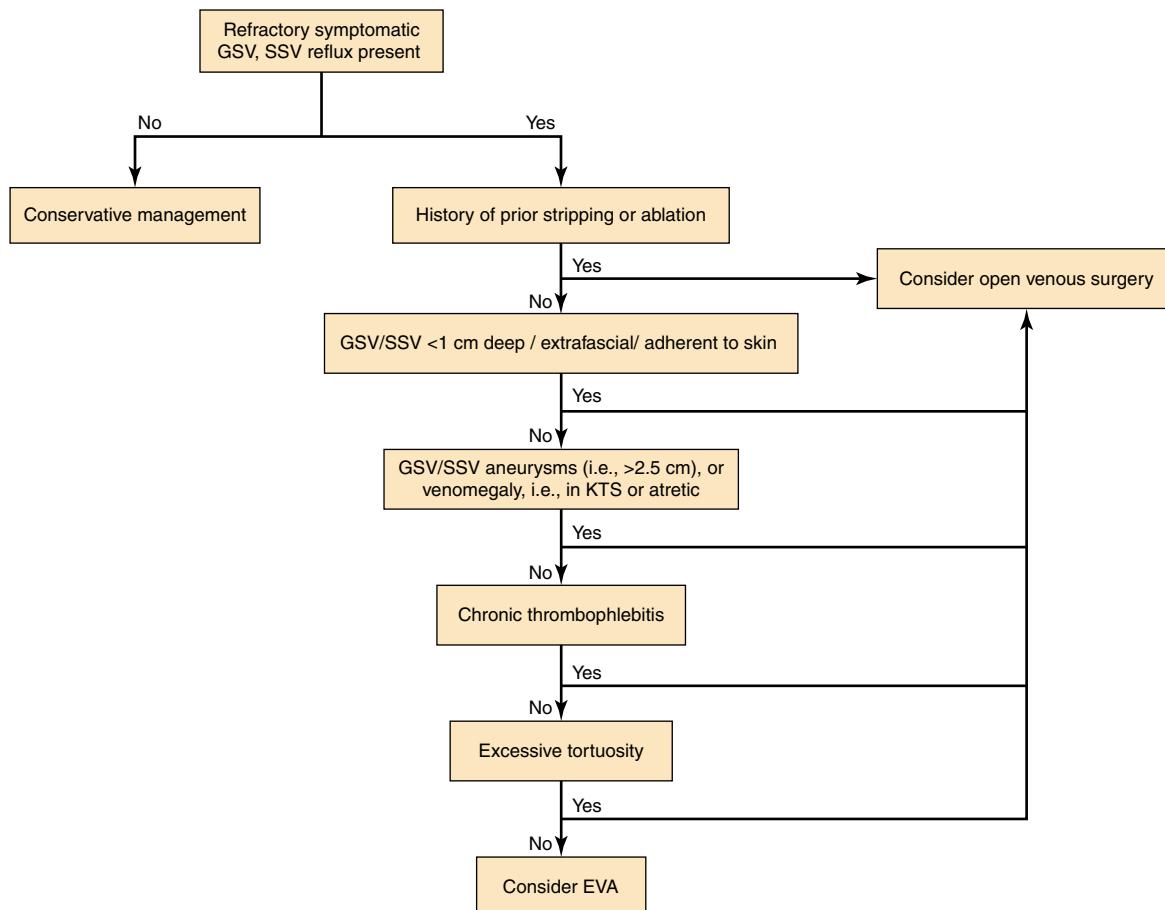
In summary, HLS has decreased in popularity as a technique for treating GSV reflux because of the less invasive nature of EVA. However, open surgery on the GSV remains a relevant procedure with a definite though diminished place in a modern venous practice.

## CHAPTER ALGORITHMS

### ALGORITHM 1



### ALGORITHM 2



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*This study provides insight into the appropriate diagnosis and surgical management of veins of the popliteal fossa. Surgical management of veins in this area has in the past suffered from lack of attention to the issues discussed in this report.*

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# Varicose Veins: Endovenous Ablation and Sclerotherapy

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## BACKGROUND

Endovenous treatments for varicose veins emerged as an alternative to open surgery and are now the standard of care due to improved safety and efficacy.<sup>1,2</sup> The most widespread technologies used for the treatment of truncal vein reflux are radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Sclerotherapy remains the treatment of choice for telangiectasias and reticular veins, but may also be used for truncal reflux. Also, the non-thermal non-tumescent (NTNT)

technologies have come to market and continue to gain traction. These include chemical ablation, mechanicochemical ablation (MOCA), adhesive closure, and others.

## RELEVANT ANATOMY

Superficial veins in the lower extremities function as the principal collecting system for the lower extremities.<sup>3</sup> This enables the collection of blood from the superficial tissues and skin, which is then routed to the deep system for return.

## Great Saphenous, Small Saphenous, and Perforating Veins

The two major veins of the superficial venous system are the great saphenous vein (GSV) and the small saphenous vein (SSV).<sup>4,5</sup> True “duplication” of the GSV is rare, and an apparent duplicate GSV is usually an accessory anterior saphenous vein (AASV).<sup>4,6,7</sup> The AASV is found in up to 14% of patients.<sup>8,9</sup> The GSV otherwise has a relatively consistent pattern of tributaries, including the AASV, posterior accessory GSV, posterior thigh circumflex, and anterior thigh circumflex.<sup>10,11</sup>

The SSV originates inferior and posterior to the lateral malleolus and ascends the posterior aspect of the calf between the gastrocnemius heads to the popliteal fossa.<sup>11</sup> In two-thirds of patients, the SSV connects to the popliteal vein at the saphenopopliteal junction (SPJ). In the remaining, the SSV may connect to the GSV using the intersaphenous vein (vein of Giacomini) or may have several termination points through its thigh extension.<sup>4,10,12,13</sup> A discussion of perforating veins can be found in Chapter 158 (Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence).

## Reticular Veins

Reticular veins are thin-walled venules lying within the superficial compartment with diameters ranging from 1 to 3 mm.<sup>14,15</sup> They may communicate with the deep system, perforators, or to the superficial system. They may communicate specifically with the saphenous system and form a network of vessels termed the *lateral subdermic venous system* (LSVS).<sup>16</sup> The LSVS is located along the lateral aspect of the leg and extends above and below the popliteal area.<sup>17</sup> Ultrasound studies have revealed that the reticular veins of the LSVS may connect to telangiectasias in up to 88% of patients.<sup>18</sup>

## Telangiectasias

Telangiectasias differ from reticular veins in both size and appearance. Telangiectasias are defined as dilated venules, capillaries, or arterioles 0.1 to 1.0 mm in diameter.<sup>12,19</sup> The color of a telangiectasia depends on the origin of the vessel. Telangiectasias that arise from the arterial side of the capillary loop are flat and red, whereas those from the venous side are raised and blue.<sup>12</sup> These veins often appear in the thigh near the LSVS. Reticular veins may serve as “feeder” veins to telangiectasias.

## DIAGNOSTIC EVALUATION

### Clinical Scoring Systems

Most clinicians have adopted the Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) system to classify the physical findings associated with chronic venous insufficiency, and the classification was recently revised (Table 155.1). Representative images for the Clinical class may be seen in Figure 155.1 (see also Ch. 156, Postthrombotic Syndrome: Natural History,

**TABLE 155.1**

Revised Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) Classification.<sup>10</sup>

C class*	Description
C <sub>0</sub>	No visible or palpable signs of venous disease
C <sub>1</sub>	Telangiectasias or reticular veins
C <sub>2</sub>	Varicose veins
C <sub>2r</sub>	Recurrent varicose veins
C <sub>3</sub>	Edema
C <sub>4</sub>	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C <sub>4a</sub>	Pigmentation or eczema
C <sub>4b</sub>	Lipodermatosclerosis or atrophie blanche
C <sub>4c</sub>	Corona phlebectatica
C <sub>5</sub>	Healed venous ulcer
C <sub>6</sub>	Active venous ulcer
C <sub>6r</sub>	Recurrent active venous ulcer
E class	Description
E <sub>p</sub>	Primary
E <sub>s</sub>	Secondary
E <sub>si</sub>	Secondary – intravenous
E <sub>se</sub>	Secondary – extravenous
E <sub>c</sub>	Congenital
E <sub>n</sub>	No cause identified
A class	Description
A <sub>s</sub>	Superficial
A <sub>d</sub>	Deep
A <sub>p</sub>	Perforator
A <sub>n</sub>	No venous anatomic location identified
P class	Description
P <sub>r</sub>	Reflux
P <sub>o</sub>	Obstruction
P <sub>r,o</sub>	Reflux and obstruction
P <sub>n</sub>	No pathophysiology identified

\*Each clinical class is subcharacterized by a subscript indicating the presence (symptomatic, *s*) or absence (asymptomatic, *a*) of symptoms attributable to venous disease.

Pathophysiology, and Etiology).<sup>10</sup> Any patient in whom an endovenous procedure is contemplated should be evaluated in terms of this classification. Photographs of the target veins should be taken to document the clinical score and to compare the pre- and post-procedural results.

Patient-reported outcomes (PROs) are becoming central to evaluating venous pathology and its meaningful effects on patient quality of life. Scoring systems include the Venous Clinical Severity Score (VCSS), Varicose Veins Symptoms Questionnaire (VVSymQ), Aberdeen Varicose Vein Questionnaire (AVVQ), Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ), and others.<sup>20–22</sup> Patients undergoing



**Figure 155.1** CEAP Clinical Classification Representative Images. (A) C<sub>0</sub>: No visible or palpable signs of venous disease. (B) C<sub>1</sub>: Telangiectasias or reticular veins. (C) C<sub>2</sub>: Varicose veins or C<sub>2r</sub>: Recurrent varicose veins. (D) C<sub>3</sub>: Edema. (E) C<sub>4a</sub>: Pigmentation or eczema. (F) C<sub>4b</sub>: Lipodermatosclerosis (pictured) or atrophie blanche. (G) C<sub>5</sub>: Healed venous ulcer. (H) C<sub>6</sub>: Active venous ulcer or C<sub>6r</sub>: Recurrent active venous ulcer.

endovenous procedures may benefit from the concomitant evaluation of physician- and patient-reported outcomes.

## Imaging

Duplex ultrasonography (DUS) of the lower extremities is the standard for evaluating and diagnosing superficial venous insufficiency. Complete evaluation includes assessment of both reflux and obstruction in the deep, superficial, perforating, and tributary veins.<sup>4</sup> A more complete description of the technique can be found in Chapters 20, Clinical Evaluation of the Venous and Lymphatic Systems and 25, Vascular Laboratory: Venous Duplex Scanning. The goals of ultrasound are to identify and map the superficial or perforator veins to be treated, and to assess for hemodynamically significant reflux. The deep system should also be interrogated given the potential for altering patient management as the collective experience grows with the treatment of deep venous disease.<sup>5</sup>

## TREATMENT SELECTION

The goals of treating superficial venous insufficiency may range from alleviating symptoms, healing wounds, preventing progression, preventing recurrence, and improving cosmesis. The randomized controlled trial by Gohel et al. comparing early versus deferred endovenous ablation in patients with venous ulceration (EVRA) demonstrated an improvement in time to wound healing, increased ulcer-free time and was cost-effective.<sup>23</sup> Generally speaking, the most central point of reflux should be treated first.<sup>7</sup> In the majority of patients this is the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ). Wong et al. evaluated 239 limbs with primary reflux and 225 limbs with recurrent reflux, and they found SFJ incompetence in 53% and 69% of limbs, respectively.<sup>8</sup> In the same patient cohort they found SPJ incompetence in 21% and 25% of limbs, respectively.<sup>8</sup> Guex et al. found that 85% of limbs showed reflux in the GSV and 20% in the SSV.<sup>13</sup>

Patients with saphenous reflux frequently also exhibit varicosities, enlarged reticular veins, or telangiectasias. There is debate as to whether adjunctive procedures to treat these varicosities and telangiectasias should be performed simultaneously with saphenous treatment, or in a staged fashion. One study in which patients were simultaneously treated with EVLA and ambulatory phlebectomy found that 94% did not have to return for additional ambulatory phlebectomy procedures.<sup>9</sup> Conversely, in a study of 181 patients who underwent isolated RFA of the GSV, only 25% were able to avoid additional treatment with ambulatory phlebectomy.<sup>24</sup> Larger analyses, including systematic reviews and registries, corroborate the findings. In a review of 3375 limbs from the Vascular Quality Initiative (VQI) Varicose Vein Registry, Brown et al. demonstrated improvements in all C2 patients undergoing combined versus staged therapies, but with a significant relative improvement in VCSS for patients undergoing combined treatments.<sup>25</sup> A systematic review and meta-analysis by Aherne et al. that included 6915 limbs demonstrated clinical equipoise for both strategies with an improvement in early disease severity and quality of life scores in the combined treatment group.<sup>26</sup>

**TABLE 155.2**

### Endovenous Options for Treatment of Reflux

Type of Treatment	Vessels Treated
Radiofrequency ablation	Saphenous vein trunks
	Perforators
Endovenous laser ablation	Saphenous vein trunks
	Perforators
Chemical ablation	Saphenous vein trunks
	Saphenous vein tributaries
	Perforators
	Varicose veins not connected to saphenous vein trunks
Mechanicochemical ablation	Saphenous vein trunks
Adhesive closure	Saphenous vein trunks
Visual or surface sclerotherapy	Varicose veins
	Reticular veins
	Telangiectasias

The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) have compiled evidence-based recommendations for the care of patients with chronic venous disease.<sup>27</sup> Both EVLA and RFA are considered safe and effective and are considered first-line therapy for the treatment of symptomatic saphenous reflux. Both modalities are recommended in preference to open surgery because of a reduced convalescence time and a decreased incidence in postprocedural morbidity. EVLA and RFA are also recommended in preference to foam sclerotherapy because of improved efficacy and durability. Liquid or foam sclerotherapy is recommended for the treatment of telangiectasias, reticular veins, and varicose veins. Guidelines for choosing the appropriate endovenous intervention are listed in Table 155.2.

## THERMAL ABLATION TECHNIQUES

### Radiofrequency Ablation

RFA is a minimally invasive technology that provides efficacious treatment of superficial venous reflux with minimal post-procedural sequelae typically performed in an outpatient setting. The most commonly used RFA technology uses the “segmental ablation” method employed by the ClosureFast (Medtronic, Minneapolis, MN) procedure<sup>28</sup> (Fig. 155.2). The ClosureFast catheter is constructed such that it makes direct contact with the vein wall to deliver radiofrequency energy, and it ablates at 7-cm intervals. This results in destruction of the endothelium, contraction of vein wall collagen, and thrombus formation. Eventually, fibrosis occurs within the vein, which further constricts its lumen, resulting in a durable ablation.<sup>17</sup> Another recently approved radiofrequency device is Venclose (Venclose, San Jose, CA), which functions on the same principles using a similar “segmental ablation” method but with different lengths of treatment (2.5-cm and 10-cm intervals).



**Figure 155.2** (A) ClosureFAST Endovenous Radiofrequency Ablation Catheters brochure (Medtronic, Minneapolis, MN). (B) Dornier Medilas D laser (Dornier MedTech, Munich, Germany). (C) Sciton Pro-V laser (Sciton, Inc., Palo Alto, CA). (D) CoolTouch CTEV laser (CoolTouch, Inc., Roseville, CA). (E) Biolitec ELVeS PL laser (Biolitec AG, Jena, Germany).

Contraindications to the use of RFA include superficial venous thrombosis (SVT), deep venous thrombosis (DVT), venous aneurysm, and an ankle–brachial index of less than 0.9. Although the presence of a pacemaker is not a strict contraindication, pre-procedural evaluation by the patient's cardiologist should be considered.

### Preoperative Planning

On the day of the RFA procedure, the patient should be well hydrated to achieve maximal distention of the leg veins. Venodilation can be further enhanced by warming of the ultrasound gel and keeping the patient warm in the procedure room. Duplex ultrasonography may be performed prior to the procedure to mark the skin overlying the target treatment vein.<sup>29</sup>

### Radiofrequency Ablation Procedure

For ablation of the GSV, the general teaching is to ablate the lowest point of reflux. For C2 or C3 disease, access is initiated

no more than a hand's breadth (~10 cm) below the popliteal fossa. Should there be evidence of tissue damage (i.e., C4a/b, C5, C6 disease), consideration may be given to ablating further peripherally, taking care to separate the saphenous or sural nerve from the adjacent vein using tumescent anesthesia. To minimize the risk of thermal injury, treatment may be performed where the vein is deep to the saphenous fascia or 1 cm below the skin. With the patient in the reverse Trendelenburg position, lidocaine is administered at the selected site, and a 21-gauge needle is used to gain access under ultrasound guidance. A 0.018-inch guide wire is inserted into the GSV, and the needle is removed. The selected sheath is advanced over the wire, the 0.018-inch wire is removed, and the RFA catheter is inserted. The catheter is advanced to the point where treatment will begin. If it does not advance easily, a 0.025-inch guide wire may be back-loaded into the device to assist passage. Optimal positioning of the catheter tip is 2 to 2.5 cm distal to the SFJ, which is thought to reduce the risk of endothermal

heat-induced thrombosis (EHIT), which refers to the extension of thrombus into the common femoral vein.<sup>30,31</sup>

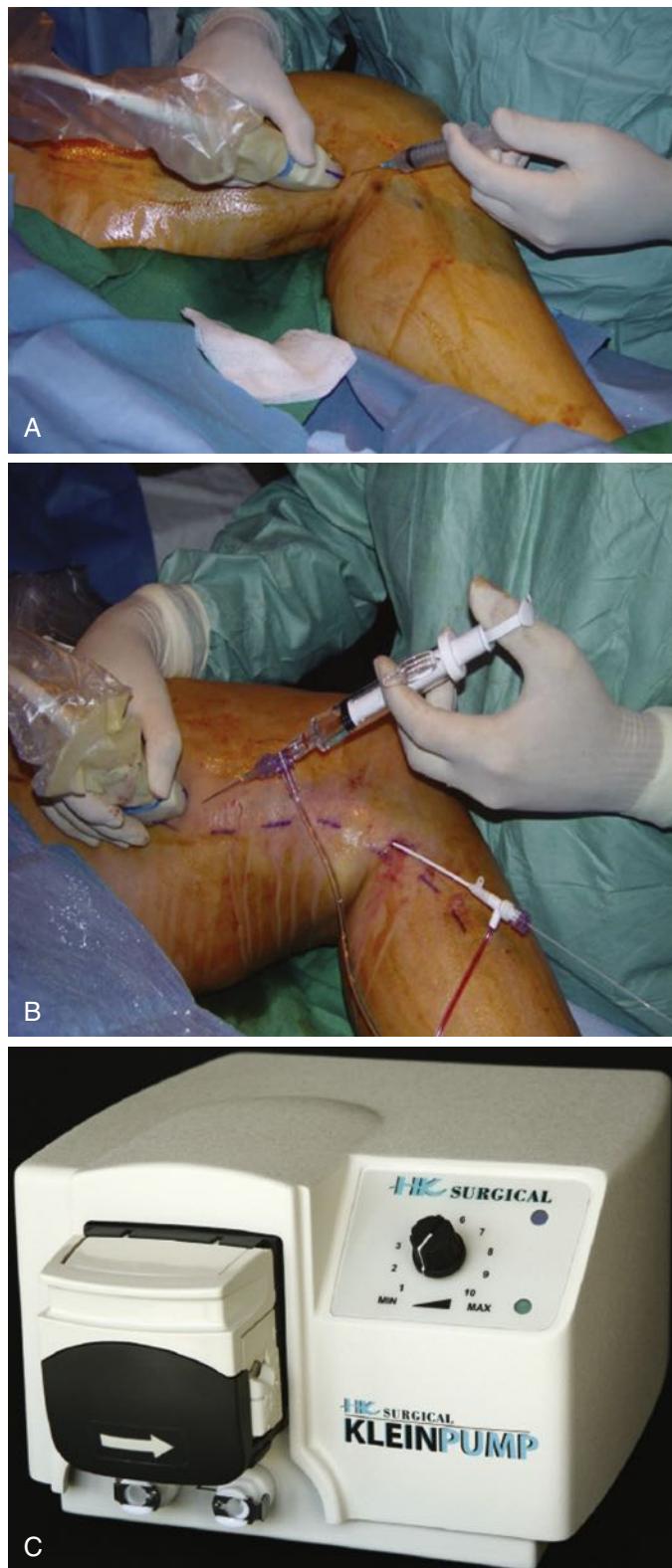
Once tip placement is confirmed by ultrasound, perivenous tumescent anesthesia is administered under ultrasound guidance along the entire treatment length of the GSV. Tumescent anesthesia serves not only as an anesthetic but also apposes the vein to the catheter and protects the surrounding tissues and skin from thermal damage.<sup>30,32</sup> Enough fluid should be instilled to create a 10-mm diameter around the vein (Fig. 155.3). A typical tumescent mixture includes 50 mL of 1% lidocaine with epinephrine in 450 mL of normal saline neutralized with 5 to 10 mL of 8.4% sodium bicarbonate.<sup>29</sup> The safe limit for tumescent lidocaine administration has been described as 35 mg per kg body weight.<sup>33</sup>

Many physicians use a pump system with a 22-gauge hypodermic needle to deliver the tumescent anesthesia because it decreases the time needed for administration as well as the number of needle punctures. Ideal needle positioning is within the saphenous compartment. After administration, the patient should be placed in the Trendelenburg position to assist in vein collapse, apposition, and exsanguination.<sup>32</sup> Following treatment completion, the sheath and catheter are withdrawn.<sup>32</sup>

During the procedure, compression over the treated vein and catheter with the ultrasound transducer in a longitudinal position improves vein wall apposition and technical success.<sup>34</sup> With the segmental ablation technique of the ClosureFAST system, each 7-cm segment of vein is treated independently for a 20-second interval. The initial treatment segment 2 to 2.5 cm peripheral to the SFJ requires two 20-second cycles to ensure successful ablation. Aneurysmal or large-diameter segments may be treated twice at the user's discretion, with a maximum of three treatment cycles.<sup>30</sup> For each 20-second cycle, the temperature must reach 120°C within 5 seconds. The generator monitors all parameters during the treatment cycle and alerts the user if the parameters are not successfully met. After treatment, duplex ultrasonography is utilized to assess the treated vein for ablation, absence of reflux, and DVT.

### *Discharge and Follow-Up*

Postoperative compression with graduated compression stockings (i.e. 20–30 or 30–40 mm Hg) or a multilayer compression dressing is recommended for at least 1 week.<sup>32,35,36</sup> Although commonly used as post-procedural care, the mandatory use of compression has come into question. The data have not shown a difference in patient-reported outcomes between patients who wear compression and those who do not, except possible transient improvement in patients undergoing concomitant microphlebectomy.<sup>37–39</sup> Patients are instructed to ambulate post-procedure.<sup>35</sup> A duplex ultrasound follow-up examination is advised at 72 hours to 1 week to assess for EHIT and ablation of the treated vein(s).<sup>35</sup> Further follow-up evaluations are performed according to physician preference. The American Venous Forum and Society for Vascular Surgery have compiled a set of guidelines for the diagnosis, management, prevention and surveillance for EHIT.<sup>40</sup>



**Figure 155.3** (A) Delivery of tumescent anesthesia with the hand injection method. (B) Delivery of tumescent anesthesia with a refillable syringe. (C) HK Klein tumescent pump (HK Surgical Inc., San Clemente, CA).

### *Clinical Results: Complications*

Complications of RFA include vessel perforation, thrombosis, pulmonary embolism (PE), phlebitis, EHIT, infection, nerve injury, and skin burns or discoloration.<sup>32</sup> Probstle

et al. initially reported comprehensive findings from 6-month data showing a low rate of side effects: ecchymosis, 6.4%; paresthesia, 3.2%; hyperpigmentation, 2.0%; hematoma, 1.6%; erythema, 1.6%; and phlebitis, 0.8%.<sup>30</sup> Thermal skin injury and DVT were not observed; however, during the first year of use of the ClosureFAST in 2007 numerous adverse events related to DVT were reported.<sup>41</sup> The rate of these events has decreased significantly as the current procedures/catheters were developed and clinicians gained experience with the procedure.

The European Closure Fast Clinical Study Group reported on the 3-year European follow-up on the ClosureFAST device.<sup>42</sup> The incidence of complications was low; the majority manifested and subsided within the first week after treatment. They included ecchymosis, 5.8%; erythema, 2.0%; hematoma, 1.4%; and phlebitis, 1.0%. Complications persisting beyond the first week included paresthesias (initial rate of 3.4%, which declined to 0.4% at 36 months) and pigmentation (initial rate of 2.4%, which also declined to 0.4% at 36 months). There were no reported cases of DVT or PE.

### Clinical Results: Outcomes

The European Closure Fast Clinical Study Group also reported the efficacy of the ClosureFAST device, demonstrating ablation rates of 92.6% and 91.9% on 3- and 5-year follow-up.<sup>42,43</sup> The reflux free rate at 5 years was 94.9%.<sup>43</sup> The VCSS improved from an average of 3.9 before treatment and persistently improved at 0.9 and 1.3 at 3 and 5 years, respectively.<sup>42,43</sup>

## Endovenous Laser Ablation

EVLA exhibits many procedural similarities to RFA, with the primary differences related to the type of catheter and mechanism of action. EVLA uses a bare-tip or jacket-tip fiber, and uses varying wavelengths, to deliver laser energy to a target area, resulting ultimately in fibrosis and occlusion of the target vein.<sup>44–46</sup>

### Laser Wavelength and Fiber Type

Different laser wavelengths have been used including 810, 940, 980, 1064, 1319, 1320, and 1470, 1540 and 1920 nm (see Fig. 155.2).<sup>47</sup> Research on the optical properties of blood has shown that different wavelengths have varying absorption characteristics; these may be categorized into the hemoglobin-specific laser wavelengths (HSLWs) and the water-specific laser wavelengths (WSLWs).<sup>48</sup>

A limited number of studies have evaluated these wavelengths for both efficacy and adverse events. Proebstle et al. compared the 940- and 1320-nm wavelengths.<sup>49</sup> The study demonstrated equal efficacy, but ecchymosis and pain occurred less commonly with the 1320-nm laser.<sup>49</sup> An analysis of the 810-nm wavelength versus the 980-nm wavelength also favored the higher wavelength in reducing post-procedural symptoms.<sup>50</sup> Additional studies have confirmed these findings.<sup>51</sup> Current research suggests that the various laser wavelengths are equally efficacious, but that there is a trend toward less pain and bruising with the higher-wavelength lasers.

More significantly, fiber type appears to contribute to post-procedural symptoms to a greater extent than laser wavelength. *In vitro* studies suggest that vein wall perforation may contribute to exacerbating post-procedural pain and bruising.<sup>52</sup> Radial and jacket-tip fibers are designed either to disperse the laser energy or to prevent direct contact with the vein wall, thereby reducing the risk of perforation. Clinically, radial- and jacket-tip fibers may cause less pain and bruising as compared to bare-tip fibers, and this relationship holds even with the use of longer wavelength lasers.<sup>52–54</sup>

### Preoperative Planning

Preoperative planning for EVLA is similar to that for RFA. Laser certification is required typically, and preparations should be made to have protective eyewear for the staff and patients.

### Endovenous Laser Ablation Procedure

GSV access is obtained just distal to the popliteal fossa (a micropuncture set may be used), and the distance from the access site to the SFJ is measured. A 0.035-in guide wire is advanced to the SFJ under ultrasound guidance. A long sheath is advanced to a point 2 to 2.5 cm peripheral to the SFJ.<sup>50</sup> The inner dilator and guide wire are removed, and the laser fiber is advanced within the sheath. The fiber is connected to the generator, and the aiming beam is turned on to help visualize the fiber tip under the skin. With the fiber held in place, the sheath is withdrawn to the locking mechanism of the fiber, with the tip of the fiber exposed 2 cm past the end of the sheath. An alternative method of access uses a direct method, whereby through a short sheath the laser fiber is negotiated directly to the targeted vein position. Positioning 2 to 2.5 cm peripheral to the SFJ is reconfirmed with ultrasound, and tumescent anesthesia is administered accordingly, as in RFA.<sup>50,55,56</sup>

### Procedural variations

Variations have developed with regard to procedural technique. Most are related to pullback time and the amount of energy delivered. In 2004, Timperman et al. introduced a modification whereby the amount of energy delivered per centimeter of vein treated was assessed, known as the linear endovenous energy density (LEED).<sup>49,57,58</sup> The authors found a direct correlation between LEED and treatment efficacy. The mean energy delivered for successfully treated veins was  $63.4 \pm 26.6 \text{ J/cm}$ , whereas in failed treatments an average of  $46.6 \pm 13.8 \text{ J/cm}$  was emitted.<sup>58</sup> No failures occurred in limbs receiving energy doses of  $80 \text{ J/cm}$  or greater.<sup>58</sup> In a subsequent study, veins treated with an average of  $95 \text{ J} \pm 16 \text{ J/cm}$  had a treatment success rate of 91% 9 months after the procedure.<sup>59</sup> In an attempt to assess the efficacy of treatment using higher LEEDs tempered by the increased risk of complications associated with higher energy use, an evaluation of the 1470-nm laser was performed comparing an average LEED higher than  $100 \text{ J/cm}$  to a LEED lower than  $100 \text{ J/cm}$ . Although the treatment was technically successful 100% of the time in patients treated using a LEED greater than  $100 \text{ J/cm}$ , there was an increased incidence of paresthesias in the group receiving the higher LEED. In addition, postprocedural analgesia intake was significantly less in the

lower LEED group.<sup>60</sup> The instructions range from as low as 30–50J/cm for the higher-wavelength lasers to 60–80J/cm for certain longer-wavelength lasers.<sup>50,61,62</sup> Continuous pullback is used while the operator watches the real-time energy readout on the generator and gauges speed with the 1-cm marks on the sheath. This method has proved to be more consistent than using time to gauge pullback because the same amount of energy is delivered in each case, regardless of wattage.

Once fiber-tip positioning is confirmed, the laser is switched from standby to ready mode and the foot pedal is depressed to deliver energy. The laser fiber and sheath are drawn through the vessel simultaneously in a continuous fashion. To prevent skin burns or trauma to the entry site, the user stops treatment when the tip of the laser fiber is approximately 1 to 3 cm proximal to the entry site.<sup>55,59</sup> Ablation of the vein and absence of DVT are visualized by duplex ultrasound.

### Discharge and Follow-Up

Discharge and follow-up for EVLA are the same as those for RFA.

### Complications

The incidence of procedure-related complications with EVLA has been relatively low and includes vessel perforation, thrombosis, PE, phlebitis, hematoma, infection, skin pigmentation, neovascularization, paresthesias, complications from tumescent anesthesia, irradiation of non-target tissue, hemorrhage, necrosis, skin burns, and pain.<sup>62</sup> Rates vary widely in the literature: DVTs, 0% to 5.7%; skin burns, less than 1%; nerve injury, 0% to 22%; and superficial thrombophlebitis, 0% to 25%.<sup>63,64</sup> Recently, Healey et al. performed a systematic review of thrombotic complications referable to EVLA.<sup>65</sup> Of the 15,676 patients evaluated, the rates were as follows: EHIT (2.92%), DVT (0.31%) and pulmonary embolus (0.04%).<sup>65</sup> A rare complication reported in both RFA- and EVLA-treated patients is the development of an arteriovenous fistula, occurring where the external pudendal artery crosses posterior to the GSV.<sup>66</sup>

As discussed earlier, some evidence suggests that higher-wavelength lasers produce less pain and bruising. The mechanism of the EVLA procedure that causes pain and bruising remains unclear, although some experts speculate that it is due to perforation of the vein wall by laser energy.<sup>49,67</sup> Aside from laser wavelengths, a novel adaptation to laser fibers that has shown a beneficial effect on perforation of the vein wall is the jacket-tip fiber. This technology features either a stainless steel or ceramic jacket that completely covers the tip of the fiber, with the tip being recessed within the jacket.<sup>68,69</sup> This design prevents the flat emitting face of the fiber tip from coming in contact with the vein wall.<sup>68,69</sup> Kabnick et al. carried out a pilot study to evaluate the efficacy and complications associated with jacket-tip fibers versus bare-tip fibers.<sup>67</sup> At 72 hours post-procedure, both treatment groups demonstrated 100% success; however, in the group treated with the jacket-tipped fiber, pain and bruising scores were lower.<sup>67</sup> Because vessel perforation has been directly linked to bruising, the study concluded that the lower bruising scores achieved in the jacket-tipped fiber

group could be attributed to fewer perforations.<sup>67</sup> In order to assess the use of a jacket-tipped fiber in a higher-wavelength laser, Maurins et al. evaluated a 1470-nm laser and compared treatments using a bare-tipped fiber, a jacket-tipped fiber, and a fiber with a radial-emitting tip.<sup>70</sup> All demonstrated similar efficacy in ablation. Kabnick and Sadek showed that fiber type may mitigate post-procedural pain and bruising to a greater extent than laser wavelength.<sup>52</sup>

### Outcomes

In addition to the low rate of complications demonstrated by EVLA, treatment outcomes of EVLA are at least equivalent to those of all other modalities. The seminal trial for establishing EVLA as an efficacious treatment was published by Min et al. in 2003.<sup>55</sup> Initial treatment results with an 810-nm laser showed a 98.2% initial success rate and an ablation rate of 93.4% at 2 years.<sup>45,55</sup> Proebstle et al. performed a study evaluating 1320- and 940-nm (15- and 30-W) lasers and reported favorable efficacy rates at 3 months of 90.3% (940 nm, 15 W), 100% (940 nm, 30 W), and 97% (1320 nm).<sup>49</sup> A prospective trial using the 980-nm laser on 500 limbs was published in 2007.<sup>61</sup> A 98% ablation rate was reported at the 1-week follow-up and remained constant with a 97.1% ablation rate at 4 years.<sup>61</sup>

More recently, the International Endovenous Laser Working Group evaluated long-term outcomes using EVLA for the treatment of patients with truncal reflux. The international registry evaluated 1020 limbs treated using a 980-nm bare-tipped laser. Treatment success rates were 92.3% at 1 year and 86.9% at 2 years, with no additional treatment failures at 3 years.<sup>71</sup> Furthermore, a Cochrane review evaluated 8 series comparing EVLA to traditional saphenectomy.<sup>72</sup> Safety, efficacy, durability, and patient-reported outcomes were found to be the same, but there was an increased incidence of neovascularization in the patients treated with surgery.<sup>72</sup>

Brittenden et al. conducted a three-way randomized controlled trial comparing EVLA, surgery and foam sclerotherapy, and they also reported on the 5-year follow-up.<sup>73,74</sup> Seven hundred and ninety-eight limbs were evaluated, and they did not find any differences in patient-reported outcomes between EVLA and surgery. Clinical outcomes were also favorable at the 6-week, 6-month and 5-year intervals.<sup>73,74</sup>

## NON-THERMAL NON-TUMESCENT ABLATION TECHNIQUES

### Chemical Ablation

The newer treatments that do not require the use of tumescent anesthesia are referred to as the non-thermal, non-tumescent (NTNT) techniques. Chemical ablation using foam sclerotherapy represents perhaps the longest-standing NTNT ablation technique. Physician-compounded foam using the Tessari method has a large body of literature supporting its safety and efficacy. Successful ablation rates range from 60%–95%.<sup>75–80</sup> Varithena (polidocanol injectable foam) represents the first proprietary foam sclerosant to gain FDA approval in the United

States. It has an indication for treatment of the GSV, AASV, and visible varicose veins in the lower extremities.<sup>81</sup> The VANISH-1 and VANISH-2 trials were the prospective trials that validated Varithena and demonstrated a 1-year ablation rate of 85% with concomitant improvements in patient-reported outcomes using the VVSymQ metric.<sup>82–84</sup> There were no cerebrovascular events or PEs, but 13 patients developed DVT, all of which resolved with anticoagulation.

## Outcomes

The VANISH-1 trial demonstrated that quality of life as measured by the VVSymQ improved regardless of the concentration of polidocanol endovenous microfoam (0.5%, 1% and 2%).<sup>82,83</sup> In the Polidocanol Endovenous Microfoam versus Vehicle for the Treatment of Saphenofemoral Junction Incompetence (VANISH-2) trial, elimination of reflux as demonstrated by DUS occurred in 85% of patients treated with foam compared with 2% in the placebo group. Patient-reported outcomes were improved in 80% of the treatment group compared with 20% of the placebo group. There were no cerebrovascular events or PEs, but 13 patients developed DVT, of which 6 were proximal. Half were treated with anticoagulation at the discretion of the investigator, and all resolved within a median of 29 days. The results were durable at 1 year, with no recurrent DVTs.<sup>84</sup>

A study published by the Varithena Study Group demonstrated that there were greater improvements in patient- and physician-reported outcomes using polidocanol endovenous microfoam compared with placebo. The HASTI score (heaviness, achiness, swelling, throbbing, itching) improved by 30.7 versus 16.7 ( $P < 0.001$ ) in the Varithena group. The m-VEINES-QOL/Sym (modified Venous Insufficiency Epidemiological and Economic Study – Quality-of-Life/Symptoms) and VCSS scores also improved in the Varithena group. Adverse events were mild and transient, including contusion, hematoma, limb discomfort.<sup>85</sup>

## Mechanochemical Ablation

Another NTNT methodology utilizes a combination of both mechanical and chemical treatments, again foregoing the use of heat energy entirely. This mechanochemical ablation (MOCA) is performed using the ClariVein device (Vascular Insights LLC, Madison, CT). The device consists of a single-use catheter with a rotating wire that protrudes from its tip, which causes mechanical damage to the endothelium and vein wall spasm by rotating at 3500 rpm at 2- to 3-second intervals.<sup>86</sup> The treatment is initiated 2 cm peripheral to the SFJ and, as the catheter is withdrawn, a sclerosant is dispersed onto the vessel wall. In a recent study, technical success for truncal veins was 99%, and 88% of veins remained closed at 1 year. No major complications occurred. VCSS decreased from 4.0 prior to the procedures to 1.0 at 1 year ( $P < 0.001$ ).<sup>87</sup>

These data have been corroborated for the SSV by Boersma et al. Their prospective series of 50 consecutive patients undergoing MOCA for treatment of SSV reflux demonstrated

100% technical success, with a 1-year closure rate of 100%. Clinical improvements in the VCSS were also observed.<sup>88</sup> Data continue to accrue, and a systematic review evaluated 1267 GSVs and 254 SSVs treated using Clarivein.<sup>89</sup> The procedure exhibited technical success 87%–92% of the time with a complication rate of <0.25.<sup>90</sup> Most recently, the LAMA trial was a randomized controlled trial comparing EVLA to MOCA.<sup>90</sup> 150 patients were randomized, and both cohorts exhibited improvements in symptoms, quality of life with low pain scores. Ablation rates at 1 year were improved in the EVLA as compared to the MOCA group (91% vs. 77%,  $P = 0.020$ ).<sup>90</sup>

## Adhesive Closure

The VenaSeal Closure System (Medtronic, Minneapolis, MN), which delivers n-butyl cyanoacrylate glue through a catheter, also avoids the use of tumescent anesthesia. The glue polymerizes when it contacts ionic compounds such as the components of blood, and it is considered a permanent implant. The VenaSeal cyanoacrylate closure (CAC) system is composed of an introducer sheath, an infusion catheter, a dispenser gun, and a proprietary cyanoacrylate adhesive. Access is gained into the refluxing truncal vein, and the catheter with the attached loaded dispenser gun is advanced to within 5 cm of the SFJ. Under ultrasound guidance, the glue is injected twice most centrally; then single injections are performed at 3-cm intervals while the catheter is withdrawn.

Almeida evaluated the treatment of eight limbs with GSV reflux and reported a technical success rate of 100%.<sup>91</sup> The safety, efficacy, and durability of this procedure were evaluated in a postmarket trial, the European Sapheon Closure System Observational Prospective (eSCOPE) trial.<sup>91</sup> Thirty-eight patients were treated, 36 of whom were available for follow-up at 24 months. The vein occlusion rate was 92% at 24 months, and the VCSS score also improved in all patients in this period ( $6.1 \pm 2.7$  vs.  $2.7 \pm 2.5$ ;  $P < 0.0001$ ).<sup>92</sup> Morrison et al. conducted a randomized controlled trial comparing CAC to RFA.<sup>93</sup> Two hundred and twenty-two patients were evaluated; post-procedural pain was similar, and ecchymosis was less in CAC as compared to RFA.<sup>93</sup> At 3 months, the effective ablation rate for CAC and RFA were 99% and 96%, respectively.<sup>93</sup> At the 24-month follow-up, durable ablation was noted in 95.3% in the CAC group and 94.0% in the RFA group.<sup>94</sup> Quality-of-life metrics improved equally in both groups, and there were no significant complications.<sup>94</sup> At 36 months, the results showed stability with ablation noted in 94.4% in the CAC group and 91.9% in the RFA group.<sup>95</sup> In the WAVES Study post-market registry a variety of treated veins were evaluated (48 GSV, 14 AASV, 8 SSV), and the real-world experience demonstrated a 100% ablation rate at 1 month with commensurate improvements in quality of life.<sup>96</sup> A type IV hypersensitivity reaction has been reported with CAC, and a commensurate evaluation was performed by Gibson et al.<sup>97</sup> In a study of 286 patients, a hypersensitivity reaction occurred in 6% of patients with the majority being mild and self-limiting. There was one severe case that persisted beyond 1 month.<sup>97</sup>

## Comparison of Outcomes for Radiofrequency Ablation, Endovenous Laser Ablation, Chemical Ablation, and Surgery

In a meta-analysis including 12,320 patients from 64 studies who had undergone treatment of truncal veins with RFA, EVLA, foam sclerotherapy, or surgery, the results over 32 months demonstrated better outcomes for RFA and EVLA compared with surgery and foam sclerotherapy. "Success" rates were 84% for RFA, 94% for EVLA, 78% for surgery, and 77% for foam sclerotherapy.<sup>98</sup> Rasmussen et al. performed a randomized controlled trial comparing RFA, EVLA, ultrasound-guided foam sclerotherapy, and surgical stripping for the treatment of GSV reflux in 500 patients.<sup>99</sup> Concomitant microphlebectomy was performed during every procedure. Foam sclerotherapy demonstrated the highest technical failure rate at 1 year (RFA, 4.8%; EVLA, 5.8%; foam sclerotherapy, 16.3%; surgery, 4.3%;  $P < 0.001$ ). One patient in the sclerotherapy group had a PE, and one person in the surgical group experienced a DVT. The highest post-intervention pain scores occurred in the surgical and laser groups (RFA, 1.21; EVLA, 2.58; foam, 1.60; surgery, 2.25;  $P < 0.001$ ). All sub-categories of patients had similarly improved Venous Clinical Severity Scores and quality-of-life scores at 1-year follow-up. Furthering the well-studied literature comparing the three modalities, the Cochrane Review by Nesbitt et al. evaluated 14 studies that compared RFA, EVLA, foam sclerotherapy and surgery.<sup>72</sup> The data were rather heterogeneous, and definitive conclusions could not be derived except that RFA, EVLA, and foam sclerotherapy are all safe, effective, and exhibit relative clinical equipoise, and are at least as effective as surgery.<sup>72</sup> One of the most recent systematic reviews of randomized controlled trials evaluating long-term outcomes of endovenous treatments evaluated 2185 limbs undergoing RFA, EVLA, foam sclerotherapy and surgery. Efficacy and recurrence rates did not differ significantly when comparing the endovenous modalities (RFA vs. EVLA) to each other or to surgery.<sup>75,100</sup>

## Sclerotherapy

Sclerotherapy can be used to treat a myriad of vein types and sizes, although it is most commonly used to treat smaller vessels such as the reticular veins and telangiectasias. It may be defined as the introduction of a chemical into the lumen of a vein to induce endothelial damage that results in thrombosis and eventually fibrosis.<sup>101</sup>

Relative contraindications to sclerotherapy include asthma, late complications of diabetes, hypercoagulable state, leg edema, advanced peripheral arterial occlusive disease, and chronic kidney disease. Absolute contraindications are a known allergy to the sclerosant, acute cellulitis, acute respiratory or skin disease, phlebitis migrans, acute superficial thrombophlebitis, pregnancy, hyperthyroidism, and a bedridden status.

The method used to deliver the sclerosing agent depends on the diameter of the target vein. For smaller veins such as telangiectasias, venulectases, and small reticular veins, liquid sclerotherapy is used.<sup>102</sup> Larger reticular veins and varicosities

may also be treated by liquid sclerotherapy with a higher concentration of sclerosing agent or by using foam sclerotherapy. Foam sclerotherapy involves the addition of air to a detergent sclerosing agent by means of agitation to produce a foam-like consistency, which allows for enhanced contact with the vein wall. Given that the sclerosing agent must make contact with the vein wall to cause endothelial damage, the primary limitation of sclerotherapy is vein diameter.

### Sclerosing Agents

Sclerosing agents are most commonly grouped into categories based on their mechanism of action.<sup>12</sup> Categories of currently available solutions include osmotics, alcohols, and detergents (Table 155.3).<sup>17</sup> Ideal sclerosing agents should effectively damage the endothelium, exhibit a low incidence of adverse events, and be painless to inject.<sup>12</sup>

#### Osmotic agents

Osmotic agents are thought to cause dehydration of endothelial cells through osmosis, which leads to endothelial destruction.<sup>17</sup> The primary osmotic agent used in the United States is hypertonic saline (23.4% sodium chloride). Although not FDA-approved for use in sclerotherapy, it has been used by physicians for many years. The second agent consists of 10% sodium chloride mixed with 25% dextrose.<sup>103</sup> The most widely known commercial version of this agent is Sclerodex, manufactured by Omega Laboratories, Ltd. (Montreal, Canada).<sup>103</sup>

#### Alcohol agents

Alcohol agents are relatively weak sclerosants that cause irreversible destruction of endothelial cells on contact.<sup>104</sup> The main alcohol agent used for sclerotherapy is 72% chromated glycerin (Chromex, Omega Laboratories, Ltd. Montreal, Quebec, Canada), which is popular in Europe but is not FDA-approved in the United States. Because of its weak nature, glycerin is used only for telangiectasias.<sup>105</sup> Nonchromated glycerin is also used but is available only through compounding pharmacies. A typical mixture for this solution consists of two parts 72% non-chromated glycerin to one part 1% lidocaine with epinephrine.

#### Detergent agents

Detergent agents are potent sclerosants that destroy the target vein by aggregating on the endothelial wall, disrupting the cell surface membrane, and causing thrombosis.<sup>104</sup> Three agents are currently FDA-approved in the United States: sodium morrhuate (Scleromate, Glenwood, LLC, Englewood, New Jersey), ethanolamine oleate, and sodium tetradecyl sulfate (STS) (Mylan Pharmaceuticals, Pittsburgh, PA).

Although sodium morrhuate is FDA-approved, it exhibits a high incidence of skin necrosis and anaphylaxis.<sup>106</sup> Similarly, ethanolamine oleate is a viscous solution that is difficult to inject and not commonly used.<sup>104</sup> STS has a long history of safety and efficacy in treating telangiectasias, reticular veins, and varicose veins and is the most frequently used detergent sclerosant.

A fourth detergent agent popular in both Europe and the United States is polidocanol (Aethoxysklerol, Kreussler

**TABLE 155.3** Sclerosing Agents

Agent	Manufacturer	Category	FDA Approved?	Strength	Advantages	Disadvantages
Hypertonic saline	Multiple	Osmotic	Off-label use	++	Low risk of allergic reaction, wide availability, rapid response	Off-label use, painful to inject, hyperpigmentation, necrosis, rapid dilution; not recommended for facial veins
Sclerodex (hypertonic saline and dextrose)	Omega Laboratories, LTD, Montreal, Canada	Osmotic	No	++	Low risk of allergic reaction, low risk of necrosis, high viscosity	Not FDA-approved, stings when injected, hyperpigmentation
Chromex (72% chromated glycerin)	Omega Laboratories, LTD	Alcohol	No	+	Low incidence of hyperpigmentation, necrosis, and allergic reaction	Not FDA-approved, weak sclerosing agent, highly viscous and painful to inject, may cause hematuria at high doses
Nonchromated glycerin	Compounded at pharmacy	Alcohol	Off-label use	+	Low incidence of hyperpigmentation, necrosis, and allergic reaction	Weak sclerosing agent, typically used only for telangiectasias
Scleromate (sodium morrhuate)	Glenwood, LLC, Englewood, NJ	Detergent	Yes	+++	FDA-approved	High incidence of skin necrosis and anaphylaxis
Sotradecol (sodium tetradecyl sulfate)	BionichPharma, Inc., Morgantown, WV (distributed by AngioDynamics, Latham, NY)	Detergent	Yes	++++	FDA-approved, low risk of allergic reaction, potent sclerosant	Potential necrosis with extravasation, matting of telangiectasias
Varithena (polidocanol 1%)	BTG International Inc., West Conshohocken, PA	Detergent	Yes	+++	FDA-approved, very low risk of allergic reaction, painless to inject	Matting of telangiectasias

FDA, U.S. Food and Drug Administration.

Pharma, Wiesbaden, Germany).<sup>107</sup> It currently has FDA approval in the United States and is distributed under the trade name Asclera (Merz Aesthetics Inc., San Mateo, CA). In previous studies comparing polidocanol with STS, fewer complications were reported with polidocanol.<sup>108,109</sup> As stated previously, the first proprietary foam sclerosant to gain FDA approval in the United States is Varithena, polidocanol injectable foam 1% (Boston Scientific Corporation, Marlborough, MA), and it is comprised of a low-nitrogen (<0.8%) microfoam mixture with an O<sub>2</sub>:CO<sub>2</sub> ratio of 65:35.<sup>81</sup>

### Preoperative Planning

Digital photographs of the target veins should be obtained to document their appearance pre-procedure. Larger target veins such as varicose veins should be traced with a surgical marker with the patient standing because they may be challenging to identify with the patient recumbent. Preoperative marking is typically not required for smaller veins such as telangiectasias and reticular veins. Truncal ablation and peripheral sclerotherapy may be used in a combined or staged approach.<sup>110</sup>

Depending on the quantity and severity of pathologic veins, multiple sclerotherapy treatments may be necessary. It

is important to establish the expectation with the patient that several sessions may be required to achieve the desired result.

In planning sclerotherapy, another decision point is whether to use liquid, foam or a combination of the two.<sup>111</sup> In the selection of an agent, the strength of the agent should match the size of the vessel so that the smallest volume and concentration can be used.<sup>112</sup> Sclerosants are diluted by blood immediately on injection, making it challenging to treat larger-diameter veins with liquid sclerotherapy. Liquid sclerotherapy is best reserved for small reticular veins and telangiectasias.<sup>102</sup> Foamed agents have increased surface area related to the bubbles and stay in contact with the endothelium longer. They are therefore more effective in the treatment of larger reticular veins and varicose veins, and Varithena has an indication for treatment of the GSV as well as varicose veins in the thigh and leg.<sup>113</sup>

### Sclerotherapy Procedure

After preoperative preparation, the sclerosing agent is diluted with 0.9% saline according to the size of the vein (Table 155.4). In general, dilutions for STS range from 0.1% to 3%, and for polidocanol from 0.25% to 1%. Although rare, anaphylaxis can occur, and it is essential to have resuscitation equipment available.<sup>114</sup>

**TABLE 155.4**

## Recommended Concentrations for Sodium Tetradecyl Sulfate

Indications	Recommended STS Concentration (%)
Varicose veins 4–8 mm in diameter	0.5–3.0
Reticular veins 2–4 mm in diameter	0.25–0.5
Telangiectasias 0.1–2.0 mm in diameter	0.125–0.25
Recurrent varicosities	0.5–3.0
Failed segments of endothermal ablation	0.5–3.0
Unsightly veins of the hands and feet	0.25–0.5
Congenital malformations	0.125–0.25
Vascular malformations	0.125–0.25
Facial telangiectasias	0.125–0.25

STS, sodium tetradecyl sulfate.

### Liquid sclerotherapy

After dilution of the agent, multiple syringes are filled and assembled with 30-gauge needles. Veins should be treated from the largest diameter to the smallest diameter and in a central-to-peripheral orientation.<sup>115</sup> For instance, the reticular veins of the LSVS feed telangiectasias. When an agent is injected into a reticular vein, the agent may flow into the telangiectasias as well, thereby reducing the number of treatments necessary. Transillumination can be beneficial for identifying reticular and feeding veins associated with telangiectasias.

The amount of sclerosant injected per site depends on the size of the vein; for larger varicose veins, 1 mL or less per site is advisable.<sup>101</sup> Reticular veins typically require 0.25 to 0.5 mL per site, with smaller telangiectasias necessitating 0.1 to 0.2 mL per injection.<sup>111,114</sup> While avoiding forceful pressure, injections should be made slowly and not more than a few centimeters from the puncture site (Fig. 155.4). Strong pain during injection may be an indicator of extravasation; in such cases the injection should be stopped immediately given the risk for skin necrosis.<sup>6</sup> Injections are delivered in 2- to 3-cm intervals until the entire length of the target vessel has been treated.<sup>116</sup> To help minimize bleeding, a 2- by 2-inch gauze sponge is placed over each injection site and secured with tape. Graduated compression hose is applied to the treated limb(s), and patients are instructed to wear them from 3 days to 3 weeks to reduce thrombus formation and improve outcomes.<sup>117</sup> A typical initial sclerotherapy session consists of 10 to 20 injections.

### Ultrasound-guided foam sclerotherapy

The method widely used today involves the use of a three-way stopcock connected to two syringes; it was developed by Tessari in 1999.<sup>118</sup> One of the main criteria for foam to be viable is that bubble size must be 100 µm or less.<sup>119,120</sup> The pure form of the sclerosing agent is contained on the bubble surface; therefore, concentration is related to bubble size and air-to-liquid ratio. For the Tessari method, a ratio of one part liquid to four



**Figure 155.4** Liquid Sclerotherapy Injection.

or five parts air is highly effective.<sup>121</sup> The amount of foam to be injected can be calculated using the formula  $V = \pi \times (D/2)^2 \times L$  (where V is volume, D is diameter, and L is length).<sup>122,123</sup> Other factors which contribute to success with foam sclerotherapy are stability and longevity.<sup>120</sup> Using the Tessari method, significant coalescence does not begin until after the first 1 to 2 minutes.<sup>119,120,122–125</sup>

Depending on the size and depth of the target veins, duplex ultrasound can be helpful in guiding the injection of foamed sclerosants.<sup>111</sup> Foam is highly visible with ultrasound, allowing for more accurate injection. It also enables immediate postinjection observation of vein compressibility as a predictor of treatment efficacy.<sup>126</sup>

Ultrasound-guided sclerotherapy using a Tessari-like method is performed in a similar fashion to foam sclerotherapy without ultrasound.<sup>126</sup> Target vein segments should be marked before the procedure. Prior to starting, the patient should be placed in a Trendelenburg position. After the treatment area is mapped, access to the first vein to be treated is achieved with a regular or butterfly needle under ultrasound guidance. Access is confirmed by return of blood, and the needle/butterfly is taped to the patient's leg. The foam solution is created by a rapid mixing of the air and chemical back and forth between two syringes connected via a three-way stopcock for a total of 20 cycles.<sup>119</sup> After most of the solution has been moved to one syringe, the filled syringe is connected to the needle, and intravascular positioning is reconfirmed with ultrasound. Varithena represents the FDA-approved proprietary foam. A small amount of foam should be injected initially, under ultrasound, to confirm needle placement within the vein. The amount of foam delivered is determined during injection with the use of ultrasound to visualize when the targeted vein is filled (Fig. 155.5). Upon completion, full-length graduated compression stockings (30 to 40 mm Hg) are applied.

### Catheter-directed sclerotherapy

Sclerosants can also be injected using catheters. An end-hole catheter can be placed distal to the SFJ using ultrasound



**Figure 155.5** Ultrasound-Guided Foam Sclerotherapy Injection.

guidance.<sup>122</sup> The catheter is then withdrawn while the user delivers a foamed sclerosing agent under ultrasound guidance.<sup>125</sup> The technique is similar to that used in ablation procedures. Kolbel et al. achieved clinical success by injecting foamed polidocanol through a long introducer sheath as it was retracted through the GSV.<sup>127</sup> In 2000, Min and Navarro reported using a 5-F infusion catheter to deliver STS into the GSV with the patient in the Trendelenburg position.<sup>75</sup> A recent meta-analysis looking at 62 studies comprising 3689 patients demonstrated possibly improved ablation rates and reduced complication rates when compared to ultrasound-guided sclerotherapy, with the caveat that the source data exhibited significant limitations.<sup>128</sup>

### Discharge and Follow-Up

Some authors recommend that the patient wear a 30- to 40-mm Hg compression stocking for 24 hours after treatment of reticular veins and telangiectasias and for 7–10 days after treatment of varicose veins and perforators.<sup>76</sup> Compression may improve the efficacy of treatment by reducing the diameter of treated veins and by lessening reflux during walking.<sup>111</sup> A recent systematic review evaluating nine studies for patients receiving post-sclerotherapy compression demonstrated beneficial outcomes in the short term, including reduced post-procedure symptoms.<sup>129</sup> This is corroborated further by the AVF-SVS guidelines on compression therapy.<sup>130</sup> They may return to activities of daily living but should avoid heavy aerobic exercise involving the lower extremities for 2 weeks. Tylenol may be taken if needed; however, patients should avoid aspirin, ibuprofen, and other anti-inflammatory medications for at least 48 hours. In addition, whirlpools, saunas, and hot baths should be avoided for at least 48 hours after the procedure.

### Complications

The majority of complications from sclerotherapy are minor and transient.<sup>131</sup> They include hyperpigmentation, telangiectatic matting, pain, and urticaria.<sup>115,131</sup> Hyperpigmentation

occurs in 10% to 30% of patients and is believed to depend on the concentration of sclerosant and to a lesser degree the vessel size and agent used (Fig. 155.6).<sup>126,131,132</sup> Spontaneous resolution is observed in 70% and 99% of cases at 6 months and 1 year, respectively.<sup>132</sup> Telangiectatic matting occurs in 15% to 20% of patients, but usually resolves in 3 to 12 months.<sup>132,133</sup> Pain on injection largely relates to the sclerosing agent used. Detergent agents cause little or no pain, whereas hypertonic saline may be painful to inject. Urticaria is very common but fades within the first 24 hours.<sup>131</sup>

Rarely observed are more serious complications including cutaneous necrosis, superficial thrombophlebitis, nerve damage (saphenous, sural), allergic reaction (anaphylaxis), DVT, PE, and inadvertent arterial injection.<sup>115,131</sup> Necrosis is rare and most often caused by extravasation with hypertonic saline. Superficial phlebitis is usually a result of direct injury to the vein and typically occurs 1 to 2 weeks after the procedure.<sup>131</sup> It is characterized by pain, tenderness to touch, heat, and erythema and can be treated by removal of the coagula via puncture extraction.<sup>131</sup> The incidence of DVT is low after sclerotherapy, with less than 2% of patients affected.<sup>134</sup> Bradbury et al. evaluated one of the largest contemporary series for foam sclerotherapy used in the treatment of truncal reflux.<sup>135</sup> A total of 1252 limbs were treated, three patients experienced DVT, and there was 1 PE. Five patients experienced neurologic sequelae in the form of transient visual disturbances, presumably from embolization of foam.<sup>136</sup> Treatment for neurologic sequelae consists of administration of 100% oxygen with the selective use of hyperbaric oxygen. The safety evaluation during the VANISH-1 trial demonstrated mild sequelae that resolved with conservative management, and there were no PEs.<sup>82</sup>

### Clinical Results

Sclerotherapy is safe and efficacious. Kern et al., in a study using the liquid sclerotherapy method with chromated glycerin to treat telangiectasias and reticular veins, found that 76% of patients who wore compression stockings after the procedure had a successful outcome.<sup>137</sup> Goldman reported the results of a prospective trial in 2002 comparing Sotradecol and polidocanol and found both agents to have a 70% rate of efficacy.<sup>108</sup> Belcaro et al. collected data from numerous trials evaluating STS liquid sclerotherapy versus STS foam sclerotherapy and reported efficacy rates of 90.2% and 92.2%, respectively.<sup>127</sup> A related study by Yamaki et al. compared polidocanol duplex ultrasound-guided liquid sclerotherapy and polidocanol duplex ultrasound-guided foam sclerotherapy of the GSV and reported complete closure rates of 17.5% and 67.6%, respectively.<sup>75</sup>

Studies evaluating foam sclerotherapy alone have also shown positive treatment results. Frullini and Cavezzi performed foam sclerotherapy with STS via the Tessari method and reported a success rate of 93.3%.<sup>112</sup> Using ultrasound-guided foam sclerotherapy with polidocanol, Bergan et al. treated 328 lower extremity veins and recorded complete absence of reflux in 79.8% of treated veins.<sup>77</sup> Other studies have reported similar results.<sup>76,78–80</sup>



**Figure 155.6** (A) Reticular veins and telangiectasias before treatment. (B) Hyperpigmentation after the procedure.

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# Postthrombotic Syndrome: Natural History, Pathophysiology, and Etiology

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## INTRODUCTION

Chronic venous disorders (CVD) are a spectrum of venous diseases that affect the lower limb. The manifestations include varicose veins, pain, edema, skin changes, and venous ulcerations. The pathophysiology involves reflux within the deep, superficial, and perforating vein valves and/or venous obstruction, usually postthrombotic in etiology. Both reflux and residual obstruction can produce venous hypertension and the manifestations of CVD. Compared with nonthrombotic etiologies, lower extremity deep venous thrombosis (DVT) often leads to higher rates of the advanced forms of CVD, with skin changes and ulcerations.<sup>1</sup> DVT often begins in the legs (calf) near valve cusps and may propagate proximally.<sup>2</sup> About 50% of leg thrombi resolve spontaneously; however, nearly 20% will extend more proximally into the popliteal, femoral, and iliac veins.<sup>3</sup> The consequences can range from minor leg swelling at the end of the day to severe complications such as chronic debilitating lower-limb pain, intractable edema, and venous leg ulceration.<sup>4</sup> Other symptoms associated with postthrombotic syndrome (PTS) include leg cramping, pruritus, fatigue, heaviness, venous claudication, paresthesias, and bursting thigh pain with exercise, termed *venous claudication*. It is estimated that PTS occurs in 20% to 50% of patients from a few months to 1 to 2 years, following

a lower extremity DVT.<sup>5</sup> The importance of PTS is the significant morbidity and reduction of quality of life, and the economic costs associated with treatment of this disease. Early recognition and intervention may reduce the sequela of PTS.

## ETIOLOGY AND EPIDEMIOLOGY

DVT affects up to three individuals per 1000 annually in the general population. DVT is the major cause of secondary CVD, and is strongly associated with PTS.<sup>1</sup> Although primary CVD (CVD in which no etiologic factor can be identified; see Chapters 154, Varicose Veins: Surgical Treatment 155, Varicose Veins: Endovenous Ablation and Sclerotherapy and 157, Treatment of Chronic Venous Disorders) is much more common than secondary CVD, DVT is responsible for CVD in 18% to 28% of limbs. In a study of 64 patients with 73 limbs affected by DVT, 4% of limbs had skin changes at 1 year, increasing to 25% at 5 years.<sup>1</sup>

Recurrent ipsilateral DVT is the most important risk factor for developing PTS, with a sixfold increased risk in one study.<sup>5</sup> Numerous other studies have found significant associations between ipsilateral recurrent DVT and the risk of developing PTS, with increases of up to 630% (Table 156.1).<sup>1,7</sup> Recurrent ipsilateral DVT is also the most important clinical factor for progression of CVD (relative risk [RR] 4.4; 95% CI, 1.4 to 13.3,  $P = 0.0049$ ).<sup>6,7</sup>

**TABLE 156.1** Clinical Progression in Relation to Duplex Ultrasound Findings

DU Findings	Progression (N = 23)	Unchanged (N = 50)	RR (95% CI)	P
Recurrent DVT	10	6	4.4 (1.4–13.3)	0.0049
Progression reflux	7	11	0.74 (0.4–1.5)	0.56
No change	6	33	0.76 (0.35–1.69)	0.6

CI, confidence interval; DU, duplex ultrasound; DVT, deep vein thrombosis; RR, relative risk.

From Table III of Labropoulos N, Gasparis AP, Tassiopoulos AK. Prospective evaluation of the clinical deterioration in post-thrombotic limbs. *J Vasc Surg*. 2009;50:826–830.

The incidence of recurrent DVT is 17% at 2 years, 24% at 5 years, and 30% at 8 years.<sup>1,8</sup> It is estimated that 5% to 10% of patients with recurrent DVT develop severe PTS (lipodermatosclerosis, ulceration) after a proximal DVT. Ulceration as a consequence of PTS has a cumulative incidence of approximately 5% over 10 years.<sup>4</sup> However, some studies have reported that the cumulative incidence of PTS continues to increase, even up to 20 years after DVT diagnosis.<sup>9</sup>

The postthrombotic syndrome has been shown to occur in 20%–50% of patients within 1–2 years following a DVT.<sup>10</sup> Features of venous thrombosis including extensive DVT, ipsilateral recurrent DVT, and insufficient anticoagulation increase the risk of developing clinically significant CVD. Factors found to affect the onset of secondary CVD were the event type and site of venous thromboembolism. Several studies have found that the persistence of obstruction following a DVT, and not the presence of reflux, imparts the greater risk of developing PTS and progression of the disease.<sup>11,12</sup> Another cross-sectional study of patients with previous DVT determined that the combination of reflux in the superficial and deep venous systems, and involving the entire limb, resulted in significant symptoms and signs of skin changes including ulcerations.<sup>13</sup> It appears that the combination of obstruction and reflux together are more detrimental than each factor alone in the development of PTS.<sup>14</sup>

In one study, 355 patients (55% male) with a first time symptomatic DVT were followed at 6-month intervals for 8 years. A total of 245 patients (69%) completed 5 years of follow-up, and 148 patients (42%) completed 8 years of follow-up. The mean age was 63 years old (range 29 to 83). The cumulative incidence of recurrent venous thromboembolism was 4.9% after 3 months, 8.6% after 6 months, 17.5% after 2 years, 24.6% after 5 years, and 30.3% after 8 years.<sup>8</sup> Eighty-four patients developed PTS, with a cumulative incidence of 22.8% after 2 years and 28.0% after 5 years. The incidence did not change substantially thereafter. Of the 84 patients with PTS, 30.2% had severe PTS. Of note, the development of ipsilateral recurrent DVT was associated with an increased risk for PTS (hazard ratio 6.4; 95% CI, 3.1 to 13.3) and more predictive of skin damage (odds ratio 5.3; 95% CI, 1.2 to 24.2) compared with non-recurrence ( $P = 0.001$ ).<sup>8</sup>

Other features of venous thrombosis, including location and extent of DVT and insufficient anticoagulation, also increase the risk of developing clinically significant CVD.

In one study, patients with DVT were followed for a mean of 3.4 years with duplex ultrasound, to determine the effects of location and extent of DVT on the development of CVD. Patients were divided into a group which presented with multisegment DVT and a group which presented with single-segment DVT. More patients with multisegment disease were found to be symptomatic, and the prevalence of skin damage and ulceration was higher in this group compared with that in the group with single segment DVT (61 of 79 vs. 26 of 41,  $P < 0.001$ ; 29 of 79 vs. 6 of 41,  $P = 0.019$ , respectively).<sup>15</sup>

The most severe forms of PTS, such as venous leg ulcers, produce adverse social and economic outcomes, and significant decreases in quality of life.<sup>16</sup> The economic burden of PTS is significant; costs increase by roughly 50% compared with those associated with DVT without PTS. The high cost of treating venous leg ulcers is due largely to the need for surgery, lost workdays, and loss of employment. It is estimated that 2 million workdays are lost annually in the United States as a result of venous leg ulcers.<sup>4</sup>

Further examination of all causes (primary CVD and secondary PTS) of venous leg ulcers shows that the annual US expenditure for treating venous leg ulcers is approximately \$14.9 billion (quantification of the incremental resource use and costs of treating these patients [\$6391 per Medicare patient, and \$7086 per privately insured patient]).<sup>17</sup> In addition, PTS has a significant impact on quality of life, which worsens with advanced forms of PTS compared with patients with DVT but no PTS. One study demonstrated that patients with venous ulceration missed more workdays than those without ulceration, which resulted in increased work-related costs of 29% in the ulceration group ( $P < 0.0001$ ). It has been shown that patients with PTS have a generic physical quality of life that is worse than for patients with osteoarthritis, angina, and chronic lung disease.<sup>4</sup>

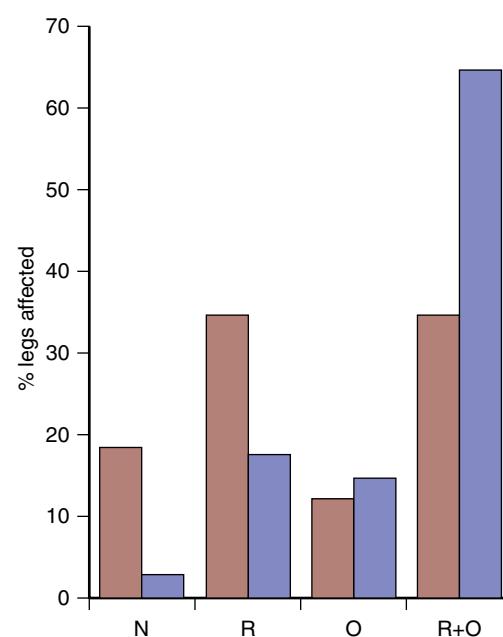
## CELLULAR AND MOLECULAR MECHANISMS

The critical factor in PTS is DVT formation, with vein wall injury, poor recanalization of thrombus, persistent obstruction of venous outflow, and valvular insufficiency.<sup>18</sup> This leads to ambulatory venous hypertension. Thrombosis of the valve and vein wall involves an acute proinflammatory and prothrombotic state, with damaged endothelium and expression of tissue

factor and plasminogen activator inhibitor-1, release of von Willebrand factor, P-selectin and E-selectin, and amplification of the coagulation cascade. DVT results in a complex process of leukocyte recruitment and microparticle release. Microparticles are phospholipid vesicles shed from platelets, leukocytes, and endothelial cells. Fusion of microparticles with activated platelets initiates the release of tissue factor and thrombosis. P-selectin localizes pro-thrombotic microparticles to areas of stasis and promotes thrombosis. P-selectin receptor P-selectin glycoprotein ligand-1 (PSGL-1) is expressed on platelets and leukocytes and concentrated in the area of thrombus formation leading to thrombus amplification. Microparticles are prothrombotic by inhibiting fibrinolysis and expressing PAI-1, and are localized to the P-selectin:PSGL-1, increasing thrombosis.<sup>19</sup> The initiating molecular factors for DVT progression include the following interactions that are time-dependent and simultaneously occurring: activation of adhesion molecules leading to interactions of endothelium and neutrophils via increased P- and E-selectins, activation of monocytes and macrophages, activation of toll-like receptors, release of microparticles from platelets, endothelial cells, and procoagulant monocytes and macrophages which are then concentrated into the area of thrombosis leading to thrombus amplification, galectin-3-binding protein expression and galectin-3, chemokines, cytokines, matrix metalloproteinases, and growth factors. All of these functions and complex steps are important factors involved in determining the progression or mitigation of coagulation, recanalization with resolution of thrombosis, and/or persistent inflammation and thrombosis with vein wall damage and eventual fibrosis.<sup>6,19,20</sup> Given the importance of the selectins in promoting thrombosis, several important and landmark studies were performed to evaluate the inhibition of both P-selectin and E-selectin. Previously and recently published data involving a baboon model of iliac vein thrombosis demonstrated that inhibition of P-selectin and E-selectin caused significant recanalization of the lumen and decreased inflammation and fibrosis within the vein wall with no difference in coagulation parameters or increased clinical bleeding.<sup>21,22</sup> Clinical application of an E-selectin inhibitor was successfully utilized in two patients with lower extremity venous thrombosis resulting in clinical improvement, and the pharmacology studied in healthy adult subjects.<sup>23</sup> Additional data addressing molecular and cellular mechanisms of PTS formation can be found in Chapters 9, Venous Pathophysiology and 146, Acute Deep Venous Thrombosis: Epidemiology and Natural History.

## NATURAL HISTORY, PATHOPHYSIOLOGY, AND CLINICAL IMPLICATIONS

Initial studies suggested that venous valvular insufficiency constituted the primary pathophysiology in patients with PTS. In an older study, strain-gauge plethysmography was used to measure venous outflow (a measure of chronic obstruction after DVT) and venous refilling times (a measure of valvular incompetence) in normal patients and those with PTS. The authors



**Figure 156.1** Proportion of limbs demonstrating no abnormality (N), reflux alone (R), obstruction alone (O), and reflux with obstruction (R + O) after DVT with respect to symptoms. Blue bars indicate asymptomatic legs; brown bars indicate legs with clinical features of PTS. (From Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. *J Vasc Surg*. 1995;21:307–312.)

demonstrated that significantly reduced venous refilling times were associated with severe PTS, including skin changes and ulceration. There were no significant differences in venous outflow between patients with PTS and those without.<sup>24</sup>

More recently, however, studies have found that both the persistence of obstruction and valvular incompetence following DVT impart a greater risk of developing PTS as well as progression of disease.<sup>1,25,26</sup> In a study of 217 limbs in 183 patients, all with previous DVT, the combination of reflux in both the superficial and deep venous systems, especially when reflux involved the entire limb or below the knee, led to the most significant symptoms and signs of skin changes and ulceration.<sup>27</sup> In another study of 34 patients with PTS, 65% were found to have both reflux and obstruction in the deep veins of limbs with PTS. Obstruction alone was present in 15%, reflux alone in 18%, and normal findings in 3% (Fig. 156.1). Hyperpigmentation was present in 11 limbs; both reflux and obstruction were found in 9 of the 11 cases.<sup>26</sup>

Understanding the natural history of DVT and PTS is important in determining the factors that are associated with thrombus resolution and avoidance of debilitating, costly PTS. Prior investigations sought to clarify the relationships between lysis of venous thrombi and the development of incompetent valves, and to determine the relationships between development of symptoms of PTS and residual venous occlusion and valvular incompetence. An early study described outcomes in 21 patients (21 limbs) with acute DVT (mean age of 46 years) followed at intervals of 7, 30, 90, 180, and 270 days. The study endpoints were the percentage of patients with lysis