

Chapter 2

Acute venous disease: Venous thrombosis and venous trauma

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Acute venous disorders include deep venous thrombosis, superficial venous thrombophlebitis, and venous trauma. Deep venous thrombosis (DVT) most often arises from the convergence of multiple genetic and acquired risk factors, with a variable estimated incidence of 56 to 160 cases per 100,000 population per year. Acute thrombosis is followed by an inflammatory response in the thrombus and vein wall leading to thrombus amplification, organization, and recanalization. Clinically, there is an exponential decrease in thrombus load over the first 6 months, with most recanalization occurring over the first 6 weeks after thrombosis. Pulmonary embolism (PE) and the post-thrombotic syndrome (PTS) are the most important acute and chronic complications of DVT.

Despite the effectiveness of thromboembolism prophylaxis, appropriate measures are utilized in as few as one-third of at-risk patients. Once established, the treatment of venous thromboembolism (VTE) has been defined by randomized clinical trials, with appropriate anticoagulation constituting the mainstay of management. Despite its effectiveness in preventing recurrent VTE, anticoagulation alone imperfectly protects against PTS. Although randomized trials are currently lacking, at least some data suggests that catheter-directed thrombolysis or combined pharmaco-mechanical thrombectomy can reduce post-thrombotic symptoms and improve quality of life after acute iliofemoral DVT. Inferior vena caval filters continue to have a role among patients with contra-indications to, complications of, or failure of anticoagulation. However, an expanded role for retrievable filters for relative indications has yet to be clearly established.

The incidence of superficial venous thrombophlebitis is likely under-reported, but it occurs in approximately 125,000 patients per year in the United States. Although the appropriate treatment remains controversial, recent investigations suggest that anticoagulation may be more effective than ligation in preventing DVT and PE. Venous injuries are similarly under-reported and the true incidence is unknown. Current recommendations include repair of injuries to the major proximal veins. If repair not safe or possible, ligation should be performed. (*J Vasc Surg* 2007;46:25S-53S.)

THE EPIDEMIOLOGY OF ACUTE DVT

The incidence of deep venous thrombosis (DVT) is highly dependent on the population studied as well as the means by which DVT is documented. It is generally be-

lieved that incidence rates from epidemiological studies are underestimates since autopsy studies indicate that up to 50% of venous thromboembolism (VTE) are not recognized ante mortem. Community based studies of hospitalized patients have suggested an annual incidence of 56 per 100,000¹ while population based studies of healthy volunteers have produced estimates of 122 per 100,000. Studies of venographically confirmed DVT in Sweden have suggested a somewhat higher incidence of 160 cases of new or recurrent DVT per 100,000 population per year.² Extrapolated to the population of the United States, this represents 116,000 to over 250,000 new cases of clinically recognized DVT per year.^{1,3}

Well-established risk factors for thrombosis are shown (Table I). However, clinically manifest thrombosis most often occurs with the convergence of multiple genetic and acquired risk factors.⁴ Hospitalized patients have an average of 1.5 risk factors per patient, with 26% having three or more risk factors.⁵ Multiple risk factors often act synergis-

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Table I. Thromboembolic risk factors

<i>Risk factor</i>	<i>Risk</i>
Age	Relative risk 1.9 per 10-year increase
Surgery	General surgery – 19% Neurosurgery – 24% Hip/knee – 48% – 61%
Trauma	58% of patients
Malignancy	15% of patients
History of VTE	2% to 9% of VTE patients (40% of pts with Factor V Leiden–2.4X)
Primary hypercoagulable states	
AT, C&S deficiency	10X
Factor V Leiden	
Heterozygous	8X
Homozygous	80X
Prothrombin 20210A	4X
Increased factor VIII	6X
Hyperhomocyst(e)inemia	2.5 – 4X
Family history	2.9X
Oral contraceptives	2.9X (30-50X with factor V Leiden)
Estrogen replacement	2 – 4X
Immobilization	2X (pre-operative)
Pregnancy and puerperium	Pregnancy – 0.075% of pregnancies Postpartum – 2.3 to 6.1 per 1000 deliveries
Femoral catheters	12% of trauma patients
Antiphospholipid antibodies	Lupus anticoagulant – 6X Anticardiolipin antibody – 2X
Inflammatory bowel disease	1.2 to 7.1% of patients
Obesity	Variable
Varicose veins	Variable
Myocardial infarction/CHF	Variable

VTE, Venous thromboembolism; AT, antithrombin; C&S, Protein C and protein S; CHF, Congestive heart failure.

tically to increase risk dramatically above the sum of individual risk factors. In symptomatic outpatients, the odds ratio for an objectively documented DVT increases from 1.26 for one risk factor to 3.88 for three or more risk factors.⁶

THE NATURAL HISTORY OF ACUTE DVT

Venous thrombogenesis

According to Virchow's postulates, three factors are of primary importance in the development of venous thrombosis – abnormalities of blood flow, abnormalities of blood, and vessel wall injury. However, it is now clear that all three components are not equally important in individual patients. Overt venous injury appears to be neither a necessary or sufficient condition for thrombosis, although the role of biologic injury to the endothelium is increasingly apparent. Under conditions favoring thrombosis, the normally antithrombogenic endothelium may become prothrombotic, producing tissue factor, von Willebrand factor, and fibronectin. Stasis alone is probably also an inadequate stimulus in the absence of low levels of activated coagulation

factors.⁷ Although stasis may facilitate endothelial leukocyte adhesion and cause endothelial hypoxia, its most important role may be in permitting the accumulation of activated coagulation factors. Imbalanced activation of the coagulation system appears to be the most important factor underlying many episodes of acute DVT and is associated with many thrombotic risk factors including age, malignancy, surgery, trauma, primary hypercoagulable states, pregnancy, and oral contraceptive use.

Lower extremity thrombi originate in areas where imbalanced coagulation is localized by stasis – in the soleal sinuses, behind venous valve pockets, and at venous confluences. The calf veins are the most common site of origin, although Browse showed that 40% of proximal thrombi arose primarily in the femoral or iliac veins. If local conditions favor propagation, laminated appositional growth occurs outward from the apex as platelets are surrounded by a red cell, fibrin, and leukocyte network.

After venous thrombosis, an acute to chronic inflammatory response occurs in the vein wall and thrombus leading to thrombus amplification, organization, and thrombus recanalization. The selectins (P- and E-selectin) appear to be critically important in these processes. Selectins are the first upregulated glycoproteins on activated endothelial cells and platelets. In rat and mouse models of inferior vena cava (IVC) thrombosis, the cell adhesion molecule P-selectin has been found to be up-regulated in the vein wall as early as 6 hours after thrombus induction, while E-selectin was up-regulated at day 6, with increases in gene expression preceding the protein elevations.⁸

The importance of the selectins in the inflammatory and thrombotic response has been further defined using genetically modified knock-out (KO) mice in which P-selectin, E-selectin, or both were deleted. In these studies, deletion of E-selectin and combined P-selectin/E-selectin deletion was associated with decreased thrombosis, while the vein wall inflammatory response was most inhibited in the combined P-selectin/E-selectin and P-selectin KO groups.

The importance of P-selectin and its receptor PSGL-1 has also been demonstrated in a primate model of stasis-induced IVC thrombosis produced by a temporary 6-hour balloon occlusion. In this model, an antibody to P-selectin or a receptor antagonist (termed rPSGL-Ig) inhibits inflammation and thrombosis when given prophylactically.^{9,10} Further study has demonstrated a significant dose-response relationship between rPSGL-Ig and thrombosis and rPSGL-Ig and spontaneous recanalization.¹¹ No systemic anticoagulation, bleeding time prolongation, thrombocytopenia, or wound healing complications were found in rPSGL-Ig treated animals. Direct selectin inhibition also effectively *treats* venous thrombosis in a primate model of iliofemoral DVT formation.¹²

Selectin upregulation is associated with the formation of microparticles (MP), fragments of phospholipid cell membranes that promote coagulation and modulate a number of inflammatory cell-vessel wall interactions. Platelet-derived MPs are involved in thrombosis in heparin-induced thrombocytopenia.¹³ Less is known regarding leu-

kocyte-derived MPs, although they are associated with endothelial cell activation and cytokine gene induction.^{14,15} Additionally, MPs derived from endothelial cells induce monocyte tissue factor (TF) antigen release and increased expression.¹⁶

The thrombogenic potential of MPs is dependent on TF expression and their anionic, prothrombotic surface capable of assembling prothrombinase and tenase.¹⁷ The influence of elevated levels of soluble P-selectin on MPs has been studied using the delta CT mouse (Δ CT)¹⁸ which demonstrates fourfold elevations in circulating soluble P-selectin. A 50% to 60% increase in thrombus mass was noted in this mouse in relation to IVC thrombosis at days 2 and 6 after thrombosis, and this increase was associated with the occurrence of procoagulant MP in the circulation, most prominent from leukocyte origin. Animals deficient in P-selectin and E-selectin had decreased thrombosis and MPs.

These data suggest that with initial thrombosis, selectin up-regulation leads to MP formation, which are then recruited into the area of developing thrombosis, amplifying the process. Selectin inhibition and combined P-selectin/E-selectin gene deficiency results in less MP formation and thrombosis. Fluorescent labeled MP injected intravenously were found to be recruited into a growing thrombus in the microcirculation of the mouse cremasteric muscle, but were not found in areas of the vessel free of thrombus.¹⁹ The procoagulant nature of these MPs was demonstrated by their ability to normalize bleeding in factor VIII deficient mice. Additionally, there is growing evidence that blood TF associated with leukocytes, or circulating in soluble form, is also involved in venous thrombogenesis.²⁰ Such blood-borne capability may relate to MPs. However, despite the existence of blood-borne TF, vessel wall TF appears to drive the formation of venous thrombosis in rodent models of stasis-induced DVT.²¹

Thrombus resolution after acute DVT

Although once regarded as static structures that changed little over time, it is clear that the venous lumen is most often re-established after an episode of acute DVT. In animal models of DVT, an early neutrophilic infiltrate appears within the thrombus followed by a predominantly monocyte infiltrate by day 8.²² Monocytes may play a particularly important role in thrombus organization and recanalization, functioning as a source of both fibrinolytic and cytokine mediators. Thrombus associated monocytes also appear to be the primary source of both tissue-type (t-PA) and urokinase-type plasminogen activators (u-PA) and may direct cytokine mediated neovascularization of the thrombus.^{22,23} Cytokines, chemokines, and inflammatory factors such as tumor necrosis factor alpha (TNF α) facilitate inflammation. DVT resolution resembles wound healing and involves profibrotic growth factors, collagen deposition and matrix metalloproteinase (MMP) expression and activation.²⁴⁻²⁷

The fact that leukocytes invade the thrombus in a specific sequence suggests their importance in the normal thrombus resolution.²⁸ The first cell type in the thrombus

is the neutrophil (PMN), which may contribute both to lysis as well as vein wall damage.^{29,30} Though PMNs may cause vein wall injury, they are essential for early thrombus resolution by promoting both fibrinolysis as well as collagenolysis. In a rat model of stasis DVT, neutropenia was associated with larger thrombi at 2 and 7 days³¹ and was correlated with increased thrombus fibrosis and significantly lower thrombus levels of both u-PA and MMP-9.³⁰

Stimulating the proinflammatory PMN response accelerates experimental DVT resolution. The chemotactic peptide interleukin-8 (IL-8) accelerates thrombus resolution.³² It is speculated that IL-8 increases intrathrombus PMN activation. Targeted deletion of the CXC receptor (CXCR2 KO), whose ligands include KC and MIP-2 (analogs of human IL-8), have been used to investigate the role of chemokines in PMN influx into resolving mouse thrombus.²⁴ The CXCR2 KO mice had larger, less organized thrombi, fewer intrathrombus PMNs and fewer monocytes over the first 8 days.³³ Decreased late (day 12 and 21) thrombus neovascularization was also observed as well as impaired fibrinolysis.

Despite the importance of PMNs in early thrombus resolution, the monocyte is the most important cell for later DVT resolution. Monocyte influx into the thrombus peaks at day 8 after thrombogenesis, and correlates with elevated MCP-1 levels, one of the primary CC chemokines that direct monocyte chemotaxis and activation^{24,34} and which has also been associated with DVT resolution.³⁵ Targeted deletion of CC receptor-2 (CCR-2 KO) in the mouse model of stasis thrombosis was associated with late impairment of thrombus resolution, probably via impaired gamma interferon (gIFN) mediated MMP-2 and -9 activity. Indeed, CCR-2 KO mice with stasis thrombosis supplemented with exogenous gIFN had full restoration of thrombus resolution, in part due to recovery of MMP-2 and -9 activities, without an increase in thrombus monocyte influx.

Healing tissue depends on physiologic neovascularization. The aforementioned experiments with chemokine receptor deleted-mice have confirmed a strong association between thrombus resolution and neovascularization. However, neovascularization may reflect thrombus organization and not impact thrombolysis. For example, in the rat model of stasis DVT, no decrease in thrombus size was found after exogenously administered pro-angiogenic agents despite an increase in thrombus microvascular blood flow.³¹ However, other investigators have found a potential role for vascular endothelial growth factor (VEGF) in accelerating thrombus resolution when administered exogenously.³⁶

As the thrombus resolves, numerous proinflammatory factors, including IL-1 β , and TNF α ,^{28,33} are locally released. The cellular sources of these different mediators have not been specifically defined but likely include leukocytes and fibroblast-like cells within the resolving thrombus. The cellular leukocyte kinetics in the vein wall after DVT is similar to what is observed in the thrombus with an early influx of PMN, followed by monocytes. Based on the

rat model of stasis DVT, elastinolysis seems to occur early, with partial recovery by 28 days, as measured by an increase in vein wall stiffness (the inverse of compliance, a property of normal veins). The increased vein wall stiffness continues through 14 days and is accompanied by elevated MMP-2 and -9 activities.

Associated with this biomechanical injury from the DVT is an elevation of profibrotic mediators including TGF β , RANTES, and MCP-1. Late fibrosis has been observed in the mouse model of DVT with a significant increase in vein wall collagen after stasis thrombogenesis. Correlating with this increase in fibrosis is an increase in collagen I and III gene expression as well as an increase in MMP-2 and -9 gene expression and activity. The profibrotic growth factor TGF β is also present in the thrombus and is released with normal thrombolysis.³⁷ This factor may be one local mechanism promoting vein wall fibrosis. However, early vein wall collagenolysis (rather than collagen production) seems to occur within the first 7 days in stasis DVT in the rat model, representing an acute response to injury. Ultimately, vein wall fibrosis may lead to vein valve dysfunction, valvular reflux, and the syndrome of chronic venous insufficiency.

Similar phenomena appear to occur in human thrombi, recanalization occurring through a complex process involving intrinsic and extrinsic fibrinolysis, peripheral fragmentation, neovascularization, and retraction.^{38,39} In the absence of propagation, the ultimate result is a restored venous lumen with a slightly raised fibro-elastic plaque at the site of initial thrombus adherence to the vein wall. However, these processes may be accompanied by alterations in vein wall compliance and the development of valvular incompetence.

The clinical importance of these processes has been confirmed in natural history studies employing serial ultrasonography. Among 21 patients prospectively followed with ultrasound, Killewich⁴⁰ noted that some recanalization was present by 7 days in 44% of patients and by 90 days in 100% of patients. Van Ramshorst⁴¹ similarly noted an exponential decrease in thrombus load over the first 6 months after femoropopliteal thrombosis. Most recanalization occurred within the first 6 weeks, with flow re-established in 87% of 23 completely occluded segments during this interval. These clinical observations suggest that recanalization begins early after an episode of acute DVT, with the majority of thrombus regression occurring within the first 3 months after the event. Approximately half of subjects will show complete recanalization within 6 to 9 months of thrombosis.

Recurrent thrombotic events

Despite the importance of recanalization, recurrent thrombotic events are also common. Clinical trials have demonstrated symptomatic recurrent thromboembolic events to occur in approximately 5% of patients treated with standard anticoagulation measures for 3 months. Others have noted a 13% cumulative incidence of symptomatic recurrent thromboembolism 5 years after diagnosis. Prox-

imal propagation has been similarly noted in approximately 20% of patients with untreated isolated calf vein thrombosis. However, natural history studies have shown the incidence of occult recurrent thrombotic events to be much higher than the symptomatic events documented in clinical trials. Serial duplex studies have demonstrated propagation of thrombus in 26% to 38% of treated patients within the first few weeks after presentation.^{42,43} In a larger series of 177 patients followed for a median of 9.3 months, recurrent thrombotic events were observed in 52% of patients.⁴⁴

VTE occurring in conjunction with a major reversible risk factor has a low risk of symptomatic recurrence: about 3% in the first year and 10% over 5 years. Patients who fall into the category of idiopathic VTE without an inciting etiology have a relatively high risk of recurrent disease, about 10% in the first year and 30% over 5 years. Patients with minor reversible risk factors associated with their VTE have an intermediate risk of recurrence, approximately 5% in the first year and 15% over 5 years.^{45,46} Thus, assessment of clinical risk factors associated with the first episode of VTE may provide useful prognostic information for recurrence. Interestingly, when a recurrent VTE event does occur, it tends to manifest itself as the original event. That is, pulmonary embolism (PE) begets recurrent PE and DVT begets recurrent DVT.

COMPLICATIONS OF ACUTE DVT

Pulmonary embolism

PE occurs in approximately 10% of cases⁴⁷ and is the most important acute complication of DVT. Hospital discharge data suggests an incidence of PE of 23 per 100,000 population.¹ Mathematical estimates, based on a number of assumptions, have suggested an incidence as high as 630,000 cases per year in the United States.⁴⁸

VTE is therefore the fourth leading cause of death in western society and the third leading cause of cardiovascular death behind myocardial infarction and stroke. Up to 10% of hospital deaths are due to PE, 76% occurring in nonsurgical patients. VTE-related deaths exceed the combined annual number of deaths in the United States attributed to breast cancer and AIDS. PE is also recognized as the most frequent cause of maternal death associated with childbirth.⁴⁹ However, up to 75% of pulmonary emboli are asymptomatic^{50,51} and as many as 25% to 52% patients with documented DVT but no symptoms of pulmonary embolism will have high probability lung scans.

The post-thrombotic syndrome

The post-thrombotic syndrome is the most important late complication of acute DVT. Although some post-thrombotic symptoms may be present in 29% to 79% of patients, severe manifestations and ulceration occur in only 7% to 23% and 4% to 6% of patients, respectively.⁵²⁻⁵⁶ Population based studies have suggested that skin changes and ulceration are present in 6 to 7 million and 400,000 to 500,000 people in the United States, respectively.³

Ambulatory venous hypertension, the underlying hemodynamic mechanism in chronic venous insufficiency, may result from either venous reflux or persistent venous obstruction. Although valvular incompetence appears to be clinically more important, limbs developing edema, hyperpigmentation, or ulceration are more likely to have a combination of reflux and residual obstruction than either abnormality alone.⁵⁷ Despite its importance, valvular dysfunction is not universal after acute DVT, reflux developing in only 33% to 59% of involved venous segments.

The determinants of post-thrombotic manifestations have been incompletely characterized but include the rate of recanalization, recurrent thrombotic events, the global extent of reflux and the anatomic distribution of reflux and obstruction. Long-term ultrasound follow-up studies of patients treated with standard anticoagulation measures have demonstrated a relationship between the time to complete recanalization and the development of reflux.⁵⁸ Depending upon the venous segment involved, complete recanalization required 2.3 to 7.3 times longer in segments developing reflux than in segments in which valve function was preserved.

Recurrent thrombotic events also have a detrimental effect on valvular competence and development of the post-thrombotic syndrome. Reflux has been observed in 36% to 73% of segments with rethrombosis, a considerably higher rate than in segments without rethrombosis.⁴⁴ Consistent with these observations, recurrent thrombotic events have been noted in 45% of patients with post-thrombotic symptoms in comparison with only 17% of asymptomatic subjects.⁴⁷ Others have reported the risk of post-thrombotic syndrome to be six times greater among patients with recurrent thrombosis.⁵⁴

The development of clinical signs and symptoms is also related to the global extent of reflux and the anatomic distribution of reflux and obstruction. Reflux in the distal deep venous segments, particularly the popliteal and posterior tibial veins, is most significantly associated with post-thrombotic skin changes.⁵⁹⁻⁶¹ However, superficial reflux is also critically important and has been reported in 84% to 94% of patients with chronic skin changes and 60% to 100% of patients with venous ulceration.

Mortality after acute DVT

Mortality after an episode of acute DVT exceeds that in an age-matched population. Although the in-hospital case-fatality rate for DVT is only 5%, 3- and 5-year mortality rates of 30% and 39%, respectively have been noted.^{1,47} Most deaths are related to malignancy or cardiovascular disease.

PREVENTION OF VENOUS THROMBOEMBOLISM: COMPLIANCE WITH THE GUIDELINES

As discussed above, VTE represents a major cause of morbidity and mortality in the United States.⁶²⁻⁶⁴ Most cases of VTE occur in the peri-hospitalization period. In the DVT Free registry, a large multicenter prospective

ultrasound study of 5451 patients, nearly 60% of VTE were diagnosed within the peri-hospitalization period and 38% occurred within 3 months of surgery.⁶⁵ Furthermore, with the evolution toward expanded outpatient delivery of medical and surgical services, only the sickest and frailest of patients are hospitalized. The VTE risk profile of contemporary hospitalized patients has therefore increased greatly with most carrying more than one recognized risk factor for VTE (Table 1).

Without prophylaxis, VTE rates are high for both surgical and nonsurgical hospitalized patients. Underscoring the magnitude of this disease is the fact that more than 23 million operations are performed and more than 31 million nonsurgical patients are admitted each year to US hospitals. The incidence of VTE varies by both patient and procedure specific variables; without prophylaxis, venous thrombotic events may occur in up to 20% of surgical patients and 16% of nonsurgical patients.^{66,67} Yet, venous thromboembolism can be a preventable disease, particularly in the hospitalized patient.⁶⁷ Appropriately delivered prophylaxis is cost-effective, reduces VTE rates by 50% to 70% and carries an acceptably low risk of hemorrhage.

For the vast majority of both surgical and nonsurgical inpatients, extensive guidelines based on data from a large numbers of randomized patients currently exist.⁶⁷ These guidelines are summarized in Table II and are available online for ready access to most physicians (www.chestjournal.org/cgi/content/full/126/3_suppl/338S).

The practice of evidence-based medicine requires both the awareness and access to these published guidelines as well as development and implementation of disease-specific critical pathways within local institutions.^{67,68} Unfortunately, the delivery of venous thromboembolism (VTE) prophylaxis is a prime example of the disparities between published guidelines and the realities of clinical practice. VTE prevention has become an important topic of national societies, foundations, and healthcare agencies.^{67,69} Indeed, the appropriate delivery of VTE prophylaxis has been given the highest priority among other patient related safety interventions by the Agency on Healthcare Research and Quality.⁶⁹ Proper implementation of the guidelines has important implications including: improved patient safety and outcomes; improved education of house-staff, residents, and students (those frequently writing the medical orders for hospitalized patients); improved satisfaction of health care providers knowing that they have adhered to the latest and highest standards; reduced health care delivery costs by reducing outcome events; and improved consistency of healthcare delivery within and between institutions.⁶⁸ Furthermore, if the medical community fails to champion this endeavor, regulatory agencies may link compliance with reimbursement or other punitive actions.⁷⁰

The reality, however, is that many eligible patients in clinical practice are not currently receiving appropriate prophylaxis. Rates of delivery of appropriate VTE prophylaxis vary from 29% to 56% and appear to be higher in academic

Table II. DVT Prophylaxis Guidelines

<i>Clinical Setting</i>		<i>Recommendations</i>
General Surgery		
● Low risk:	minor procedure <40 years, no risk factors*	● Early and frequent ambulation
● Moderate risk:	minor procedure, 40–60 years, no risk factors minor procedure, additional risk factors major procedure, <40 years, no risk factors	● LDUH 5000 U BID or ● LMWH < 3400 U once daily
● High risk:	minor procedure, >60 years, no risk factors major procedure, <40 years, additional risk factors major procedure, additional risk factors	● LDUH 5000 U TID or ● LMWH > 3400 U once daily
● High risk:	minor procedure, >60 years, no risk factors major procedure, <40 years, additional risk factors major procedure, additional risk factors	● LDUH 5000 U TID or ● LMWH > 3400 U once daily ● GCS/SCD for all patients
Gynecologic Surgery		
● Low risk:	minor procedure (< 30 minutes)	● Early ambulation
● Laparoscopic surgery:	additional risk factors	● LDUH 5000 U BID or ● LMWH 3400 U once daily ● GCS/SCD
● Moderate risk:	major procedure, benign disease, no risk factors	● LDUH 5000 U BID or ● LMWH < 3400 U once daily
● High risk:	major procedure for malignancy	● LDUH 5000 U TID or ● LMWH > 3400 U once daily ● GCS/SCD
Urologic Surgery		
● Low risk:	minor procedure or transurethral procedure	● Early and frequent ambulation
● Moderate risk:	major open procedure	● LDUH 5000 U BID (or TID) or ● GCS/SCD
● Moderate risk:	major open procedure, <i>high risk for bleeding</i>	● GCS/SCD
● High risk:	major procedure, additional risk factors	● LDUH 5000 U (BID or TID) or ● LMWH 3400 U once daily ● GCS/SCD for all patients
Orthopedic Surgery		
● Elective hip arthroplasty		● LMWH > 3400 U once daily ● fondaparinux ● warfarin (INR 2.0–3.0)
● Elective knee arthroplasty		● LMWH > 3400 U once daily ● fondaparinux ● warfarin (INR 2.0–3.0)
● Elective knee arthroscopy:	no risk factors additional risk factors	● Early ambulation ● LMWH
● Hip fracture surgery		● LMWH > 3400 U once daily ● fondaparinux ● warfarin (INR 2.0–3.0)
● Elective spine surgery:	no risk factors additional risk factors	● Early ambulation ● LDUH or ● LMWH once daily or ● GCS/SCD
Vascular Surgery		
● Low risk:	no risk factors*	● Early ambulation
● High risk	major procedure, additional risk factors	● LDUH 5000 U BID or ● LMWH 3400 U once daily
Laparoscopic Surgery		
● Low risk:	no risk factors*	● Early ambulation
● High risk:	additional risk factors	● LDUH 5000 U BID or ● LMWH 3400 U once daily or ● GCS/SCD

Table II. Continued.

<i>Clinical Setting</i>	<i>Recommendations</i>
Neurosurgery	
● Intracranial surgery	● GCS/SCD or ● LDUH or ● LMWH
Major Trauma	
● No active bleeding or high risk for hemorrhage	● LMWH (began when safe to do so)
● Active bleeding or high risk for hemorrhage	● GCS/SCD if possible ● Screening DUS (if not possible)
● During rehabilitation phase of recovery	● warfarin (INR 2.0–3.0) or ● LMWH once daily
● Spinal cord injury (acute phase)	● GCS/SCD ● LMWH (hemostasis ensured) or ● LDUH with GCS/SCD
● Spinal cord injury (rehabilitative phase)	● LMWH or ● warfarin (INR 2.0–3.0)
Medical Illness	
● Acutely ill	hospitalized and CHF, respiratory disease, bed rest or additional risk factors* Contraindication to anticoagulants
	● LDUH or ● LMWH ● GCS/SCD

LDUH, low dose unfractionated heparin; *LMWH*, low molecular weight heparin; *GCS*, graduated support stockings; *SCD*, sequential compression device. Modified from Geerts et al. *Chest* 2004;126: 338S-400S.

Adapted from Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126: 338S-400S.⁶⁷

*Risk factors for venous thromboembolism: cancer, cancer therapy, previous VTE, increasing age, pregnancy and the postpartum period, hormonal therapy, acute medical illness, congestive heart failure, respiratory failure, nephrotic syndrome, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, inflammatory bowel disease, obesity, smoking, varicose veins, central venous catheterization, inherited or acquired thrombophilia.

centers compared with community hospitals.^{65,71-73} These numbers have improved little over the past decade.^{62,63,66} In the contemporary DVT Free registry, which gathered patients with ultrasound confirmed DVT from 183 US medical centers, the vast majority (71%) received no antecedent prophylaxis therapy.⁶⁵ In the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), which assessed the clinical practice of VTE prophylaxis delivery in 21 hospitals across eight European and North American countries, only 37% of 1595 patients received prophylaxis.⁷² Rates of prophylaxis delivery were comparable across continents, whereas prophylaxis was provided in 38% and 44% for European and US patients, respectively.⁷⁴

The presence of known risk factors also does not appear to improve current prophylaxis delivery. In the DVT Free study, neither a history of prior VTE, presence of malignancy, need for malignancy related surgery, nor significant obesity increased the use of prophylaxis.^{65,75} A significantly larger proportion of patients with these risk factors did not receive prophylaxis relative to those who did. Although one might anticipate that medicine physicians would more aggressively provide prophylaxis compared with their surgical colleagues, the opposite is true. In this study, more than twice as many surgical patients received prophylaxis relative to medical patients (46.9% vs 22.2%). Furthermore, although surgery is a well-known and potent risk factor for VTE, the vast majority (75%) of fatal PEs occur in nonsur-

gical patients.⁷⁶ Clearly, strategies for improved delivery of VTE prophylaxis for both surgical and nonsurgical patients alike are needed.

The reasons for low guideline compliance are manyfold and unclear. The silent nature and late onset of VTE relative to hospital discharge do not serve to reinforce the use of prophylaxis. The use of prophylaxis is often not rewarded since it is difficult to appreciate a thrombotic event that does not occur. Furthermore, although printed and electronic versions of prophylaxis guidelines are readily available, the extremely thorough document may be a bit daunting to digest in full and simply providing guidelines has not been shown to improve compliance without active promotion by specialists within the disease-specific field.⁷⁷ Cited reasons for noncompliance include: simple oversight of the guidelines; economic limitations; concerns for bleeding; and unfamiliarity, nonendorsement or nonconsensus of published guidelines.⁶⁵ These reasons can largely be divided into either challenges of education or system logistics of implementation.

A number of strategies have been assessed with the goal of improving clinician behavior and positively influencing patient outcomes.⁷⁸ These strategies have included both passive and active information dissemination through continuing education; audit and feedback; computer based risk assessment, ordering algorithms and automated reminders; and quality assurance activities including the appointment

Table III.

Author (Reference)	Intervention	n	Design	Outcome (% compliance)
Agno. Haematologica. 2002;87:746-50.	PD	165	RCR	46.4
Arnold. Chest. 2001;120:1964-71.	PD	245	RCR	32.3
Bratzler. Arch Intern Med. 1998;158:1909-12.	PD	419	RCR	38
Williams. Post Grad Med. 2004;80:415-19.	PD	1534	RCR	33
Aouizerate. Therapie. 1998;53:101-6.	AF	1165	SA	81
McEleny. Scott Med J. 1998;43:23-5.	AF	1108	SA	97.4
Fagot. Presse Med. 2001;30:203-8.	DA	279	SA	65
Harinath. Ann Royal Coll Surg. 1998;80:347-9.	DA	200	SA	79
Durieux. JAMA. 2000;283:2816-21.	CBDA	1971	SA	95
Macdonald. Can J Surg. 2002;45:47-52.	CBDA	4729	SA	62
Patterson. Proc AMIA Symp 1998:573-6.	CBDA	2013	CC	99.3
Taylor. Post Grad Med. 2000;76:354-6.	CBDA	529	SA	89.2
Anderson. Arch Intern Med. 1994;154:669-77.	CME, QAA, DA	3158	RCT	52
Frankel. J Am Coll Surg. 1999;189:533-8.	CME, QAA, DA	200	SA	74
Hall. Clin Perf Qual Health Care. 2000;8:72-82.	CME, AD	192	SA	75
Peterson. J Clin Pharm Ther 1999;24:279-87.	CME, AD, DA	500	CC	70
Ryskamp. Chest. 1998;113:162-4.	CME, QAA	209	PC	86
Stratton. Arch Intern Med. 2000;160:334-40.	PD, DA, QAA	4729	SA	62

PD, passive dissemination; AF, audit and feedback; DA, documentation aids; CBDA, computer based decision aids; CME, continuing medical education; QAA, quality assurance activities; AD, advertisement; RCR, retrospective chart reviews; SA, sequential audit; CC, case control; RCT, randomized controlled trial; PC, prospective cohort.

Modified from Toohar et al. Ann. Surg. 2005;241:297-415.

Adapted from Toohar R, Middleton P, Pham C, Fitrudge R, Rowe S, Babidge W, et al. A systematic review of strategies to improve prophylaxis for venous thromboembolism in hospitals. Ann Surg 2005;241:397-415.

of designated staff for implementation and surveillance. Among 31 studies of such strategies, only one randomized controlled study has been published. Most studies utilized serial audits of compliance before and after initiation of the intervention (Table III). Nineteen studies used a single intervention and the remainder used multiple interventions. None of these studies were adequately powered to assess hard outcomes of VTE rates or mortality. Passive information dissemination performed the least well with less than 50% adherence to the guidelines. Active strategies performed much better and computer based systems with active automated reminders resulted in the highest success rates. Multiple active strategies provided better outcomes than single interventions. Interventions that allowed for iterative refinement of the intervention through serial audits provided the best results.

For many high-risk scenarios, randomized controlled trial data has directly compared available agents, and both risk and relative risk reduction percentages are currently available. However, for many indications, neither the optimal duration of anticoagulation prophylaxis nor the role of combined pharmacologic agents and mechanical devices (intermittent pneumatic compression, venous foot pump, graduated compression stockings) is defined. Moreover, the role of novel anticoagulants, such as oral direct thrombin, direct Factor Xa, or platelet inhibitors, and strategies such as the use of retrievable inferior vena caval filters in high risk patients has not been defined. Lastly, there are several patient specific and surgical specific areas where the precise recommendations for prophylaxis remain unclear. These include patients undergoing elective spine surgery,

patients suffering major burns, patients suffering spinal cord injury, and patients with malignancy undergoing chemotherapy.

TREATMENT OF VENOUS THROMBOEMBOLISM

Anticoagulant drugs - heparin, low-molecular-weight heparin (LMWH), and vitamin-k-antagonists (VKA) - are the mainstays in management of VTE. Their appropriate use is based upon the results of randomized clinical trials and consensus recommendations reported in the Seventh ACCP Conference on Antithrombotic Therapy and Thrombolytic Therapy (Appendix). The recommendations are based on the following rules of evidence which have been adapted from the Seventh ACCP Conference on Antithrombotic Therapy and Thrombolytic Therapy.⁷⁹

Grade A: Consistent results from randomized clinical trials (RCTs) generate Grade A recommendations,

Grade B: Inconsistent results from RCTs generate Grade B recommendations,

Grade C: observational studies generate Grade C recommendations, or secure generalizations from RCTs

Initial antithrombotic therapy

Unfractionated heparin. Clinical trials have established the need for initial heparin (or LMWH) treatment in patients with VTE.⁸⁰ Classic anticoagulant therapy for VTE was a combination of continuous intravenous heparin using a heparin protocol⁸¹ and oral vitamin-k-antagonist (VKA). Initial intravenous heparin therapy is administered

for 5 days or until the INR has been within the therapeutic range (2.0 to 3.0) for 2 consecutive days.⁸⁰ Randomized clinical trials have shown that achieving the lower limit of the therapeutic range within 24 hours is required to adequately prevent recurrent VTE for patients receiving heparin.^{82,83} Anticoagulant monitoring of UFH therapy is described elsewhere.⁸¹

The main adverse effects of heparin therapy include bleeding, thrombocytopenia, and osteoporosis.^{81,84,85} Patients at particular risk are those who have had recent surgery or trauma, or who have other clinical factors which predispose to bleeding, such as peptic ulcer, occult malignancy, liver disease, hemostatic defects, obesity, age >65 years, and female gender. The development of thrombocytopenia may be accompanied by arterial or venous thrombosis that may lead to serious consequences including death and limb amputation. Heparin must be stopped immediately on the diagnosis of heparin-induced thrombocytopenia (HIT).⁸⁵ Alternate therapy, such as argatroban, is required in patients requiring ongoing anticoagulation. Osteoporosis has also been reported in patients receiving UFH for more than 6 months. Demineralization can progress to fractures of vertebral bodies or long bones, and the defect may not be entirely reversible.⁸¹

Low-molecular-weight heparin. The LMWH given by subcutaneous injection have distinct advantages over continuous intravenous UFH including once-daily (or twice-daily) subcutaneous administration and an antithrombotic response that is highly correlated with body weight, permitting administration of a fixed-dose without laboratory monitoring. The use of LMWH has allowed outpatient therapy in many patients with uncomplicated DVT.⁸⁰ As LMWHs have become widely available for treatment, they have replaced intravenous UFH in the initial management of most patients with VTE.

Evidence is accumulating that complications such as bleeding, osteoporosis, and HIT are less serious and less frequent with the use of LMWH when compared with UFH.⁸⁰ The LMWHs all cross-react with UFH and therefore cannot be used as alternative therapy in patients who develop heparin-induced thrombocytopenia (HIT). Upon diagnosis of HIT, LMWH must be stopped immediately⁸⁵ and alternate therapy with agents such as argatroban instituted in patients requiring ongoing anticoagulation.

Fondaparinux. The synthetic pentasaccharide, fondaparinux, is effective for treating DVT and submassive PE.⁸⁰

Thrombolytic therapy. Thrombolytic therapy remains controversial due to the risk of bleeding and is not indicated for the routine treatment of VTE. It is widely accepted, however, that patients with acute massive PE may benefit from this adjunctive therapy.⁸⁰ Thrombolytic therapy for acute DVT is further discussed below.

Catheter interventions for pulmonary embolism. Catheter-based devices for the extraction or the fragmentation of PE have the potential of producing immediate relief from massive PE. Such interventions may have a role in patients in whom there is a contraindication to thrombolytic therapy.

Long-term antithrombotic therapy

Vitamin-k-antagonist therapy. The anticoagulant effect of VKA is delayed until normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36 to 72 hours after drug administration.⁸⁶ Initial daily doses of 5 to 10 mg are preferred in initiating vitamin-k-antagonist treatment; many clinicians advocate starting with 5 mg. As the dose-response relationship to vitamin-k-antagonist therapy varies widely between individuals, the dose must be carefully monitored to prevent over- or under-dosing. A number of factors influence the anticoagulant response to vitamin-k-antagonist therapy in individual patients including dietary changes and drugs that interfere with the metabolism of VKA.⁸⁶ After 5 to 10 mg per day for the first 2 days, the daily dose must be adjusted according to the INR. Heparin or LMWH therapy is discontinued on the fifth day following initiation of vitamin-k-antagonist therapy, provided the INR is prolonged into the recommended therapeutic range (INR 2.0 to 3.0) for at least 2 consecutive days. Frequent INR determinations are required initially to establish therapeutic anticoagulation.^{80,86}

Once requirements are stable, the INR should be monitored every 1 to 3 weeks throughout the course of warfarin therapy. However, if there are factors that may produce an unpredictable response to warfarin (eg, concomitant drug therapy), the INR should be monitored more frequently to minimize the risk of complications.

Laboratory monitoring. In order to promote standardization of the PT for monitoring oral anticoagulant therapy, the World Health Organization (WHO) developed an international-reference-thromboplastin from human-brain tissue and recommended that the PT ratio be expressed as the International Normalized Ratio (INR). The INR is the PT ratio obtained by testing a given sample using the WHO reference thromboplastin. For practical clinical purposes, the INR for a given plasma sample is equivalent to the PT ratio obtained using a standardized human brain thromboplastin known as the Manchester Comparative Reagent, which has been widely used in the United Kingdom. In recent years, thromboplastins with a high sensitivity have been commonly used. In fact, many centers have been using the recombinant tissue-factor that has an ISI value 0.9 to 1.0 giving an INR equivalent to the prothrombin-time ratio.⁸⁶

Duration of anticoagulation. The duration of anticoagulant therapy is influenced by the knowledge of multiple parameters including whether it is a first episode vs a recurrent episode of VTE; transient, continuing, or unknown predisposing risk factors; and the risk of bleeding. There is increasing awareness that venous thromboembolism should be considered a chronic disease with a continued risk of VTE often associated with minor provocation.⁸⁷

According to the guidelines developed by the American College of Chest Physicians (ACCP), patients with a first episode of VTE secondary to a transient (reversible) risk factor should be treated initially with LMWH or unfractionated

tionated heparin (UFH) followed by a vitamin-k-antagonist (VKA) continued for 3 months. The same regimen is appropriate for patients with a first episode of idiopathic VTE; however, LMWH or the VKA should be maintained for at least 6 to 12 months. In fact, based on the results from several large clinical trials, at least some data suggests that patients with a first-episode of idiopathic DVT may benefit from indefinite anticoagulant therapy.⁸⁰

An individual's risk for recurrent VTE is increased substantially by a prominent family history of VTE with or without identified inherited genetic thrombophilic risk factors;⁵⁴ by the persistence of acquired precipitating thrombophilic disease states (cancer, antiphospholipid antibody syndrome, etc); and by the presence of residual DVT despite adequate anticoagulation therapy, typically noted by serial duplex Doppler ultrasound examinations. Furthermore, the persistence of elevated plasma D-dimers levels following completion of anticoagulation for the acute VTE carries a poor prognosis for recurrent thrombotic events.^{88,89}

Despite the evidence-based guidelines, there will be considerable uncertainty as to the duration of long-term anticoagulant therapy in many patients. The decision to implement extended anticoagulation should be based on risk stratification for recurrent VTE and be placed in context with potential hemorrhagic risks. It is also important to include patient preferences in the decision-making process concerning duration of anticoagulant therapy. In DVT or PE patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals. Where appropriate the patient should be involved in the decision process.

Long-term low-molecular-weight heparin therapy.

Long-term LMWH has been compared with warfarin therapy in patients presenting with VTE. Long-term LMWH is a useful alternative to vitamin-k-antagonist therapy, and is preferred therapy for up to approximately 6 months in cancer patients with VTE.⁹⁰

Summary

Based on a large number of level 1 clinical trials, the accepted medical treatment for acute deep-vein thrombosis has been established. Patients with established DVT or PE require long-term anticoagulant therapy to prevent recurrent disease. Until recently, this consisted of UFH given by continuous intravenous infusion with warfarin starting on day 1 or 2 and continued for 3 months with a target INR of 2.0 to 3.0. More recently, a number of LMWHs have been shown to be at least as effective as UFH in decreasing recurrent VTE and are associated with less major bleeding. LMWH has become the treatment of choice for both in hospital and out of hospital treatment of DVT and, more recently, PE as well.

Warfarin therapy is highly effective and is preferred for long-term anticoagulation in most patients. The safety of oral anticoagulant treatment depends heavily on the maintenance of a narrow therapeutic INR range (2.0 to 3.0).

When the INR falls below the therapeutic range, the incidence of recurrent VTE increases, whereas when the INR exceeds a level of 3.5 to 5.0, the incidence of major hemorrhage markedly increases. The optimal duration of warfarin anticoagulation after a first or recurrent episode of venous thrombosis remains uncertain. Recent studies have indicated that patients with a first episode of idiopathic DVT require at least 6 months of long-term anticoagulant treatment and patients who have a first recurrence require at least 12 months of anticoagulant treatment. Because the risk of recurrent VTE continues even after these extended periods of treatment, future recommendations may be for even longer periods of treatment. These and other unanswered questions related to the management of VTE will be further clarified by the results of ongoing clinical trials.

Adjusted-dose subcutaneous heparin has been the treatment of choice where long-term oral anticoagulants are contra-indicated, such as in pregnancy, but LMWH is increasingly being considered. Adjusted-dose subcutaneous heparin, or unmonitored LMWH have been used for the long-term treatment of patients in whom oral anticoagulant therapy proves to be very difficult to control.

CATHETER-DIRECTED THROMBOLYSIS FOR THE TREATMENT OF ACUTE DVT

Rationale for early thrombus removal

When deep vein thrombosis occurs, the goals of therapy are (1) to prevent the extension or recurrence of the deep venous thrombus and fatal pulmonary embolism (PE) and (2) minimize the early and late sequelae of DVT. Antithrombotic therapy can accomplish the former, but contributes little or nothing to the second goal. Patients with extensive DVT, exemplified by those with iliofemoral involvement, can have progressive swelling of the leg leading to phlegmasia cerulea dolens (literally, painful blue swelling) and also suffer the most severe post-thrombotic morbidity.^{91,92} Ilio-femoral DVT (IFVT) may also be associated with increased compartmental pressure that can occasionally, although rarely, progress to venous gangrene and limb loss.

The clinical outcome after DVT can be categorized into four subgroups: those with neither detectable obstruction nor valvular incompetence, those with obstruction alone, those with valvular incompetence alone, and those with both outflow obstruction and distal valvular incompetence. However, it is often not appreciated that proximal obstruction, even if ultimately relieved by partial recanalization and/or collateral development, can lead to progressive failure of distal valves, resulting in reflux. As the combination of venous obstruction and valve incompetence is associated with development of the post-thrombotic syndrome,^{57,93} it appears reasonable that if large vein thrombus can be cleared and rethrombosis avoided, patients will benefit over the long term. Early thrombus removal might also prevent some of the deleterious effects of vein wall inflammation discussed above.

Table IV. Efficacy and complications of catheter-directed thrombolysis with urokinase

	<i>Bjarnasan</i> ¹⁰² (N = 77)	<i>Mewissen</i> ¹⁰⁴ (N = 287)	<i>Comerot</i> ¹⁰³ (N = 58)
Initial success	79%	83%	84%
Iliac	63%	64%	78%
Femoral	40%	47%	-
Primary patency (1 y)			
Iliac	63%	64%	78%
Femoral	40%	47%	-
Iliac patency (1 y)			
+ Stent	54%	74%	89%
- Stent	75%	53%	71%
Major bleeding	5%	11%	9%
Intracranial bleeding	0%	<1%	0%
Pulmonary embolism (PE)	1%	1%	0%
Fatal PE	0%	0.2%	0%
Death secondary to lysis	0%	0.4%	0% (*? 2%)

*Death due to multiorgan failure 30 days post lysis; thought unrelated to lytic therapy.

The options for early removal of an acute thrombus in the proximal veins of the leg are (1) catheter-directed thrombolysis (CDT), (2) thrombolysis combined with percutaneous mechanical “thrombectomy” (CDT + PMT), using one of a number of mechanical devices, and (3) surgical thrombectomy (TE).

Clinical benefits of early thrombus removal

The potential benefits of early thrombus removal are supported by experimental studies showing that thrombolysis of acute venous thrombosis preserves venous valve and endothelial function.^{94,95} These experimental findings are consistent with natural history studies of patients with acute DVT treated with anticoagulation.^{40,58,96} Furthermore, when early (within 90 days) spontaneous lysis restored venous patency, valvular function was frequently preserved.⁵⁸

The benefit of thrombus removal has been documented in randomized trials of iliofemoral venous thrombectomy plus arteriovenous fistula and anticoagulation vs anticoagulation alone in patients with iliofemoral DVT.⁹⁷⁻⁹⁹ Follow-up at 6 months, 5 years, and 10 years demonstrated obvious benefits among those randomized to venous thrombectomy. Early thrombus removal resulted in improved patency of the iliofemoral venous system, lower venous pressures, less edema, and fewer post-thrombotic symptoms. It appears that if early thrombus removal is successful, patients will have significantly fewer post-thrombotic sequelae.

Early trials of systemic thrombolytic therapy for proximal DVT showed that <50% of the patients had complete lysis.¹⁰⁰ However, those with successful lysis had significantly reduced post-thrombotic morbidity and demonstrated preservation of venous valve function. Unfortunately, the clinical benefit was frequently lost amid the significantly increased risks of major complications, predominantly bleeding.¹⁰¹ The risk of complications, as well as the limited efficacy, of systemic thrombolysis has led to the technique of catheter-directed thrombolysis.

Intrathrombus catheter-directed thrombolysis

The conclusions from the studies cited above are clear: early removal of the thrombus conveys significant benefits, and the earlier the removal, the better the outcome. Catheter-directed intrathrombus delivery of plasminogen activators theoretically accelerates thrombus resolution, increasing the likelihood of success and diminishing bleeding complications. When delivered into the thrombus, plasminogen activators efficiently activate fibrin-bound plasminogen, thereby generating plasmin that is protected from circulating antiplasmins, predominantly α_2 -antiplasmin.

Several reports suggest that initial lytic success can be achieved in the majority of patients. Three of the largest reports show an 80% to 85% success rate and relatively low (and consistent) complication rates (Table IV).¹⁰²⁻¹⁰⁴ Major bleeding complications, defined as puncture-site bleeding, hematoma requiring evacuation, and the need for blood transfusions, developed in approximately 5% to 10% of patients. Symptomatic pulmonary embolism as a complication of treatment is also rare. Mortality in these three large studies was much less than 1%, indicating that proper patient selection and thoughtful patient management can offer significant benefit without substantial risk.

Case series also suggest an improved long-term outcome following catheter-directed thrombolysis. The National Venous Registry showed an overall thrombosis-free survival in 65% of patients at 6 months and 60% at 12 months.¹⁰⁴ Perhaps not surprisingly, thrombosis-free survival correlated with the results of initial therapy. Seventy-five percent of patients with complete thrombus resolution had patent veins at 1 year compared with 37% of those in whom <50% of the clot was dissolved. The results were most favorable in the subgroup of patients with acute, first-time iliofemoral DVT who had successful lysis: 96% of the veins remained patent at 1 year. This emphasizes the importance of proper patient selection. Interestingly, 72% of the patients with complete lysis had normal valve function.

Data from the National Venous Registry also allowed patient-perceived benefit and quality-of-life to be linked to early phlebographic results. A validated quality-of-life questionnaire was used to compare the outcome in 68 patients treated with catheter-directed urokinase with a similar group of 30 patients treated contemporaneously with anticoagulation alone based on physician preference.¹⁰⁵ All patients were candidates for thrombolytic therapy. Those treated with catheter-directed thrombolysis had a significantly better quality of life at 16 and 22 months compared with those treated with anticoagulation alone. Not surprisingly, the quality-of-life results were directly related to the initial success of thrombolysis. Patients who had a successful lytic outcome reported a significantly better health utilities index, better physical functioning, less stigma of chronic venous disease, less health distress, and fewer post-thrombotic symptoms. Patients with failed lysis and patients treated with anticoagulation alone had similar outcomes.

A number of other case series have demonstrated excellent early success rates associated with minimal complications.¹⁰⁶⁻¹⁰⁸ Elsharawy¹⁰⁹ has reported a small prospective randomized trial of catheter-directed thrombolysis vs anticoagulation demonstrating improved patency rates and fewer post-thrombotic symptoms in patients treated with catheter-directed thrombolysis. Despite these favorable outcomes, we now have the responsibility of showing that early success is associated with long-term benefits in larger, appropriately designed trials.

Technique of catheter-directed thrombolysis

The technique of catheter-directed thrombolysis for iliofemoral DVT has evolved over the past decade. The preferred approach uses an ultrasound-guided popliteal vein puncture for antegrade passage of a long infusion catheter. Adjunctive mechanical thrombectomy techniques can be incorporated through this approach if desired. If the popliteal vein is thrombosed, an additional catheter is placed through an ultrasound-guided posterior tibial vein puncture. This technique maximizes the chance of restoring patency to the popliteal vein and providing optimal venous inflow to the iliofemoral venous system once it is cleared of acute thrombus.

During the past several years the volume of lytic infusate has increased and the concentration of the plasminogen activator decreased. Many now prefer to infuse 50 to 100 ml/h of a dilute plasminogen activator solution. The large volume is intended to saturate the thrombus, exposing more fibrin-bound plasminogen to the plasminogen activator. Phlebograms obtained at 12-hour intervals are used to monitor the lytic success. Vena caval filters are not routinely used but are recommended for patients with free-floating thrombus in the vena cava. Retrievable caval filters can be used in the patients in whom only temporary protection is needed.

Following successful thrombolysis, the venous system is evaluated for areas of stenosis. Residual areas of stenosis must be corrected to insure long-term patency. Such le-

sions most frequently involve the left common iliac vein, where it is compressed by the right common iliac artery. Intravascular ultrasonography improves the evaluation of iliac vein compression and the precision of any required stent deployment. Common iliac vein stents should approach the diameter of the normal common iliac vein (12 mm or larger). Post-treatment therapeutic anticoagulation is important to prevent recurrent thrombosis. The duration of anticoagulation is being extended in these patients to no less than 1 to 3 years. If an underlying hypercoagulable state is identified or if the patient had a prior episode of venous thrombosis, anticoagulation is continued indefinitely. Single stents in the common iliac vein have been associated with excellent patency.

SURGICAL AND ENDOVENOUS THROMBECTOMY FOR ACUTE ILIOFEMORAL THROMBOSIS

Prompt early removal of thrombus is indicated to avoid late post-thrombotic syndrome (PTS) in active patients with acute iliofemoral venous thrombosis (IFVT). The first line of treatment is often catheter-directed thrombolysis (CDT), or percutaneous mechanical thrombectomy (PMT) + CDT, with or without adjunct procedures such as angioplasty and stenting. When there are contraindications or failure to achieve catheter access or adequate lysis by these techniques, surgical thrombectomy (TE) with a temporary arteriovenous fistula (AVF) is an alternative in appropriately selected patients, ie, active, healthy patients with reasonable longevity and short duration of IFVT. Although duplex scanning usually confirms the presence of IFVT, a femoral venogram from the contralateral side (or alternatively a CT or MR venogram) may be required to visualize the inferior vena cava and determine the upper extent of thrombus extension.

Percutaneous mechanical thrombectomy

More than 10 percutaneous devices are currently available for clearing thrombus from dialysis grafts, of which only one is approved by the FDA for venous use. The Angiojet (Possis Medical, Inc, Minneapolis, Minn) is among the most commonly used PMT catheters and relies on high pressure saline jets to create a Venturi effect that disrupts thrombus and permits evacuation through the catheter. Drawbacks include incomplete wall contact and moderate to substantial blood loss and hemolysis. The Trellis device (Bacchus Vascular, Inc, Santa Clara, Calif) has been approved by the FDA and combines mechanical and pharmacological thrombolysis. The thrombolytic drug is contained between two occlusive balloons to prevent undesired systemic effects and complications. The thrombolytic drug is infused into the thrombus between the balloons and a wire rotates to mix and macerate the agent and the thrombus. After maceration, the "liquid" thrombus by-products are suctioned and the balloons deflated. Data from a multicenter registry¹¹⁰ comparing the two devices demonstrated 50% thrombus removal in 77% of patients (n = 40) with a device run time of 191 seconds;

corresponding data for 20 patients treated with Trellis was 75% and 26 minutes.

Sonolysis is a more recent technique that relies on the interaction between high-energy ultrasound and perflutren lipid microspheres infused into thrombus. High-energy ultrasound is applied to the skin and sends an acoustic pulse causing the microbubbles to cavitate; this microscopic “explosion” causes mechanical disruption of the thrombus.

Surgical thrombectomy

Technique. The technical aspects of venous thrombectomy has been detailed elsewhere.¹¹¹ In this era of endovascular surgery, there has been a rapid development of adjunctive catheter-based procedures to improve the results of TE including:

- Thomas Fogarty’s development of the balloon catheter 1966.
- Improved intraoperative diagnosis of iliac vein compression (May-Thurner syndrome) or residual thrombus using venography, angiography, and intravascular ultrasound (IVUS).
- Intraoperative management of residual stenosis by immediate angioplasty and stenting of the iliac vein.
- Improved preservation of the femoro-popliteal valves by combining proximal thrombectomy with intraoperative regional thrombolysis of the leg veins.¹¹²
- Prevention of fatal PE by temporary IVC filter before removal of thrombus extending into the IVC.
- Postoperative arteriovenography after 6 weeks through percutaneous catheterization of the contralateral groin to check the arteriovenous fistula (AVF) and thrombectomized iliac vein with possible angioplasty and stenting of remaining iliac vein obstruction.¹¹³
- Percutaneous coil embolization of the temporary AVF.

Complications and results. Series of over 200 patients have reported venous thrombectomy to be associated with no fatal perioperative PE and a mortality of less than one percent. In a randomized clinical trial,⁵¹ perfusion lung scans were positive on admission in 45% of all patients. Additional defects were present after 1 and 4 weeks 11% and 12% of the conservatively treated patients, respectively, in comparison with 20% and 0% in the thrombectomy group. When surgical thrombectomy was combined with a temporary AVF, 13% had early re-thrombosis of the iliac vein.⁹⁸ Among randomized patients, venographic iliac vein patency at 6 months was 76% in the surgical group compared with 35% in the conservative group.⁹⁸ These differences persisted after 5 and 10 years with 77% and 83% patency in the surgical group, respectively, vs 30% and 41% in the conservative group.^{97,99} Femoropopliteal valve competence at 6 months, determined by descending venography with valsalva, was significantly better in the surgical group (52%) compared with the conservatively treated group (26%).⁹⁸ Combining the results of all functional tests, 36% of the surgical patients had normal venous function after 5 years in comparison with 11% of the conservatively treated group.⁹⁷ Unfortunately, these differences

were not statistically significant due to loss of patients. At 10 years, duplex detected popliteal reflux was present in 32% of the surgical patients compared with 67% of the conservative group.⁹⁹

INDICATIONS AND TECHNIQUES OF INFERIOR VENA CAVA INTERRUPTION

Indications

To understand the role of the inferior vena-cava-filter in patients with VTE, it is important to consider the natural history of VTE. Patients with untreated proximal venous thrombosis, with or without PE, have a poor prognosis off therapy: intervention is required. What line-of-defence can be offered the patient with proximal venous thrombosis or PE for whom immediate anticoagulant therapy is contraindicated due to hemorrhagic complications or who have an unacceptable risk of bleeding? Since the early 1970s, the answer has been insertion of an inferior vena-cava-filter, the use of which is less harmful to the patient than inferior vena-cava ligation. The clinical use of the inferior vena-cava-filter has markedly increased over the past two decades; indeed by the late 1990s at least 30,000 to 40,000 filters were inserted in patients annually in the United States.^{114,115}

Since 1972, the categorical and most common indications for placement have been based on problems with anticoagulation in patients with venous thrombosis (DVT), either because it was contraindicated, had caused a complication forcing it to be discontinued, or had failed allowing DVT progression or PE.¹¹⁶ Filters have been less commonly used after pulmonary embolectomy and in conjunction with anticoagulation for optimal protection in very high-risk patients such as those with severe cardiac or pulmonary disease. Placement of a second suprarenal filter has also been successful when an existing filter has become filled with thrombus or thrombus has propagated through a filter. Suprarenal filters have similarly been placed for thrombus up to or within the renal veins and in pregnant patients to avoid the area of the cava compressed by the gravid uterus.¹¹⁷ Filters have also been placed in the superior vena cava for propagating subclavian vein thrombosis with PE.¹¹⁸

Over time, the success achieved with filters expanded the indications in some series to prophylaxis for free-floating thrombi longer than 5 cm;¹¹⁹ situations where the risk of anticoagulation was felt to be excessive as in older patients with DVT or following major trauma;¹²⁰ and to high risk situations such as orthopedic and bariatric operations.¹²¹ The risk of epidural hematoma from prophylactic anticoagulation has added support for perioperative filter placement in high-risk patients undergoing epidural anesthesia. Statistical data to support these indications are lacking, and enthusiasm for expanded indications has declined with case reports of late complications of caval occlusion and filter fractures.

However, the development of retrievable filters has rekindled their use for relative indications, particularly short-term periods of increased risk such as during mechan-

ical or thrombolytic treatment of large thrombi.¹²² Unfortunately, data to date show equivalent complications, less secure fixation, and the added expense of multiple procedures. Improvements in techniques and devices should overcome some of these limitations, but not the fundamental problem of knowing when the protection is no longer needed.

Contraindications and abuse of filters

The current FDA guidelines suggest that sepsis be considered a contraindication to filter placement. But long-term experience with Greenfield filters indicates that such wire-based devices can be used successfully since none has required removal. Experimental studies show that only the trapped thrombus can be infected, and that intravenous antibiotics can sterilize it.¹²³ Based on the 30 mm resting diameter of the original Greenfield filter, FDA guidelines also call for measurement of the vena cava prior to filter placement to avoid cavas larger than 28 mm in diameter. However, newer filters have larger resting diameters, and the Bird's Nest filter can be inserted into vena cavas as large as 40 mm in diameter.

The use of filters in terminally ill patients with multi-system organ failure may represent abuse of the indications since virtually all die during hospitalization. Appropriate use in patients with limited life expectancy should include a risk-benefit assessment as well as the wishes of the patient and family. The presence of orders against resuscitation should preclude filter use.

Techniques for filter insertion

Percutaneous techniques for filter placement have evolved to utilize smaller sheaths, allowing upper extremity venous access when necessary in anticoagulated patients. The focus on ease of access has overshadowed improvements in design, often sacrificing security of fixation for smaller profile. Similarly, the rush to embrace retrievable filters has overlooked an obligatory reduction in fixation security, since retrieval depends on easier detachment from the caval wall. Frequently, permanent filters are transformed to retrievable by removing hooks or limbs from the device, adding to the risk of migration. Migration, with reported fatal outcomes, has been reported and led to at least one FDA warning.

Traditional access for filter placement has been the right femoral vein, but its frequent involvement with thrombus and the straighter route from the right jugular vein to the inferior vena cava has led to increased preference for this approach. Using real-time ultrasound guidance increases the success of first pass cannulation and reduces inadvertent arterial puncture. Guidewire passage through the heart into the inferior vena cava may be difficult with a prominent Eustachian valve, but an angled catheter can facilitate the entry. Similarly, access from the left femoral vein is more difficult than the right since it joins the vena cava at a more oblique angle.

Radiographic imaging with fixed or mobile fluoroscopy has been the traditional method for measurement of caval

Table V. Estimated relative risks for a first episode of venous thromboembolism (VTE)*

<i>Thrombophilic defect</i>	<i>Relative risk</i>	<i>References</i>
Antithrombin deficiency	8–10	226,227
Protein C deficiency	7–10	226,227
Protein S deficiency	8–10	226,227
Factor V Leiden/APC resistance	3–7	228,229
Prothrombin 20210A mutation	3	230
Factor V Leiden and prothrombin 20210A	20	231
Elevated factor VIII:c (dose-dependent)	2–11	232,233
Elevated factor IX:c	2–3	234
Elevated factor XI:c (>90th percentile)	2	235
Mild hyperhomocysteinemia	2.5–2.6	236
Anticardiolipin antibodies		237
All	1.6	
High titers	3.2	
Lupus anticoagulant	11	

Adapted from Weitz JI, Middeldorp S, Geertz W, Heit JA. Thrombophilia and anticoagulation drugs. American Society of Hematology education book, 2004.

*Individuals with a thrombophilic defect compared with individuals without a defect; derived from family and population-based case-control studies.

size and filter placement. But logistical difficulty in moving critically ill patients, particularly those on respirators or requiring intensive-care monitoring, has led to newer techniques for bedside placement. Transabdominal duplex ultrasound has been the most common alternative imaging modality, but is often inadequate in the face of obesity, overlying bowel gas and open abdominal wounds. In these situations, IVUS has been more successful in vena caval visualization.^{124,125} This technique involves insertion of the IVUS catheter to the level of the right atrium and pullback to identify venous anatomical landmarks. Once the appropriate vena caval site is identified, the filter carrier can be inserted through a separate percutaneous puncture site in the same or opposite femoral vein. More recent modification of the technique allows insertion through a single puncture by matching the length of the IVUS probe, placed through the larger filter insertion sheath, to the length of the filter carrier catheter. Further refinements in imaging techniques and in the design of filters and their delivery systems should make bedside insertion progressively safer and easier.

HYPERCOAGULABLE STATES AND MOLECULAR MARKERS IN VENOUS THROMBOSIS

Hypercoagulable states

At least 50% to 70% of individuals with idiopathic VTE have underlying thrombophilic defects.¹²⁶ Such defects may be either congenital or acquired. The relative risks of developing a first episode of VTE in individuals with documented acquired or genetic thrombophilic predispositions are increased from two- to 11-fold (Table V).

The genetically based thrombophilic states for the most part include deficiencies of antithrombin, protein C, and protein S; activated protein C resistance (which is predominantly associated with the factor V Leiden gene R506Q mutation); mutated polymorphisms in the prothrombin gene (G20210A) and the methylentetrahydrofolate reductase gene (homozygous C677T or compound heterozygous for C677T and A1298C) with hyperhomocysteinemia; and elevated levels of various clotting factors (including factors VIII, IX, and XI). The most common acquired thrombophilic disorders include the antiphospholipid antibody syndrome, composed of a heterogeneous group of autoimmune antibodies (anticardiolipin/antiphospholipid antibodies and/or anti- α_2 glycoprotein-I antibodies), which functionally express themselves *in vitro* as a circulating lupus anticoagulant and *in vivo* as a thrombophilic state; hyperhomocysteinemia secondary to deficiencies of folic acid, vitamin B6, and vitamin B₁₂; hyperviscosity syndromes, such as polycythemia rubra vera and Waldenström's macroglobulinemia; paroxysmal nocturnal hemoglobinuria; and vasculitis.

Among the inherited thrombophilias, the factor V Leiden gene mutation is the most common predisposing risk factor, accounting for 40% to 50% of VTE in large population studies. However, most factor V Leiden carriers do not develop VTE and the incidence of VTE due to factor V Leiden increases with age, in contrast to the other hereditary thrombophilias, which usually manifest clinically by young adulthood. Resistance to activated protein C, a common risk factor for VTE noted in the laboratory, is attributable to factor V Leiden in up to 95% of cases; however, other factor V polymorphisms and elevated factor VIII levels also have been implicated to produce this laboratory phenomenon.

The prothrombin gene mutation and deficiencies in protein S, protein C, and antithrombin account for most of the remaining inherited thrombophilias. Extremely rare genetic causes of thrombophilia include hypo-dysplasminogenemia and dysfibrinogenemia.^{127,128} The prevalence of the factor V Leiden and the prothrombin gene G20210A mutation varies according to ethnicity, from 2% to 7% and 1% to 3% in the general Caucasian population, respectively. The mutations of these two genes are much less common in African-Americans, and are unusual in ethnically pure Asians and Africans.^{129,130} Known genetic risk factors for VTE are rare in African-American, African, and Asian populations, underscoring the need to explore for additional unique gene polymorphisms. Possible candidate genes include polymorphisms for factor VII, thrombopoietin, and platelet glycoprotein IIb/IIIa A1/A2 or A2/A2 mutations.

These genetic risk factors are predominantly associated with VTE rather than arterial thrombotic events although a recent report has indicated that the presence of factor V Leiden increases the risk of MI in young Turkish men.¹³¹ Hyperhomocysteinemia secondary to MTHFR gene mutations and plasminogen activator inhibitor type-1 inhibitor gene polymorphisms are associated with both arterial and

Table VI. Estimated relative risks for recurrent venous thromboembolism (VTE)

<i>Thrombophilic defect</i>	<i>Relative risk</i>	<i>References</i>
Antithrombin, protein C or S deficiency	2.5	238-240
Factor V Leiden mutation	1.4	45, 241-246
Homozygous factor V Leiden mutation	4.1	132
Prothrombin 20210A mutation	1.4	45, 247-250
Heterozygous factor V Leiden & 20210A	2-5	251
Elevated levels of factor VIII:c	6-11	233, 252
Mild hyperhomocysteinemia	2.6-3.1	253, 254
Antiphospholipid antibodies	2-9	255-257

Adapted from Weitz JI, Middeldorp S, Geertz W, Heit JA. Thrombophilia and anticoagulation drugs. American Society of Hematology education book, 2004.

venous thrombotic complications, and hyperlipoproteinemia (a) is associated overwhelmingly with arterial events. Acquired thrombophilic states, associated with the antiphospholipid antibody syndrome, cancer, etc. are associated with both arterial and venous hypercoagulable events.

Although thrombophilic defects are a well-established risk factor for a first episode of VTE, their association to VTE recurrence is somewhat controversial (Table VI).¹³² The published data do not consistently support the importance of antithrombin, protein C, or protein S deficiency, heterozygous factor V Leiden mutation, or prothrombin gene mutations in VTE recurrence. Mild hyperhomocysteinemia increases the risk of VTE recurrence moderately. Patients with factor VIII levels persistently above the 90th percentile; the lupus anticoagulant or antiphospholipid antibodies; homozygous factor V Leiden mutation; or compound heterozygous factor V Leiden and prothrombin gene mutations have the highest risk of VTE recurrence.

Screening for hypercoagulability

The incidence of the genetic thrombophilic defects in asymptomatic people is too low to make screening of the general population cost-effective. In unselected patients who have had a first episode of idiopathic VTE, testing for heritable thrombophilia does not usually provide helpful or prognostic information with respect to recurrent VTE after anticoagulant therapy is stopped.⁴⁵ Neither does routine testing of patients with idiopathic VTE for thrombophilic defects improve patient management. However, selected populations of patients may benefit from thrombophilic screening. For example, women with a personal history of VTE or recurrent spontaneous miscarriages who wish to become pregnant again; and men with a history of personal idiopathic VTE whose daughters wish to initiate oral estrogen birth control pills. Many physicians would advise women with strong family histories of hypercoagulable events not to initiate estrogen birth control pills or to pursue pregnancy. However, in a prospective study of 125 pregnant women with a history of isolated VTE and no

antepartum anticoagulation, there was no recurrent VTE in those without a detectable underlying inheritable thrombophilic state and whose previous VTE was associated with a temporary risk factor.¹³³ In contrast, among women with a history of idiopathic VTE, the incidence of recurrent VTE was 7.7% and 13% in those with combined underlying thrombophilic defects and idiopathic VTE, respectively.

Another special population that experiences increased incidence of VTE is cancer patients. Hypercoagulability may be produced by the intrinsic properties of the malignancy or by effects of chemotherapy, leading to disseminated intravascular coagulopathy with arterial and/or venous thrombotic complications. The association of factor V Leiden and the prothrombin 20210A variant with the VTE in cancer patients has not been established. Several small studies suggest that factor V Leiden conveys no increased thrombophilic risk to the cancer patient, while one recent publication noted greater than a sixfold increased risk for VTE in the cancer patient with the heterozygous prothrombin 20210A gene mutation.¹³⁴ Thus, genetic screening of all cancer patients may not be necessary if VTE prophylaxis is to be instituted in any case to protect against the intrinsic hypercoagulable potential of the tumor itself.

The screening of asymptomatic family members of hypercoagulable patients also provides an ethical challenge to the physician and to society. Awareness of a genetic abnormality, which may predispose to morbidity and possible mortality by VTE, would justify the initiation of prophylactic antithrombotic treatment measures for high-risk clinical situations. Unfortunately, many such individuals have been prevented from acquiring life insurance, disability insurance, and long-term care insurance or have been rated as unfavorable risks with attendant prohibitively high premiums if they have knowledge of their abnormal genome. Thus, it is difficult to recommend liberal genetic screening of asymptomatic members of a thrombophilic family unless the benefit-to-risk ratio is overwhelmingly favorable to that individual.

In summary, thrombophilic screening should be individualized. For those without a prior history of VTE but with an anticipated reversible risk factor for VTE (such as abdominopelvic surgery) and a compellingly positive family history of VTE, screening may be reasonable so that appropriate VTE prophylaxis can be initiated. Similarly, women who are habitual aborters with or without evidence of placental vessel thromboses, may benefit from genetic screening for thrombophilia. Finally, if the duration of anticoagulant management of a previous VTE will be modified dependent on the presence of inherited thrombophilic risk factors, genetic screening is justified.

SUPERFICIAL THROMBOPHLEBITIS

Although superficial venous thrombophlebitis (SVT) is a relatively common disorder with a significant incidence of recurrence and potential morbidity from extension and pulmonary embolism (PE),¹³⁵ it has been considered the stepchild of DVT and received limited attention in the literature. It has been reported that acute SVT occurs in

approximately 125,000 people in the United States per year.¹³⁶ However, the actual incidence of SVT is likely far greater as these statistics may be outdated and many cases go unreported. Traditional teaching mistakenly suggests that SVT is a self-limiting process of little consequence and small risk, leading some physicians to dismiss these patients with the clinical diagnosis of SVT and to treat them with "benign neglect."

Clinical presentation

Approximately 35% to 46% of patients with SVT are males, with an average age of 54 years old. The average age for females is about 58 years old.^{137,138} The most frequent predisposing risk factor for SVT is the presence of varicose veins, which occurs in 62% of patients. Others factors associated with SVT include: age >60 years old, obesity, tobacco use, and a history of deep venous thrombosis (DVT) or SVT. Factors associated with extension of SVT include age >60 years old, male sex, and history of DVT.

The physical diagnosis of superficial thrombophlebitis is based on the presence of erythema and tenderness in the distribution of the superficial veins with the thrombosis identified by a palpable cord. Pain and warmth are clinically evident and significant swelling may be present even without DVT. Patients may occasionally present with pain, tenderness, and an erythematous streak along the leg, but without ultrasound evidence of DVT or SVT. In these patients, the diagnosis of cellulitis or lymphangitis needs to be considered.

While most attention has been focused on SVT of the great saphenous vein (GSV), SVT of the small saphenous vein (SSV) is also of clinical importance as it may progress into popliteal DVT. In a group of 56 patients with SSV SVT, 16% suffered from PE or DVT.¹³⁶ Therefore, it is crucial that patients with SSV SVT be managed employing the same careful duplex examination, follow-up, and treatment if the SVT approaches the popliteal vein.

Etiology

Virchow's triad of altered blood flow, changes in the vessel walls, and abnormal coagulation are recognized to play a role in the etiology of thrombosis. While stasis and trauma of the endothelium have been cited as a cause of SVT, the importance of hypercoagulability has not been well documented. Furthermore, since the DVT occurring in association with SVT is often noncontiguous,^{136,138} direct extension of thrombosis from the superficial to the deep venous system needs to be questioned and systemic factors in the pathophysiology of SVT should be explored.

In order to determine whether a hypercoagulable state contributes to the development of SVT, a number of markers were determined in a population of patients with acute SVT.¹³⁹ All patients had a coagulation profile performed that included: (1) protein C antigen and activity, (2) activated protein C (APC) resistance, (3) protein S antigen and activity, (4) antithrombin (AT) and (5) lupus-type anticoagulant. Among 29 enrolled patients, 12 (41%) were found to have abnormal results consistent with a

hypercoagulable state. Five of the patients (38%) with combined SVT/DVT and seven of the patients (44%) with isolated SVT were found to be hypercoagulable. These findings suggest that patients with SVT are at an increased risk of having an underlying hypercoagulable state.

Furthermore, while the importance of leukocyte-vessel wall interactions, cytokines/chemokines, and other factors in the development and resolution of DVT have been well described, no similar data exists for the changes associated with SVT. Although some authors have suggested that the pathology underlying SVT may be analogous to DVT, this viewpoint currently remains largely unsupported.

Diagnosis

It is supposed by a few authors that SVT is a benign process that requires no further evaluation unless symptoms fail to spontaneously resolve. This is despite findings that DVT associated with SVT may not be clinically apparent.¹³⁶

Duplex ultrasound scanning is now the initial test of choice for the evaluation of SVT as well as the diagnosis of DVT. The extent of involvement of the deep and superficial systems can be accurately assessed utilizing this modality as routine clinical examination may not be able to precisely evaluate the proximal extent of involvement in either system. As duplex imaging is accurate and venography may contribute to phlebitis, venography is not routinely recommended. Duplex imaging has shown concomitant DVT to be present in 5% to 40% of patients with SVT.^{136,140-143} It is important to note that up to 25% of these DVTs may not be contiguous with the SVT and may be in the contralateral lower extremity.¹³⁶

Treatment

The location of the SVT determines the course of treatment. The therapy may be altered should the SVT involve tributaries of the GSV, distal GSV, or GSV of the proximal thigh. Traditional treatment for SVT localized in tributaries and the distal GSV has consisted of ambulation, warm soaks, and nonsteroidal anti-inflammatory agents.^{135,144,145} Surgical excision may play a role in rare cases of recurrent thrombophlebitis despite maximal medical management. However, such management does not address the possibilities of thrombus extension or concurrent DVT associated with proximal GSV SVT.

The progression of isolated superficial venous thrombosis to deep vein thrombosis has been evaluated. Among 263 patients with isolated superficial venous thrombosis by duplex ultrasonography, 30 (11%) patients had documented progression to deep venous involvement.¹⁴⁶ Progression from the greater saphenous vein in the thigh into the common femoral vein (21 patients) was most common, with 18 of these extensions noted to be nonocclusive and 12 having a free-floating component. At the time of the follow-up examination, all 30 patients were being treated without anticoagulation. As a result of this type of experience, follow-up duplex scanning 48 hours after presentation is often recommended to exclude progression.¹⁴⁷

Due to the recognized potential for extension into the deep system and embolization, high saphenous ligation with or without stripping is often recommended for SVT within 1 cm of the saphenofemoral junction.¹⁴⁸⁻¹⁵¹ In a series of 43 patients who underwent ligation of the saphenofemoral junction with and without local CFV thrombectomy and stripping of the GSV, only two patients were found with postoperative contralateral DVT, one of whom had a PE.¹³⁸ Eighty-six percent of the patients were discharged within 3 days. Complications included wound cellulitis in four patients and a wound hematoma in one. While satisfactory results were noted in these instances, several issues still remain unresolved. The question of whether or not to strip the GSV in addition to high ligation is not clearly addressed, although these patients do seem to experience less pain once the SVT is removed. Ligation was initially proposed to avert the development of deep venous thrombosis by preventing extension through the saphenofemoral junction. Since issues of noncontiguous DVT and post-ligation DVT with PE are not addressed by this therapy, alternative treatment options need to be explored.

A prospective nonrandomized study was conducted to evaluate the efficacy of anticoagulation in the management of saphenofemoral junction thrombophlebitis (SFJT).¹⁵² Duplex ultrasonography was performed before admission, both to establish the diagnosis and to evaluate the deep venous system. Patients were hospitalized, given a full course of heparin treatment, and evaluated with duplex ultrasound 2 to 4 days after admission to assess resolution of SFJT and to reexamine the deep venous system. Patients with SFJT alone and resolution of SFJT as documented by duplex ultrasound scans were maintained on warfarin for 6 weeks. Those patients with SFJT and DVT were maintained on warfarin for 6 months.

Among 20 enrolled patients, eight (40%) had concurrent DVT, including four with unilateral DVT, two with bilateral DVT, and two with development of DVT despite anticoagulation. DVT was contiguous with SFJT in five patients and noncontiguous in three patients. Seven out of 13 duplex ultrasound scans obtained at 2 to 8 months follow-up demonstrated partial resolution of SFJT, five had complete resolution, and one demonstrated no resolution. There were no episodes of PE, recurrence, or anticoagulation complications at maximum follow-up of 14 months. Anticoagulation therapy to manage SFJT was effective in achieving resolution, preventing recurrence, and preventing PE within the follow-up period. The high incidence of DVT associated with SFJT suggests that careful evaluation of the deep venous system during the course of management is necessary.¹⁵³

The appropriate management of SVT was further addressed in a prospective study consisting of 444 patients randomized to six different treatment plans (compression only, early surgery with and without stripping, low-dose subcutaneous heparin, low-molecular-weight heparin, and oral anticoagulation).¹⁵⁴ Patients presenting with SVT and large varicose veins without any suspected/documented systemic disorder were included in this study. Exclusion

criteria were obesity, cardiovascular or neoplastic diseases, nonambulatory status, bone/joint disease, problems requiring immobilization, age >70 years, and patients with superficial thrombophlebitis without varicose veins.

There was no significant difference in DVT incidence at 3 months among the treatment groups. After 3 and 6 months, the incidence of SVT extension was higher in the elastic compression and saphenous ligation groups and lowest is the stripping group. The cost for compression solely was found to be the lowest, and the treatment arm including LMWH was found to be the most expensive. The highest social cost (lost working days, inactivity) was observed in subjects treated with stockings alone. However, as the details of the treatment protocols were not specifically identified, the results of this study are difficult to evaluate. Furthermore, the exclusion criteria would eliminate many of the patients diagnosed with SVT in a clinical practice and the inclusion of almost any patient presenting with SVT, regardless of its location makes the remaining groups quite variable.

Meta-analysis of surgical vs medical therapy for isolated above knee SVT has been attempted, but has not been feasible due to the paucity of comparable data between the two groups.¹⁵⁵ This review suggested that although stripping provides superior symptomatic relief, medical management with anticoagulants is somewhat superior with respect to minimizing complications, and preventing subsequent DVT and PE. Based on these data, the authors suggest that anticoagulation is appropriate in patients without contraindications.

Although proximal GSV SVT occurs not infrequently, the best treatment regimen based on its underlying pathophysiology and resolution rate remains controversial. More recent investigations do offer some guidelines suggesting that anticoagulation is more effective than venous ligation in preventing DVT and PE.¹⁵⁶ Further examination of the unresolved issues involving SVT is fundamental.¹⁵²

THE MANAGEMENT OF EXTREMITY VENOUS TRAUMA

The early history of venous repair is not as well documented as for arterial injury. Schede is reported to have performed the first successful lateral repair of a lacerated femoral vein in 1882.¹⁵⁷ One of the first wartime repairs of a venous injury was by Goodman in 1918.¹⁵⁸ However, ligation of venous injuries was the accepted standard of care during World War I. In an attempt to improve limb salvage, Makins in 1919 recommended ligation of the uninjured vein when an arterial injury was treated by ligation.¹⁵⁹ In 1954, DeBakey and Simeone published their report on the management of vascular injuries during World War II, which included a short report on venous injuries.¹⁶⁰ However, it was not until the Korean War that a more concerted effort was made at perfecting the repair of venous injuries.¹⁶¹ Rich extended Hughes observations in 1970 and showed that repair of military venous injuries could be performed safely. Later studies reinforced this practice, as

both early and late complications of venous repair were lower than with ligation.

Incidence

Trauma is the fourth leading cause of civilian deaths in the United States and the leading cause of death among children and adults under age 45. Young males are at greatest risk, with up to 30% of males sustaining injuries in a single year. Only 20% of females sustain injuries over the same time period. Males account for 72% of injury fatalities and 56% percent of nonfatal injuries.¹⁶²

Injury due to past military conflicts has involved exclusively male soldiers, usually in their second to third decade of life. In the Global War on Terrorism (GWOT), the average age of wounded soldiers is 22 years (range 17 to 58 years). For vascular injuries specifically, the age range is 18 to 56 years with a mean of 28 years. The incorporation of women into traditional combat roles has resulted in a shift of wartime demographics. In the Global War on Terrorism, women have accounted for 2% of all injuries and 3% of all vascular injuries.

The true incidence of venous trauma is often difficult to ascertain. It is not uncommon for surgeons to repair arterial injuries and ligate the accompanying venous injury without reporting it. As such, the true incidence of venous injury is likely under reported. In the GWOT Vascular Trauma Registry, a total of 200 arterial injuries have been documented during combat operations over a 4-year period. In contrast, only 49 named venous injuries in 34 patients have been reported during this same interval. Isolated venous injuries are less common than combined arterial and venous injuries, occurring in only 25% of GWOT patients. This is very similar to previous reports on the incidence of venous injuries suffered during wartime. Venous injuries accounted for 39.4% of vascular injuries during the Korean War, although the number occurring in association with arterial injury is unknown.¹⁶³ In their preliminary report on vascular injuries suffered during the Vietnam War, Rich noted that the majority (85.6%) of venous injuries occurred in association with arterial injuries.¹⁶⁴ Rich subsequently published details of management of 1000 arterial injuries from the Vietnam Vascular Registry in 1970. Three hundred seventy seven (38%) of these arterial injuries were associated with concomitant venous injuries.^{165,166}

Several reports have documented the incidence of venous injuries in civilian trauma centers.¹⁶⁵⁻¹⁷⁰ The majority (75%) of venous injuries occur in association with arterial injuries. In these studies, 22% to 31% of arterial injuries have an associated venous injury. Isolated venous trauma occurs less frequently and accounts for 25% of venous injuries.

Etiology

The majority of injuries in the United States are the result of blunt trauma. Motor vehicle accidents are the leading cause of injury death, accounting for one-third of all fatal injuries. Injuries resulting from the use of firearms are the second leading cause of injury death but the leading

cause of vascular injury. In 1985, 31,556 people were shot to death; 39% were homicide, 56% were suicide, and 5% were unintentional.¹⁶² The majority of civilian firearm injuries are caused by low velocity handguns. In several series, gunshot wound accounted for 50% to 100% of venous injuries.¹⁶⁸ Venous injuries from other causes, including stab wounds (1% to 28%), blunt trauma (1% to 23%), and shotguns (1% to 17%), occur much less frequently.

Fragmentation injuries have historically accounted for the majority of military wounds.^{160, 165, 167, 168} The type of fragmentation munition has changed over time from mortars, to shells, to the present day improvised explosive devices (IED). In the Global War on Terrorism, 68 (64%) patients were wounded by IEDs, 27 (25%) were wounded by gunshots, and 12 (11%) experienced blunt traumatic injury.¹⁷¹

Distribution of injuries

The majority of civilian venous trauma occurs in the extremities with a near equal distribution between upper and lower extremities. Gaspar and Trieman¹⁷² documented the distribution of civilian venous injuries: 17% superficial femoral vein, 15% inferior vena cava, 15% internal jugular vein, 14% brachial vein, and 8% popliteal vein. More recent series report nearly 90% of venous trauma to occur in the extremities. Smith¹⁷³ reported 25% of venous injuries to involve the iliac veins, 45% the femoral, 20% the popliteal, and 10% the basilic veins.

Military injuries similarly largely involve the extremities. The majority of venous injuries during the Vietnam conflict involved the lower extremity. Among these, Rich reported that superficial femoral vein injuries occurred in 37% of patients with concomitant arterial injury. Injuries to the popliteal vein occurred in 29.3% in comparison with the common femoral vein in 5%. In contrast, venous injuries to the upper extremity were less common; brachial and axillary vein injuries accounting for 14% and 5% of venous injuries, respectively. The modern use of body armor provides excellent protection from direct penetrating injury to the chest, back, and abdomen. A recent review of military injuries in the GWOT reveals that trauma to the head and neck accounted for 31% of injuries, trunk 14%, lower extremities 26%, and upper extremities 30%.¹⁷¹

Diagnosis

Extremity venous injuries are often difficult to identify. Although life-threatening hemorrhage may be present, venous injuries are often difficult to diagnosis by physical examination alone. Concomitant soft tissue swelling, incisions and pain often preclude an adequate examination in the acute and sub-acute setting. Slow, persistent hemorrhage from open soft tissue wounds may be noted. However, physical evidence of venous injury is most often recognized at the time of exploration for ischemia or hemorrhage. Lacerations or transections of injured veins are easily recognized but often overlooked. Furthermore, venous injuries may require 12 to 24 hours to become symptomatic, usually with the development of swelling,

edema, or cyanosis. In cases of proximal venous injury, swelling may be massive and in extreme situations may be limb threatening and present as phlegmasia cerulea dolens.

Recognition of venous injuries in patients with non-life or limb threatening trauma can be more challenging. Rarely do patients undergo early radiologic evaluation for the acute detection of venous injury. Delayed evaluation often involves the use of B-mode or color flow duplex (CFD) ultrasonography or contrast phlebography. Other noninvasive tests such as plethysmography are too nonspecific to detect injury and are not useful in the modern setting.

Ultrasonography is the study of choice for the initial detection and evaluation of venous thromboses associated with trauma. The loss of spontaneous venous flow, respiratory variation, and compressibility confirm venous thrombosis. Gagne¹⁷⁴ reported that CFD detected seven of eight (88%) venous injuries in 37 patients with penetrating proximity extremity trauma. Venography was technically difficult to perform in this patient population and failed to detect four femoral-popliteal vein injuries. Ultrasonography may, however, be less sensitive and more labor intensive in determining the details of venous outflow from an injured extremity. Furthermore, in the current GWOT, the use of ultrasonography has often been limited by external fixators and large soft tissue defects associated with IED injuries.

Ascending phlebography is an excellent technique for determining venous injury as well as documenting the status of extremity venous outflow.¹⁷⁵ The use of multiple tourniquets for assessment of the deep venous system is useful in understanding lower extremity venous outflow.

Spiral CT venography is a new technique that may have some utility in the setting of venous injury. Not only is this technique sensitive for the detection of venous thrombosis, it also provides information on injuries to associated structures.¹⁷⁶ Finally, although somewhat time intensive, MRI can also be a useful adjunct in venous diagnosis.¹⁷⁷ Neither of these techniques, however, are useful in the trauma patient with retained missile fragments.

Pathophysiology of venous trauma

During World War I, improved limb salvage was reported for venous ligation in the presence of arterial ligation.¹⁵⁹ DeBakey and Simeone, in contrast, were unable to corroborate these observations in vascular injuries occurring during WWII. This controversy stimulated early researchers at Walter Reed Army Institute of Research to develop animal models for further investigation of the effect of venous ligation on limb physiology.

Early canine hind limb models suggested a sudden and temporally related decrease in arterial inflow accompanying acute venous occlusion.¹⁷⁸ Using the same model, Hobson subsequently confirmed these findings and further noted that femoral arterial flow improved after 48 hours.¹⁷⁹ These findings were attributed to increased venous return through recruitment of collaterals. They concluded that

maintaining patency of venous return is important in patients suffering combined arterial and venous extremity injuries, especially in the first 48 hours.

In the event that surgeons were forced to manage venous injuries by ligation, investigators at the Walter Reed Army Institute of Research Investigations searched for alternative methods to preserve limb perfusion. Among the findings from a canine model of femoral venous ligation was that arterial inflow could be improved with phenoxylbenzamine.¹⁸⁰ Improvement of limb perfusion was also verified in a primate model of venous ligation after lumbar sympathectomy.¹⁸¹ These investigations give surgeons alternate methods of avoiding arterial ischemia in the face of acute venous occlusion.

Treatment

Most surgeons agree that the best management of major axial vein injuries is to repair them if possible. Clearly, even complex repairs are possible in patients who have minimal injuries and can tolerate additional operative time. In contrast, for the patient in extremis where decisions of life over limb need to be made, repair of even major extremity veins becomes less important. The controversy regarding repair vs ligation of venous injuries thus mainly involves patients who are severely injured but not in life or death situations.

Repair of venous injuries. Until the Korean War, ligation had been the accepted historical method of managing venous injuries. After successfully repairing arterial injuries using Potts clamps for vascular control, the US Army Surgical Research Team headed by Dr Carl Hughes began attempting the repair of venous injuries.^{161,182} In 1954, Hughes reported successful repair of 13 venous injuries occurring in patients with concomitant arterial injury. The success of these reports stimulated Rich et al to continue investigation into the repair of venous injuries during the Vietnam War. They reported the success of their methods in several reports.^{157,165,183-190} Following these results, several centers have now reported their results for repair of venous injuries in civilian populations.^{169,191-195}

The repair of venous injuries is largely performed by lateral suture repair. During the Korean War, Hughes¹⁶³ reported using lateral suture repair in the management of 12 of 13 venous repairs. Lateral venorrhaphy was similarly used in 85% of venous repairs during the Vietnam War. Early data from the war in Iraq also seems to show that lateral venorrhaphy has been most often employed for the management of venous injuries. This trend is reflected in reports on the management of civilian venous trauma. Published series report that 17% to 43% of venous injuries are managed by simple lateral suture.^{169,170,172,173,191,193,194} The success of this technique ranges from 76% to 93% during short-term follow-up.

End to end anastomosis and venous patch angioplasty are useful techniques for the repair of injured veins without a large segmental loss. Hughes reported the first end-to-end anastomosis for the repair of venous injuries in 1954.

Rich subsequently reported that 15% of military venous injuries were managed using end-to-end anastomosis (8.1%), interposition vein grafts (4.0%), or vein patch angioplasty (2.4%). Hobson¹⁶⁹ reported the highest use of end to end repair in civilian femoral vein injuries, with a patency of 74% in the early postoperative period.

Interposition grafting is the most popular method of repair for injuries associated with a long segment loss of the injured vein. In general, the contralateral great saphenous vein is used in a reverse fashion. Using the ipsilateral vein may compromise venous outflow in the injured extremity. In Rich's series, 4% of patients received vein interposition grafts for military injuries. Early reports from the current military conflict indicate that this technique is rarely utilized. Interposition grafting accounts for 11% to 42% of venous repairs in several civilian series.^{169,170,172,191,193,194} However, the results of interposition grafting have been somewhat disappointing; 30-day patency rates being only 40% to 75%.

Extremity injuries occasionally result in loss of a large segment of vein in patients without suitable autologous conduit. The efficacy of alternative conduits in these situations has been previously investigated. Using a canine model, Hobson reported on the use of collagen tubes¹⁹⁶ and fresh venous homografts. Wright¹⁹⁷ similarly reported their experience with bovine heterografts in a canine model. The use of prosthetic conduits, such as polytetrafluoroethylene (PTFE), for venous bypass in civilian trauma patients has been more recently reported.^{194,198,199} The use of prosthetic conduits to manage military vascular injuries has been reported to be useful when other conduits have not been suitable maintaining limb perfusion.²⁰⁰ Experimental studies support these observations and have shown PTFE to have a lower rate of infection and complications in heavily contaminated wounds compared with autologous vein.^{199,201,202} Prosthetic conduits may be most useful when the great saphenous vein is of inadequate size, poor quality, or needed for venous outflow in the multiply injured patient. However, the long-term patency of PTFE when used for traumatic venous reconstruction is very disappointing. Of 30 PTFE grafts placed in the venous system, Feliciano reported that 100% thrombosed in the early postoperative period.

Several authors have reported the use of complex venous repairs.^{168,194,203-205} Rich¹⁵⁷ first reported using a cross femoral venous bypass for the management of military venous injuries 1974. The use of panel or spiral grafts for military injuries has not been reported. Such complex venous repairs have, however, been described for the management of civilian venous trauma.^{191,193,205} In their series, Pappas¹⁹¹ reported that 8% of patients received spiral vein grafts and 11% panel grafts in the iliac, common femoral, or popliteal arteries. However, the patency of complex venous repairs is significantly lower than simpler techniques. Meyer¹⁹³ report early thrombosis of 50% of these repairs. Such results have led several authors to question the utility of spiral and panel grafts in the management of venous trauma.

Based on the disappointing long-term patency of complex venous repairs, adjuncts for improving these results have been investigated. The use of arteriovenous fistulas as an adjunct to venous interposition grafts has been evaluated in a canine model.²⁰⁶ These studies indicated that construction of an H-type arteriovenous fistula at the distal anastomosis improved patency in comparison with a side-to-side configuration. In either case, construction of an arteriovenous fistula at the distal anastomosis improved venous bypass patency.

Potential complications of venous repair, such as pulmonary emboli and deep venous thrombosis, have been cited as reasons to avoid these techniques. However, numerous military and civilian series have found a low incidence of venous thromboembolic complications (0% to 1%) in patients managed by venous repair.^{163,169,185,189,194}

Ligation of venous injuries. Ligation has been the principle method of managing venous injuries for centuries. Although ligation continued to be used during the initial years of the Korean War, Hughes^{161,182,207} and Spencer²⁰⁸ began to explore the possibilities of venous repair. Despite this progress, increasing observations seemed to emphasize the lack of serious complications associated with venous ligation.²⁰⁹ Several reports from civilian trauma populations now suggest that immediate side effects of venous ligation are few and can be minimized by the liberal use of fasciotomy and postoperative limb elevation.^{168,210,211}

The effects of femoral or popliteal vein ligation might also be extrapolated from recent reports on harvesting the femoropopliteal vein for arterial reconstruction.²⁰⁹ Wells²¹² found that less than one third of harvested limbs had edema and no patient had major chronic venous changes or venous claudication after a mean follow-up of 37 months. The development of severe venous hypertension after complete deep vein harvest below the adductor hiatus required adjunctive measures such as fasciotomy in 20.7% of limbs. In contrast, fasciotomies were not required in patients undergoing subtotal deep vein harvest ending above the adductor hiatus. Fasciotomies were also performed in 76% of limbs undergoing concurrent ipsilateral GSV and deep vein harvest, compared with 11.7% of patients undergoing deep vein harvest alone.²¹³ Although these observations suggest that the morbidity associated with elective harvesting of the femoropopliteal vein conduit is acceptable, this may not accurately reflect the physiologic situation in the acutely injured extremity with extensive soft tissue injuries, acute interruption of lymphatics, and compromised venous drainage.

The acute physiologic changes associated with proximal venous obstruction of the lower extremity have been documented both clinically^{214,215} and experimentally.^{180,181,216} Opponents have argued that the morbidity associated with venous ligation is not always inconsequential. In a 1974 review of 125 limbs amputated after popliteal artery trauma, Rich²¹⁷ found that amputation resulted from acute venous hypertension following venous ligation

in the presence of a patent arterial repair in 19 (15%). As in these cases, predicting which patient will develop phlegmasia cerulea dolens is not always possible. Certainly, patients with ligation of the common iliac, common femoral, or popliteal veins are at highest risk due to the lack of preexisting collateral channels at these junctures. Massive fluid shifts typically accompany proximal venous ligation; often reaching several liters within a few days.²¹⁸ Shock due to these fluid losses has been reported to occur in up to one third of patients with phlegmasia cerulea dolens. Clearly, this phenomenon will make hypotensive patients with multisystem trauma worse.

Despite these observations, the long-term effects of venous ligation are not always dramatic and life threatening. Rich reported significant postoperative edema in 29 of 57 patients (50.9%) after ligation of popliteal vein injuries. In contrast, Timberlake²¹⁹ reported no difference in the incidence of lower extremity edema between patients whose popliteal vein injury was ligated or repaired.

Outcome after venous injury

Several studies have reported follow-up results 6 to 20 years after venous injury.^{204,220-222} Patency rates for simple repairs range from 67% to 100% in long-term follow-up. However, few studies have examined the effect of traumatic venous repairs on postoperative venous function. The majority of these studies have been unable to demonstrate a difference in venous hemodynamics between patients managed by repair vs ligation using color flow duplex, photoplethysmography, impedance plethysmography, or air plethysmography.^{203,221,223}

Several institutions have documented long-term adverse effects of fasciotomy on the development of chronic venous insufficiency.^{203,224,225} These observations provide yet another possible explanation for the development of venous insufficiency in the lower extremity trauma patient.

Recommendations

Injuries to major proximal veins of either the upper or lower extremity should be repaired if at all possible. Specifically, the axillary, subclavian, common iliac, external iliac, common femoral, and popliteal veins should be repaired. Even short-term patency of these veins will help avoid massive distal swelling distal and possible development of a compartment syndrome. There is currently no evidence that repair of venous injuries leads to a higher incidence of venous thromboembolic complications. If repair of these injured veins is not safe or possible, ligation is the obvious alternative and should be performed. In these cases, the surgeon should expect massive acute extremity swelling and manage it accordingly with fasciotomy and leg elevation.

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Appendix

Evidence-based guideline recommendations

With few exceptions, patients with DVT or PE are treated similarly.

Initial treatment of patients with venous thromboembolism:

Initial regimen:

- For patients with objectively confirmed DVT or PE, short-term treatment with SC LMWH or IV UFH is recommended (Grade A). SC UFH may be used in DVT patients (Grade A);
- or patients with a high clinical suspicion of DVT or PE, treatment with anticoagulants while awaiting the outcome of diagnostic tests is suggested (Grade C);
- In patients with DVT or acute nonmassive PE, LMWH over UFH is recommended (Grade A). Uncomplicated DVT patients may be treated as an outpatient.

- In patients with acute DVT or nonmassive PE treated with LMWH, routine monitoring with antifactor Xa levels is not recommended (Grade A);
- In patients with severe renal failure, IV UFH over LMWH is suggested (Grade C);

Duration of initial treatment:

- In acute DVT or PE, initial treatment with LMWH or UFH for at least 5 days is suggested (Grade C).

Commencing vitamin-k-antagonist therapy:

- Initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 is recommended (Grade A).

Adjunctive initial therapy

Thrombolytic therapy:

- In patients with DVT or PE, the routine use of systemic thrombolytic treatment is not recommended (Grade A).
- In selected DVT patients, such as those with massive iliofemoral DVT at risk of limb gangrene secondary to venous occlusion, IV thrombolysis is suggested (Grade C).
- In selected patients with PE, systemic administration of thrombolytic therapy is suggested (Grade B). For PE patients who are hemodynamically unstable, use of thrombolytic therapy is suggested (Grade B). For patients with PE who receive thrombolytic regimens, use of thrombolytic regimens with a short infusion time over those with prolonged infusion times is suggested (Grade C).
- In PE patients, it is suggested that local administration of thrombolytic therapy via a catheter should not be used (Grade C).
- In patients with DVT, the routine use of catheter-directed thrombolysis is not suggested (Grade C). In DVT patients, confining catheter-directed thrombolysis to selected patients such as those requiring limb salvage is suggested (Grade C).

Nonsteroidal anti-inflammatory agents:

- For the initial treatment of DVT, the use of nonsteroidal anti-inflammatory agents is not recommended (Grade B).

Ambulation:

- For DVT patients, it is recommended that these patients be permitted ambulation as tolerated (Grade B).

Long-term treatment of patients with venous thromboembolism

Intensity of long-term vitamin-k-antagonist therapy

- In patients with DVT or PE, adjusting the dose of VKA to maintain a target INR of 2.5 (range, 2.0 to

3.0) for all treatment durations is recommended (Grade A). High-intensity VKA therapy (INR range, 3.1 to 4.0) is not recommended (Grade A). Low-intensity therapy (INR range, 1.5 to 1.9) compared with INR range of 2.0 to 3.0 is not recommended (Grade A).

Long-term LMWH treatment

- For most patients with DVT or PE and concurrent cancer, treatment with LMWH for at least the first 3 to 6 months of long-term treatment is recommended (Grade A). For these patients, anticoagulant therapy indefinitely or until the cancer is resolved is suggested (Grade C).

Duration of long-term vitamin-k-antagonist therapy

Transient (reversible) risk factors:

- For patients with a first episode of DVT or PE secondary to a transient (reversible) risk factor, long-term treatment with a VKA for at least 3 months over treatment for shorter periods is recommended (Grade A).

Idiopathic:

- For patients with a first episode of idiopathic DVT or PE, treatment with a VKA at least 6 to 12 months is recommended (Grade A).
- Considering patients with first-episode idiopathic DVT or PE for indefinite anticoagulant therapy is suggested (Grade A).

Presence of a thrombophilia:

- For patients with a first episode of DVT or PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations), treatment for 12 months is recommended (Grade C). Indefinite anticoagulant therapy in these patients is suggested (Grade C).
- For patients with a first episode of DVT or PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended (Grade A). Indefinite therapy as for patients with idiopathic thrombosis is suggested (Grade C).

Recurrent venous thromboembolism:

- For patients with two or more episodes of objectively documented DVT or PE, indefinite treatment is recommended (Grade A).

Indefinite anticoagulant treatment:

- In DVT or PE patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade C).

Prognostic testing

- In patients with DVT or PE, repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma D-dimer is suggested (Grade C).

Vena caval filter

- For most patients with DVT, the routine use of a vena cava filter in addition to anticoagulants is not recommended (Grade A).
- In DVT or PE patients the placement of an inferior vena caval filter in patients with a contraindication for, or a complication of anticoagulant treatment is suggested (Grade C), as well as in those with recurrent thromboembolism despite adequate anticoagulation (Grade C).

Catheter interventions

- For most patients with PE, use of mechanical approaches is not recommended (Grade C). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, use of mechanical approaches is suggested (Grade C).

Thrombectomy and embolectomy

- In patients with DVT, the routine use of venous thrombectomy is not recommended (Grade C).

- In selected patients such as patients with massive iliofemoral DVT at risk of limb gangrene secondary to venous occlusion, venous thrombectomy is suggested (Grade C).
- For most patients with PE, pulmonary embolectomy is not recommended (Grade C). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, pulmonary embolectomy is suggested (Grade C).

Post-thrombotic syndrome

- The use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle during 2 years after an episode of DVT is recommended (Grade A).
- A course of intermittent pneumatic compression for patients with severe edema of the leg due to PTS is suggested (Grade B).
- The use of elastic compression stockings for patients with mild edema of the leg due to the PTS is suggested (Grade C).
- In patients with mild edema due to PTS, administration of rutosides is suggested (Grade B).

Adapted from Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:401S-28S.⁸⁰