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Upper-extremity deep vein thrombosis (UEDVT) is an increasingly important clinical entity with potential for considerable morbidity. Pulmonary embolism (PE) is present in up to one third of patients with UEDVT.[1] Other complications, such as persistent upper-extremity pain and swelling, the superior vena cava (SVC) syndrome, and loss of vascular access, can be disabling and devastating.[2] Although once considered rare, UEDVT has become more common over the past several decades. This is directly related to the increasing use of central venous catheters for chemotherapy, bone marrow transplantation, dialysis, and parenteral nutrition. UEDVT has been reported in up to one fourth of patients with these catheters.[3] For these reasons, it is imperative that physicians understand UEDVT risk factors, diagnostic options, treatment alternatives, and prophylaxis regimens.

Pathogenesis

UEDVT most commonly refers to thrombosis of the axillary and/or subclavian veins. UEDVT is classified as primary or secondary on the basis of pathogenesis.

Primary Thrombosis

Primary UEDVT is a rare disorder (2 per 100 000 persons per year)[4] that refers either to effort thrombosis (the so-called Paget-Schroetter Syndrome) or idiopathic UEDVT. Patients with Paget-Schroetter Syndrome develop spontaneous UEDVT, usually in their dominant arm, after strenuous activity such as rowing, wrestling, weight lifting, or baseball pitching, but are otherwise young and healthy. The heavy exertion causes microtrauma to the vessel intima and leads to activation of the coagulation cascade. Significant thrombosis may occur with repeated insults to the vein wall, especially if mechanical compression of the vessel is also present.[5]

Thoracic outlet obstruction refers to compression of the neurovascular bundle (brachial plexus, subclavian artery, and subclavian vein) as it exits the thoracic inlet. Although this disorder may initially cause intermittent, positional extrinsic vein compression, repeated trauma to the vessel can result in dense, perivascular, fibrous scar tissue formation that will compress the vein persistently.[6] Compression of the subclavian vein typically develops in young athletes with hypertrophied muscles who do heavy lifting or completely abduct their arms. Cervical ribs, long transverse processes of the cervical spine, musculofascial bands, and clavicular or first rib anomalies are sometimes found in these patients. Therefore, cervical spine and chest plain films should be obtained in all patients undergoing evaluation for thoracic outlet syndrome.[7]

In contrast to patients with Paget-Schroetter Syndrome, patients with idiopathic UEDVT have no known trigger or obvious underlying disease. Idiopathic UEDVT may, however, be associated with occult cancer. In one study, one fourth of patients presenting with idiopathic UEDVT were diagnosed with cancer (most commonly lung cancer or lymphomas) within 1 year of follow-up. Most of these cancers were discovered during the first week of hospital admission for the venous thrombosis.[8]

The prevalence of hypercoagulable states in patients with UEDVT is uncertain because observational studies report varying results (Table 1).[1,9–12] Furthermore, screening for coagulation disorders is controversial and has never been shown to be cost-effective. The yield of these tests is highest for patients presenting with idiopathic UEDVT, a family history of deep vein thrombosis (DVT), a history of recurrent, unexplained pregnancy loss, or a personal history of a prior DVT. Physicians who recommend life-long anticoagulation for protein C, protein S, and antithrombin III deficiencies should test for these rare causes of inherited thrombophilia. In our practice, we test for factor V Leiden, the prothrombin gene mutation, hyperhomocysteinemia, and antiphospholipid antibodies. Elevated antiphospholipid antibodies in the presence of UEDVT establish the diagnosis of the antiphospholipid antibody syndrome. We manage these patients with indefinite, intensive anticoagulation with a target international normalized ratio (INR) of 3.0 to 4.0.[13] Hyperhomocysteinemia is easily corrected with folic acid supplementation. The optimal duration of anticoagulation for a thrombotic event associated with other hypercoagulable disorders, such as factor V Leiden or coexisting thrombophilias, is unknown.[14]

Secondary Thrombosis

Secondary UEDVT develops in patients with central venous catheters, pacemakers, or cancer and accounts for most cases of UEDVT. Catheter-related thrombosis is caused by several factors. The vessel wall may be damaged during catheter insertion or during infusion of medication. Also, the catheter may impede blood flow through the vein and cause areas of

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TABLE 1. Prevalence of Coagulation Disorders in Patients With UEDVT

Study	Factor V Leiden	Prothrombin Gene Mutation	Hyperhomocysteinemia	Antiphospholipid Antibodies	Antithrombin III Deficiency	Protein S Deficiency	Protein C Deficiency
Heron et al[9]	10.6	0	Not tested	22	0	4.3	0
Leebeek et al[10]	4.9	0	Not tested	26.8	2.4	0	0
Martinelli et al[11]	8.3	Not tested	5.6	0	0	0	0
Prandoni et al[1]	7.4	Not tested	Not tested	3.7	3.7	3.7	7.4
Ruggeri et al[12]	3.7	Not tested	Not tested	14.8	0	0	3.7

Values are presented as percentages.

stasis. Patients with incorrectly placed catheters are more likely to develop deep vein thrombosis. Blood flow is most rapid in the SVC, which may sufficiently dilute the infusate and reduce the risk of thrombophlebitis.[3] Therefore, catheter tips should be positioned in the lower third of this vessel or at the junction of the superior vena cava and right atrium.[15]

Presenting Symptoms and Signs

Axillary or subclavian vein thrombosis may occasionally be completely asymptomatic. More often, though, patients complain of vague shoulder or neck discomfort and arm edema.[1] If thrombosis causes obstruction of the superior vena cava, the patient may complain of arm and facial edema, head fullness, blurred vision, vertigo, or dyspnea.[16]

Patients with thoracic outlet obstruction may have pain that radiates into the fourth and fifth digits via the medial arm and forearm, attributable to injury of the brachial plexus. Symptoms may be position dependent and worsen with hyperabduction of the shoulder or lifting. If thoracic outlet syndrome is suspected, the examiner should palpate the supraclavicular fossa for brachial plexus tenderness, inspect the hand and arm for atrophy, and perform provocative tests, such as Adson's and Wright's maneuvers. To perform the Adson test, the examiner extends the patient's arm on the affected side while the patient extends the neck and rotates the head toward the same side. Weakening of the radial pulse with deep inspiration suggests compression of the subclavian artery. Wright's maneuver tests for reproduction of symptoms and weakening of the radial pulse when the patient's shoulder is abducted and the humerus is externally rotated.[7]

Physical examination may reveal low-grade fever attributable to thrombosis. Higher fevers may suggest septic thrombophlebitis or may be related to the underlying malignancy in patients with cancer. SVC syndrome reduces venous return to the heart and, like PE, may cause sinus tachycardia. Patients with UEDVT may have mild cyanosis of the involved extremity, a palpable tender cord,[17] arm and hand edema, supraclavicular fullness, jugular venous distension, and possibly dilated cutaneous collateral veins over the chest or upper arm.[1] If a central venous catheter is present, one or multiple ports may be occluded.[16]

The signs and symptoms of UEDVT (Table 2), however, are non-specific and may occur in patients with lymphedema, neoplastic compression of the blood vessels, muscle injury, or superficial vein thrombosis. Fewer than half of these symptomatic patients will have imaging evidence of an UEDVT. Therefore, it is important to confirm or exclude the diagnosis with objective testing.[1]

Diagnostic Imaging

The advantages and disadvantages of the different imaging modalities used to diagnose UEDVT are listed in Table 3.

Duplex Ultrasound

Duplex ultrasound is the initial imaging test of choice for diagnosing UEDVT because this technique is noninvasive

TABLE 2. Presenting Signs and Symptoms of UEDVT

	Symptoms	Signs
Axillary or subclavian vein thrombosis	Vague shoulder or neck discomfort	Supraclavicular fullness
	Arm or hand edema	Palpable cord
		Arm or hand edema
		Extremity cyanosis
		Dilated cutaneous veins
		Jugular venous distension
		Unable to access central venous catheter
Thoracic outlet syndrome	Pain radiating to arm/forearm	Brachial plexus tenderness
	Hand weakness	Arm or hand atrophy
		Positive Adson* or Wright† maneuver

*Adson maneuver: The examiner extends the patient's arm on the affected side while the patient extends the neck and rotates the head toward the same side. The test is positive if there is weakening of the radial pulse with deep inspiration, and suggests compression of the subclavian artery.

†Wright maneuver: The patient's shoulder is abducted and the humerus is externally rotated. The test is positive if symptoms are reproduced and there is weakening of the radial pulse.

TABLE 3. Advantages and Disadvantages of Imaging Modalities Used to Diagnose UEDVT

	Advantages	Disadvantages
Ultrasound	Inexpensive	May fail to detect central thrombus that is directly below the clavicle
	Noninvasive	
	Reproducible	
CT scan	May detect central thrombus	Contrast dye
	May detect the presence of extrinsic vessel compression	Not fully validated
Magnetic resonance	Accurately detects central thrombus	Limited availability
	Provides detailed evaluation of collaterals and blood flow	Claustrophobia
		Not suitable for some patients with implanted metal

and has high sensitivity and specificity for peripheral (jugular, distal subclavian, axillary) UEDVT.[1] Acoustic shadowing from the clavicle, however, will limit visualization of a short segment of the subclavian vein and may result in a false-negative study.[18]

Contrast Venography

Venography provides excellent characterization of venous anatomy but has several drawbacks. There may be technical difficulty in cannulating the vein in an edematous arm. The test requires an iodinated contrast agent, which may cause an allergic reaction, nephrotoxicity, or a chemical phlebitis that can worsen the preexisting thrombosis. There is little enthusiasm for using venography during pregnancy, even though iodinated contrast is rated pregnancy class B, and radiation exposure from venography has been reported to confer minimal risk to the fetus.[19]

Despite these disadvantages, venography may be required to confirm the diagnosis of UEDVT if suspicion for clot remains high despite a negative ultrasound. Venography is also required as a prelude to interventions, such as catheter-directed thrombolysis and angioplasty, and is used to assess response to these treatments.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is an accurate, noninvasive method for detecting thrombus in the central thoracic veins, such as the SVC and brachiocephalic veins (Figure 1). MRA correlates extremely well with venography and provides more complete evaluation of central collaterals, all central veins, including contralateral vessels, and blood flow. MRA is noninvasive and may, therefore, be preferred for diagnosis, especially when contrast venography is contraindicated or impossible.[20]

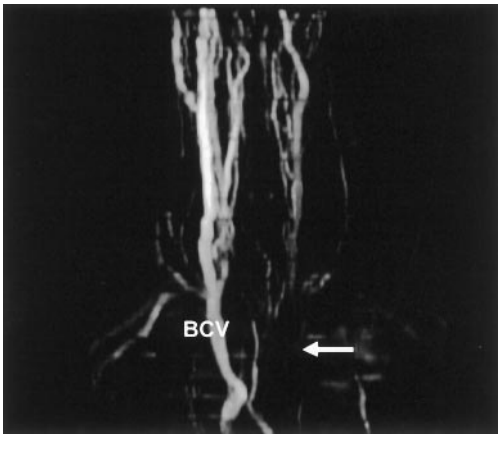

Figure 1. Magnetic resonance venogram demonstrating left brachiocephalic vein thrombosis (arrow). BCV indicates brachiocephalic vein. Figure courtesy of E. Kent Yucel, MD, Brigham and Women's Hospital, Boston, Mass.

Treatment

Treatment options for patients with UEDVT are listed in Table 4.

Anticoagulation

Anticoagulation is the cornerstone of therapy. Anticoagulation helps maintain patency of venous collaterals and reduces thrombus propagation even if the clot does not completely resolve.[3] Typically, unfractionated heparin is used as a "bridge" to warfarin. Low molecular weight heparin as a bridge may be safe and effective for outpatient treatment, or for reducing the duration of hospitalization.[21] Warfarin or other anti-vitamin K agents are typically continued for a minimum of 3 months, with a goal INR of 2.0 to 3.0.[17] We recommend at least 6 months of anticoagulation therapy if a coagulation abnormality is detected.

TABLE 4. Treatment Options for UEDVT

Limb elevation
Graduated compression arm sleeve
Anticoagulation
Unfractionated heparin as "bridge" to warfarin
Low-molecular-weight heparin as "bridge" to warfarin
Low-molecular-weight heparin as monotherapy
Catheter-directed thrombolysis
Suction thrombectomy
Angioplasty
Vein stenting
Surgical thrombectomy
Thoracic outlet decompression
Surgery
Physical therapy
Superior vena cava filter

TABLE 5. Risk of Major and Minor Bleeding Complications With Thrombolytic Therapy*

Study	Number of Patients	DVT Site	Major Bleeding			Minor Bleeding
			Intracranial Hemorrhage	Gastrointestinal Bleeding	Other	
Machleder[27]	23	Upper	0	0	1 (4.3)	0
Fraschini et al[25]	31	Upper	0	0	1 (3.2)	13 (41.9)
Beygui et al[28]	31	Upper	0	0	0	0
Seigel et al[29]	38	Upper	0	1 (2.6)	1 (2.6)	1 (2.6)
Bjarnason et al[30]	77	Lower	0	1 (1.3)	4 (5.2)	11 (14.3)
Mewissen et al[31]	473	Lower	2 (0.4)	No data†	54 (11.4)	77 (16.3)
Martin[32]	1498	Lower	21 (1.4)	No data	2 (0.1)‡	No data

Values are expressed as n (%).

*Martin study included catheter-directed and systemic thrombolysis. All other studies used catheter-directed thrombolysis only.

†Gastrointestinal bleeds were included in the "Other" category.

‡Fatal mediastinal and hepatic subcapsular bleeding in association with systemic treatment.

Thrombolysis

Young and healthy UEDVT patients have significant long-term morbidity if treated only with conventional anticoagulation.[22,23] Thrombolysis restores venous patency early, minimizes damage to the vessel endothelium, and reduces the risk of long-term complications, especially the troubling post-thrombotic syndrome, which is characterized by chronic arm and hand aching and swelling.[17,22,23] In contrast, thrombolysis is rarely used for the treatment of lower extremity DVT because those patients are generally not sufficiently concerned by the potential risk of chronic leg swelling.[24]

Catheter-directed thrombolysis achieves higher rates of complete clot resolution with lower doses of medication and reduces the risk for serious bleeding compared with systemic thrombolysis. The catheter should be positioned as close to the clot as possible; otherwise, collateral circulation will carry the medication away from the thrombus.[25] Thrombolysis works best if used within several weeks of the onset of symptoms, because progressive thrombus organization will limit its effectiveness at later dates.[17,25,26]

Many case series of thrombolysis in carefully selected patients have reported excellent outcomes with only minor bleeding complications, such as occasional hematomas or oozing at venipuncture or catheter sites.[25,27–29] The thrombolysis studies are small, however, so the risks of intracranial or gastrointestinal hemorrhage may not be fully appreciated, although they probably approximate those for catheter-directed thrombolysis of lower extremity DVT (Table 5).[30–32]

The best thrombolysis candidates are young, otherwise healthy patients with primary UEDVT, patients with symptomatic SVC syndrome, and those who require preservation of a mandatory central venous catheter. Contraindications include active bleeding, neurosurgery within the past 2 months, a history of hemorrhagic stroke, hypersensitivity to the thrombolytic agent, and surgery within the preceding 10 days. Heparin is usually given concurrently with the thrombolytic agent to prevent thrombus formation around the catheter.[17] Venipunctures, intramuscular injections, and invasive procedures should be minimized.

No controlled trials have compared the different thrombolytic agents. Although urokinase is an effective thrombolytic,[25,29] it has been unavailable in the United States since 1999 because the Food and Drug Administration raised concerns about the safety of the manufacturing process. Subsequently, Abbott Laboratories has addressed the concerns raised by the Food and Drug Administration and hopes to reintroduce Abbokinase within the next year.

Streptokinase, an alternative thrombolytic agent, has a high rate of allergic reactions and may be ineffective if administered within months of a prior dose or streptococcal infection. Therefore, recombinant tissue plasminogen activator (rtPA) is currently the agent of choice for treating UEDVT in the United States. At our institution, catheter-directed rtPA is usually administered as a continuous infusion of 1 to 2 mg/h for at least 8 hours. Serial venography is used to assess response to treatment. Chang and colleagues[26] have reported an innovative, successful technique of delivering rtPA over 15 minutes via a pulse-spray catheter lodged in the obstructing thrombus. This method may be as effective as longer infusions and may carry a lower risk of bleeding.

Percutaneous mechanical thrombectomy with devices such as the AngioJet (Possis Medical Inc) is often used in combination with thrombolytics (Figure 2). This procedure can rapidly extract large quantities of thrombus, thereby reducing the dose and duration of thrombolytic therapy.[33]

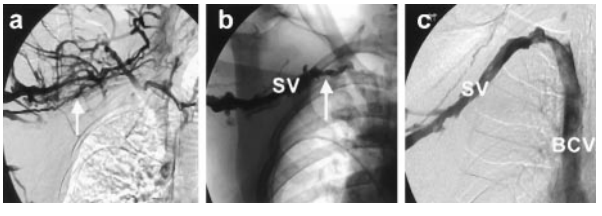

Figure 2. A 51-year-old weight lifter complaining of right arm pain. Initial venogram (a) shows occluded right axillary and subclavian veins with flow through collateral vessels (arrow). After percutaneous thrombectomy (b), there is persistent occlusion of the proximal subclavian vein (SV) (arrow). After thrombolysis (c), the subclavian vein (SV) is fully patent, with flow into the brachiocephalic vein (BCV). Figure courtesy of Michael F. Meyerovitz, MD, St Vincent Hospital, Worchester, Mass.

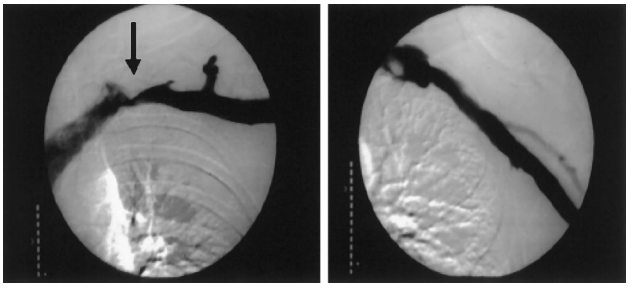

Figure 3. Venogram showing intermittent compression (arrow) of the left axillary-subclavian vein with arm abduction. Figure courtesy of Magruder C. Donaldson, MD, Brigham and Women's Hospital, Boston, Mass.

Surgery

Several studies have emphasized the importance of eradicating vein compression in patients with primary UEDVT to reduce the risk of recurrent thrombosis and long-term morbidity.[17,27] Therefore, after successful thrombolysis, repeat ultrasound or venography in the neutral and shoulder-abducted position can help determine whether vein compression is present (Figure 3).[17] Most vascular surgeons recommend early surgical correction of extrinsic vein compression,[17,27,34] which usually involves resection of part of the first rib or clavicle.[2] Lysis of dense adhesions around the subclavian vein may also be required if anatomic anomalies have caused chronic, repeated trauma to the vessel.[6] After surgery, venography can assess residual stricture, which should be treated with balloon venoplasty; if this fails, vein stenting can be considered. Long-term patency has been documented with this multimodal approach.[23,27,35,36] Surgical thrombectomy restores venous patency but is invasive, carries the risk of general anesthesia, and may be complicated by pneumothorax and brachial plexus damage. Therefore, we reserve this technique for refractory cases.[17]

After thrombolysis, we prefer a trial of conservative therapy rather than early surgical decompression for patients with thoracic outlet syndrome. Conservative treatment, which includes a structured physical therapy program to loosen muscles compressing the subclavian vein, weight loss if obese, and nonsteroidal anti-inflammatory drugs, may obviate the need for surgery. Those with neurological symptoms due to thoracic outlet syndrome ordinarily require at least several months of physical therapy before improvement is noted.[7]

Patients with UEDVT who have contraindications to anticoagulation, such as major gastrointestinal bleeding, or patients who develop PE despite adequate anticoagulation may be candidates for SVC filter placement. SVC filters are not widely used because data regarding their safety and efficacy are sparse. There are concerns that the risks of SVC filters, including filter migration, dislodgment, fracture, and precipitation of SVC syndrome, outweigh the benefits, especially because fatal PE from UEDVT is considered rare. The very limited trials that have been completed show that SVC filters are probably safe and that they protect against clinical PE.[37,38]

Complications and Prognosis

Up to one third of patients with UEDVT have PE.[1] Rarely, PE secondary to UEDVT may be recurrent and fatal, despite adequate heparin therapy. Catheter removal is also a risk factor for PE. As catheters are withdrawn, fibrin sheaths may peel off the catheter, break loose from the vessel wall, and embolize.[16]

The post-thrombotic syndrome, caused by venous hypertension secondary to outflow obstruction and valvular injury, varies from mild edema with little discomfort to incapacitating limb swelling with pain and ulceration. Graduated compression stockings markedly reduce the rate of the post-thrombotic syndrome in patients with lower extremity DVT.[39] Therefore, we recommend graduated compression sleeves for all symptomatic patients with acute UEDVT. Those with refractory swelling may need to use these sleeves indefinitely.

The frequency of the post-thrombotic syndrome in UEDVT patients treated only with conventional anticoagulation is uncertain, because studies are small and report conflicting results. As few as one half to as many as three fourths of these patients may develop this long-term complication.[22,40,41] Multimodal therapy that includes thrombolysis, will prevent these symptoms in the majority of patients.[22,35,36,40] Those with primary UEDVT are usually young and healthy, more active, live longer, and are not troubled by other chronic medical conditions. Therefore, they should receive more aggressive treatment, such as thrombolysis and correction of outlet obstruction, to reduce the risk of chronic venous insufficiency. Patients with secondary UEDVT are less bothered by symptoms and are often not candidates for surgery or thrombolysis, so conservative treatment with anticoagulation alone is generally recommended. These patients have very high short-term mortality rates compared with patients who have lower extremity deep vein thrombosis. Most die from underlying medical problems such as infection, cancer, or multisystem organ failure rather than from complications of the UEDVT (Table 6).[42]

Other complications include SVC syndrome, septic thrombophlebitis, thoracic duct obstruction, and brachial plexopathy.[2] Loss of vascular access can be especially problematic if UEDVT prevents administration of essential medication or nutrition.

Prophylaxis

On the basis of studies by Bern et al[43] and Boraks et al,[44] some physicians prescribe a "mini-dose" (1 mg) of warfarin daily to their cancer patients with central venous catheters to potentially reduce the risk of developing subsequent UEDVT. This low dose usually does not prolong the prothrombin time or cause clinical bleeding. Patients with poor nutrition, those receiving broad spectrum antibiotics, or those with advanced liver disease or liver metastases may not be suitable candidates for warfarin prophylaxis, because in these situations, even the tiny dose of 1 mg may be sufficient to elevate the prothrombin time excessively.

Low molecular weight heparin is an alternative to warfarin for UEDVT prophylaxis in cancer patients with central venous catheters. Monreal and colleagues[45] showed that once daily subcutaneous administration of 2500 IU of dalteparin starting 2 hours before catheter insertion greatly reduces the frequency of UEDVT. There were no bleeding complications, even when patients received chemotherapy that caused bone

TABLE 6. Long-Term Outcomes of Conventional and Multimodal Therapies for UEDVT

Study	Number of Patients	Therapy	Residual Thrombosis After Treatment, n (%)	Recurrent Thrombosis	Post-Thrombotic Syndrome, %	Mean Duration of Follow-Up
AbuRahma et al[22]	45	Anticoag	10/14* (71)	Not reported	73	>1 year
	7	Lytic	2 (29)	Not reported	29	>1 year
Adelman et al[35]	17	Multimodal	3 (18)	0	0	21 months
Kreienberg et al[36]	23	Multimodal	2 (9)	0/9 PTA	0/9 PTA	4 years
				5/14 stent†	6/14 stent	3.5 years
				(36)	(43)	
AbuRahma and Robinson[40]	8	Anticoag	7 (88)	0	88	72 months
	15	Multimodal	1 (7)	3 (20)	20	59 months
Heron et al[41]	54	Anticoag	29/49 (59)	Not reported	54	5 years

Anticoag indicates conventional anticoagulation with heparin and warfarin; lytic, thrombolysis; multimodal, thrombolysis±surgical decompression±venoplasty±stenting; and PTA, percutaneous transluminal angioplasty.

*Post-treatment venography was obtained in only 14 of the 45 patients treated with conventional anticoagulation.

†Recurrent thrombosis and the post-thrombotic syndrome occurred in some patients who received venous stents but in no patients treated only with PTA.

marrow suppression. Low molecular weight heparin is a better choice than warfarin for prophylaxis of patients with liver dysfunction or malnutrition.

Future Directions

Future research should assess the safety and efficacy of low molecular weight heparin as monotherapy or as a bridge to warfarin and also define the optimal duration of anticoagulation for UEDVT. Although aggressive multimodal treatment, such as thrombolysis and surgical decompression, is generally recommended for patients with primary UEDVT, this practice should be evaluated critically with prospective clinical trials.

Preliminary studies suggest that ultrasound (without pharmacotherapy) may accelerate thrombolysis by enhancing enzymatic fibrinolysis and mechanically disrupting the thrombus.[46] Significantly lower doses of thrombolytics may be effective when used in combination with ultrasound, thereby reducing bleeding complications. Further research is needed to evaluate the safety and efficacy of this novel treatment approach.

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