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Current Trends In The Management of Deep Venous Thrombosis and Postthrombotic Syndrome

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Introduction

The heparin/warfarin regimen has been the mainstay of treating deep venous thrombosis (DVT) for several decades. The very high incidence and disabling morbidity of post-thrombotic syndrome following standard heparin therapy was poorly recognized mainly because of its indolent evolution and late presentation. Compression therapy, often ineffectual, and of historic vintage has remained the standard for treating postthrombotic syndrome. Yet in the last very few years, major advances in pharmacotherapy, endovascular instrumentation and surgical technique have introduced major shifts in these treatment paradigms. Ambulatory low molecular weight heparin (LMWH) has replaced standard inpatient heparin therapy for the treatment of DVT in many centers. Catheter directed thrombolysis, a modality, that aims to eliminate the venous thrombus altogether is being selectively applied in some patients. Similar major changes are occurring in the management of postthrombotic syndrome. There is now greater awareness of this complication resulting in the more aggressive approach to the treatment of DVT. New endovascular and surgical therapies are being selectively applied to the large group of patients who fail conventional compression therapy. This article highlights these evolving trends in the treatment of DVT and postthrombotic syndrome with illustrative cases.

Case 1: Ambulatory LMWH treatment of DVT.

A 72 year-old-female was admitted seven days after undergoing a hip replacement with leg swelling and pain. A duplex examination and a subsequent venogram confirmed the diagnosis of deep venous thrombosis involving the calf and the femoropopliteal venous segment. Because of her advanced age and recent surgery she was not considered a candidate for catheter directed thrombolysis. She was placed on therapeutic doses of daltaparein sodium administered subcutaneously once daily (250 u/Kg), and started on warfarin sodium 5 mg daily at the same time. After being fitted with support stockings, she was discharged the next day to the care of her local physician with arrangements to monitor her prothrombin time (INR). Daltaparin sodium was to be discontinued 7 to 10 days later when her warfarin treatment was expected to have reached therapeutic levels. She was instructed to ambulate with the

stockings and no restrictions on activity was placed. She was seen in the clinic six weeks later, doing well. The leg swelling and pain had disappeared and she was otherwise asymptomatic.

Case 2: Catheter directed thrombolysis.

A 28 year-old-female was admitted six weeks postpartum after caesarian delivery with documented DVT involving the left iliac and femoropopliteal veins. Massive swelling and pain of the affected extremity was present. A hypercoagulability work up was negative. After informed consent, she was taken to the endovascular suite and a pulse spray catheter was placed across the clot with popliteal venipuncture under ultrasound guidance. After 48 hrs of Retavase (0.5 mg/Kg/hr) administered through the catheter, the thrombus completely resolved (Fig. 1). Post-lysis venogram revealed May-Thurner syndrome which was balloon dilated and stented. She had received therapeutic doses of intravenous heparin during the catheter thrombolysis and subsequently during coumadin induction to maintain continuous anticoagulation and avoid warfarin induced skin necrosis. The patient was discharged after Warfarin sodium had reached therapeutic levels. She was seen in follow up six weeks later, when duplex examination confirmed continued venous patency and competent valve function. Clinically she was asymptomatic.

Fig 1.— *Above:* Deep vein thrombosis of the iliac vein (left) cleared by catheter-directed thrombolysis (right).

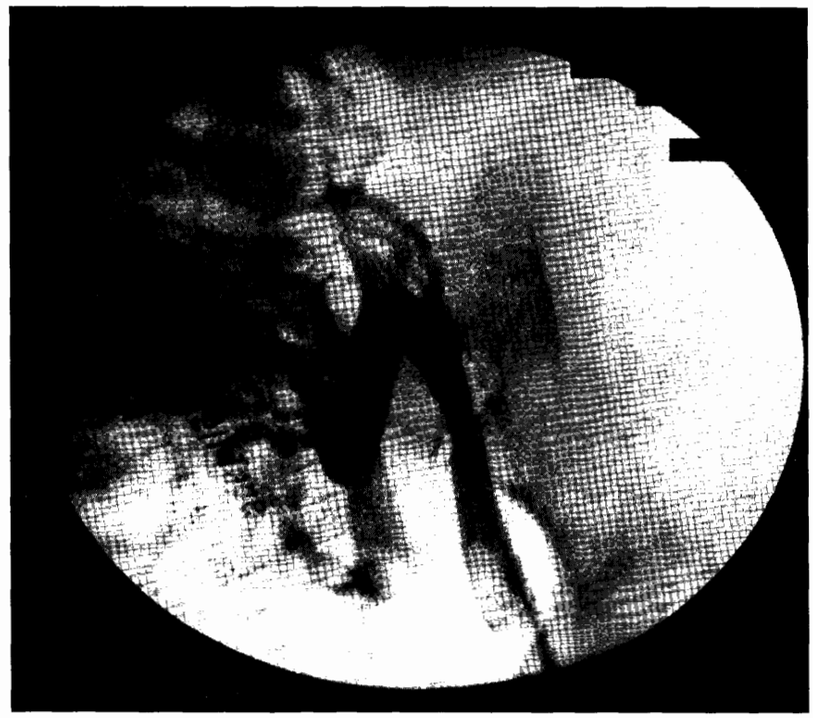

Fig 2 A.— *Above:* occlusion of left iliac vein with extensive collaterals.

Case 3: Recannalisation and stenting of occluded iliac vein segment for treatment of postthrombotic syndrome.

A 39 year-old-female was seen with severe left leg swelling and pain. She had been treated for DVT that occurred following a motor bike accident nine months previously. A venogram revealed an occluded iliac vein with extensive collaterals that were clearly inadequate to compensate for the occlusion (Fig. 2A). She was taken to the endovascular suite and the ipsilateral femoral vein was entered percuataneously under ultrasound guidance. Using a combination of flexible and stiff guide wires with guiding catheter support the occluded

venous segment was successfully traversed and gradually balloon dilated to 16 mm. Several stents placed in an overlapping manner were required to reconstitute the occluded segment. Completion venogram showed successful recannalisation with disappearance of collaterals (Fig. 2B). She was seen in the clinic six weeks later when the swelling was markedly reduced and she was pain free for the first time since the original accident. She had discontinued round the clock analgesic narcotics she was taking to control the chronic severe pain.

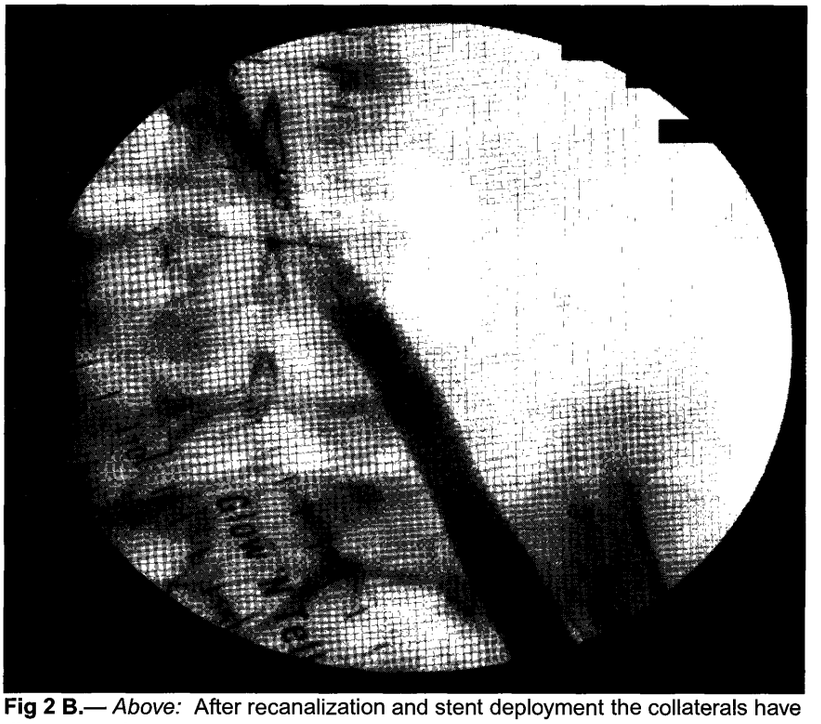

Fig 2 B.— *Above:* After recanalization and stent deployment the collaterals have disappeared.

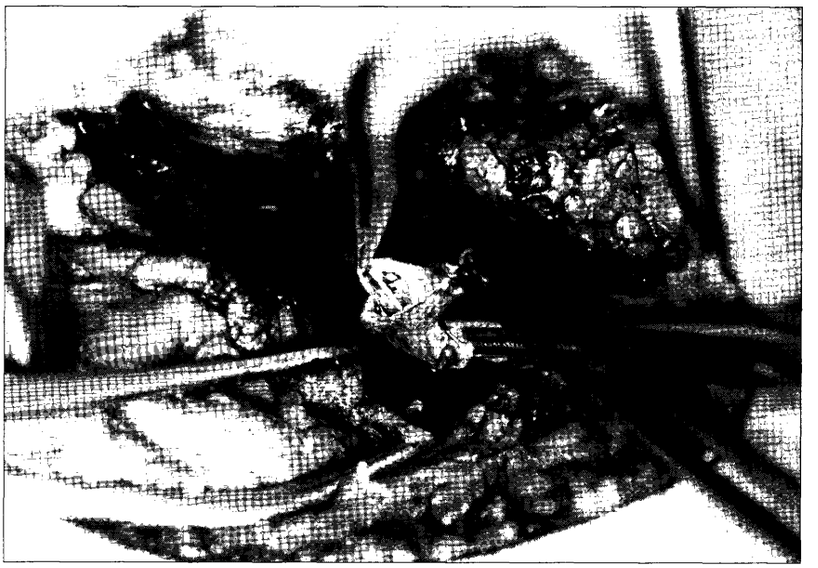

Fig 3 A.— *Above:* Technique of valve reconstruction in trabeculated veins. The trabeculi can be locally excised at the anastomosis.

Case 4: Venous valve reconstruction for postthrombotic stasis ulceration.

A 56 year-old-male presented with painful venous stasis ulceration that had been resistant to standard compression therapy including intensive Unna boot application. He gave a history of DVT that had occurred 12 years previously following arthroscopic knee surgery. He had been treated in conventional fashion with Heparin/Warfarin anticoagulation. An ascending venogram revealed trabeculated postthrombotic veins with massive reflux being evident on descending venogram. He underwent axillary vein valve transfer to the femoral segment utilizing the technique shown in Figure 3A and 3B prompt healing of the ulcer. This patient has been followed up for 3 years with maintenance of ulcer healing without recurrence.

Discussion

Low molecular weight heparin (LMWH) represents a major pharmacotherapeutic advance over conventional standard unfractionated heparin.[1,2,3] The latter contains molecules of varying sizes and compositions. Furthermore, the molecular mix varies from batch to batch since standardization in this area is difficult. Since bioavailability and therapeutic efficiency of heparin varies according to molecular size, weight based standard dosing is impossible. Frequent monitoring of partial thromboplastin time (PTT) with titration of heparin dos-

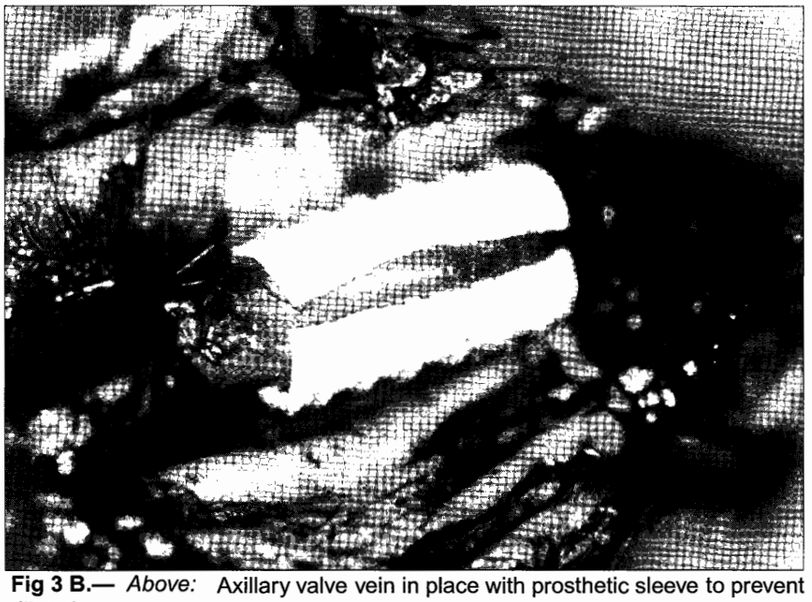

Fig 3 B.— *Above:* Axillary valve vein in place with prosthetic sleeve to prevent dilatation.

age is necessary to assure adequate therapeutic levels. Because of this and the time required to convert to oral Warfarin anticoagulation, in patient admission is required to institute and maintain standard intravenous heparin therapy. Because of the uneven and unpredictable dosimetry, overshoots above desirable safe levels of anticoagulation are common; bleeding complications of 4% to 9% have been reported with standard heparin therapy. Heparin induced thrombopenia (HIT)[4] is now well recognized as a complication that occurs in 4% to 25% of patients receiving standard unfractionated heparin.

In contrast LMWH contains molecules of uniform size that are selected for their small size veering on the low end of the wide weight spectrum of unfractionated standard heparin. Several analogues such as Daltaprin sodium (Fragmin™) and Enoxaparin (Lovenox) are commercially available now in US. The different analogues differ in their molecular size and have shown minor differences in therapeutic efficiency according to clinical application. Because of their uniform low molecular composition LMWH has a very high predictable bioavailability and therapeutic efficiency. For this reason they can be prescribed on weight based dosimetry and PTT or other monitoring is not required for most patient groups. Patients with renal failure may, however, require anti Xa monitoring to adjust the dosage as LMWH is eliminated through the kidneys. Because monitoring can be eliminated in most, hospital admission is not necessary and the drug can be administered subcutaneously on an outpatient basis or self-administered at home. LMWH also evince greater anti Xa activity and reduced antithrombin action compared to unfractionated heparin. Thus, LMWH are optimally suited to function prophalacticaly with reduced risk of bleeding. The subcutaneous route has been shown to be superior to intravenous administration for most commercially available preparations due to predictable slow absorption from the subcutaneous site. Some preparations require only a single daily dose while others are recommended to be given twice daily. Because of their uniformity of action and predictable response, bleeding complications with LMWH administration are rare. The incidence of HIT though not completely eliminated is much less than with standard heparin. Initial concerns about the occurrence of pulmonary embolism in patients receiving LMWH unmonitored and ambulatory at home have now been allayed; several clinical trials have demonstrated no difference in this dreaded complication between patients receiving LMWH on an ambulatory basis and those receiving standard heparin in the hospital. Currently the cost advantages of eliminating hospital stay and monitoring have been largely offset by the very high cost of LMWH compared to standard heparin.[5] The argument for replacing standard heparin with LMWH now largely rests on the latter's therapeutic efficiency, ease of use and patient convenience.

Standard unfractionated heparin has some direct thrombolytic properties and LMWH has even less. The major mode of action of both standard heparin and LMWH is to prevent thrombus growth and propagation and stabilize the clot. Once formed the venous thrombus seldom resolves completely from endogenous fibrinolytic mechanisms. Clinical improvement is largely predicated on clot retraction and organization accompanied by recannalisation/collateral formation. Though patients may return to a compensated state and become asymptomatic with anticoagulation therapy, functional reserve is depleted by the thrombotic occlusion. It is not uncommon for such patients to become symptomatic years or even decades later following a recurrent

episode of DVT or other insult[6] (trauma cellulitis) that leads to functional decompensation and manifestations of full-blown postthrombotic syndrome. The initial unresolved thrombus load is now recognized[7,8] as the major factor in the evolution of postthrombotic syndrome. Serial prospective studies[9] have now documented that approximately a third of patients suffering DVT become severely symptomatic with post-thrombotic syndrome; another third are mildly symptomatic and the remaining third are asymptomatic five years after the original onset of DVT. There is now increasing recognition of the staggering direct costs of treatment and indirect costs in work hours lost imposed by this disabling complication.[10] These realities have led to more aggressive attempts to eliminate the initial thrombus load altogether (rather than stabilize it with heparin) by various modalities both surgical and pharmacological. Additionally, mechanical devices that can be inserted percutaneously and seek to pulverize the thrombus and aspirate it are under active commercial development. In this realm, catheter directed thrombolysis with Urokinase™ [11] has probably received greater clinical exposure than the other modalities. The thrombus is traversed by an infusion or 'pulse spray' catheter that is introduced percutaneously. Pulse spray catheters are thought to add a mechanical component to pharmacological lysis. Continuous infusion of the lytic agent may be required for up to 72 hours to achieve complete lysis, taking precaution not to lower fibrinogen levels below desirable levels (125 mg%). Intracerebral hemorrhage is a significant complication with a reported incidence of 3% to 6% following Urokinase infusion. Urokinase is no longer available following FDA concerns related to the manufacturing process. Several institutions have since switched to TPA (Activase™) since. Unfortunately, bleeding complications appear to be even higher with this drug when used as a continuous infusion compared to Urokinase.[12] Reducing the dosage of TPA to 0.5 mg/Kg/hr or even less appears to reduce the incidence of bleeding complications without com-

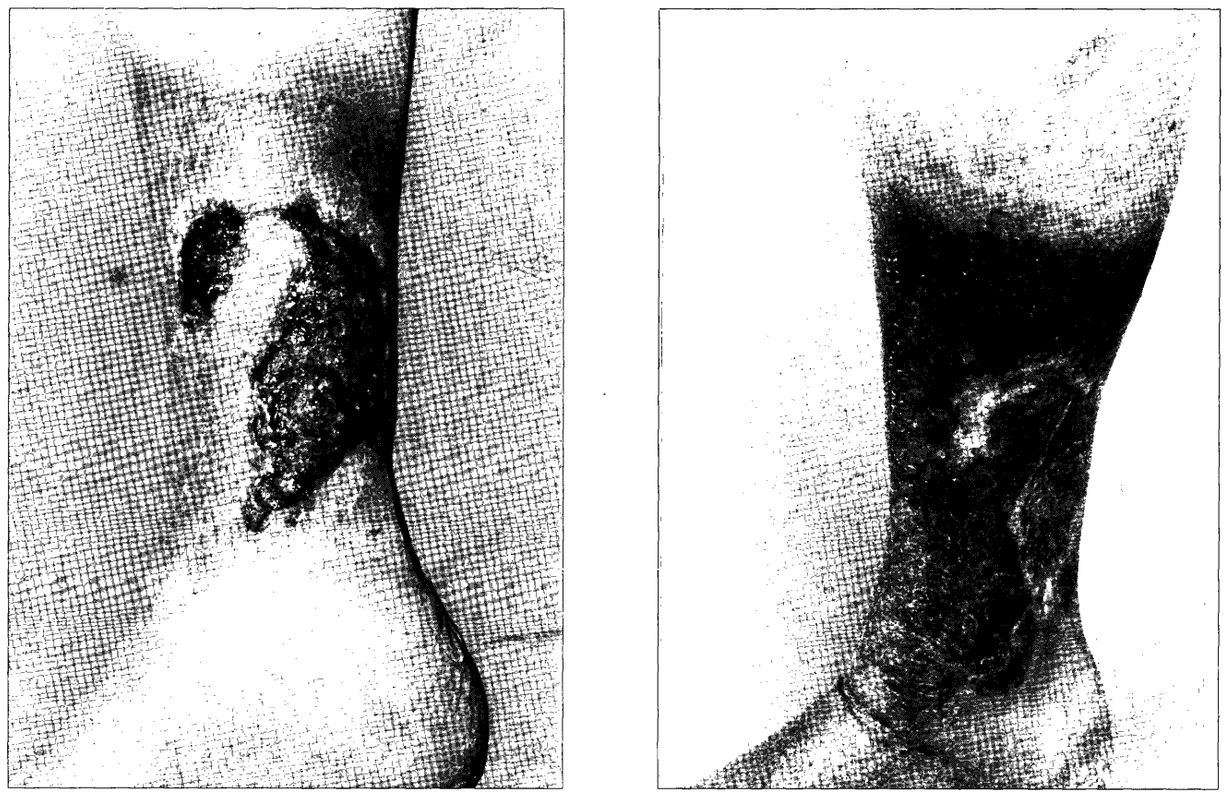

Fig 4 A&B.— Postthrombotic ulcer (4A) healed (4B) by valve reconstruction. The ulcer remained healed in this patient for over a 10-year follow-up.

promising lytic efficacy in the venous system. A newer agent Reteplase TM[13] shows promise of being efficacious without the increased bleeding associated with TPA. A nationwide registry[14] of catheter directed thrombolysis revealed complete resolution of clot in 31% and partial resolution in 52%. Our own experience in 24 patients was somewhat better. Fifty percent in our series [15] and 34% in the national registry required balloon dilatation/stenting of residual stenotic lesions after thrombolysis was achieved. The lesions were most frequently situated in the iliac vein segment and likely predated and accentuated the thrombotic episode. The rationale of thrombolytic therapy is to preserve long term function by eliminating thrombotic obstruction (patency) and preserve valve function (competence). As in many rapidly evolving technologies to address slowly evolving disease processes, clinical confirmation of efficacy may not be forthcoming for years or even decades. Preliminary indications[15,16] are that patency, valve function and quality of life[17] are favorably impacted by catheter directed thrombolytic therapy. Thrombolysis is contraindicated in patients with clinical situations that predispose to bleeding, e.g., peptic ulcer, hematuria, cerebral aneurysms or AV malformations, stroke or recent (< 12 days) surgery. Atrial or ventricular thrombi with potential for embolization are also absolute contraindications for thrombolytic therapy. Surgical venous thromboembolectomy[18,19] with a temporary adjunctive AV fistula in the groin for six weeks to maintain patency of the cleared iliac venous segment until endothelial recovery is completed has a proven track record and may be substituted for thrombolytic therapy if the clinical situation warrants.

The advent of endovenous stenting[20] represents a major advance in the management of postthrombotic syndrome. The pathology of this syndrome is a combination of venous obstruction and reflux. Obstruction particularly at the iliac venous segment is now recognized as a major component in the majority of patients.[21,22] Previously corrective treatment was restricted to veno-venous bypasses such as femoral crossover bypass, Palma bypass). Despite impressive patency short term (up to 6 months), patency rate of the crossover bypass declined to about 30% beyond 1 year.[23] Endovenous stenting has rendered bypass surgical treatment obsolete and reduced it to use only in those situations when stenting is not feasible or fails. Iliac vein stenting has impressive patency rates (> 90%) up to 2 years of follow-up currently available.[21] The actuarial patency curve shows little indication of decline at this point and the expectations for long term durability of this modality are high. Furthermore, stenting has resulted in excellent relief of pain and swelling to an extent not seen before with other therapies both conservative and surgical. To be successful, some details unique to the venous stenting that are different from arterial stenting should be observed: 1. balloon dilatation alone is not adequate, as recoil of dilated venous lesions is universal; stenting should always follow balloon dilatation with few exceptions. 2. A large caliber (14 to 16 mm) self-expanding type of stent should be used to provide for a hemodynamically unrestricted outflow path in the stented iliac venous segment. 3. The stent should be extended into the vena cava in cases of proximal common iliac vein lesions to avoid the frequent occurrence of restenosis; obstruction of the opposite iliac flow has not been observed in large series with extension of the stent into the vena cava. "Kissing" balloon technique is not necessary for caval extension. 4. Venography is not a reliable method to assess iliac vein obstruction; even transfemoral venography with better contrast visualization of the iliac vein segments than routine ascending venography has poor sensitivity in this regard. Intravascular ultrasound (IVUS) is currently the method of choice for assessing the iliac venous segment. It should be employed liberally in symptomatic postthrombotic patients and in others with unexplained leg swelling. A large percent of latter patients will turn out to have discrete severe proximal iliac vein stenosis (May-Thurner syndrome) or occult lesions at other iliac locations not readily apparent on even transfemoral venography.

The utility of venous valve reconstruction for non-thrombotic "primary" valve reflux is now well recognized.[24] We have reported comparable results for valve reconstruction in postthrombotic patients in general and several subsets[25,26] as well with up to 10 years of follow-up. Even patients with trabeculated postthrombotic veins, often considered "inoperable" can benefit from valve reconstruction with surprisingly good results and healing of stasis ulceration. The utility of valve reconstruction in postthrombotic syndrome has now been confirmed by others.[27,28] The extension of surgical valve correction to postthrombotic patients with stasis ulceration allows one to consider alternative options to a set of patients for whom the only available recourse previously was conservative therapy which was often unsuccessful.

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