Modern Management of Deep Venous Thrombosis

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ABSTRACT: Deep venous thrombosis (DVT) is a common and underdiagnosed disease spectrum with a high mortality and morbidity. For over 50 years it has been treated with different forms of heparin and vitamin K antagonists (VKA). It is not merely an acute event but the beginning of a chronic disease process that could continue for the rest of a patient’s life. Over the last 5 years new oral anticoagulants have been introduced that can replace VKA in the majority of patients. Additionally there are now emerging data from randomized trials on the superiority of percutaneous endovenous intervention (PEVI) over conventional treatment in the reduction of post-thrombotic syndrome and recurrent venous thromboembolism (VTE). This paper reviews the important literature and discusses the author’s approach, which is a combination of new oral anticoagulants in conjunction with PEVI and the utilization of the concept of “safe dose” thrombolysis in the treatment of VTE.

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Deep venous thrombosis (DVT) is an underdiagnosed disease spectrum with high mortality and morbidity. It is estimated that approximately 1 million episodes of DVT occur annually in the United States alone.1 It is the main cause of pulmonary embolism (PE), which claims 100,000 lives annually in the United States.1 DVT should not be regarded as a transient acute event but the harbinger of a chronic disease process which could linger on for the rest of the patient’s life.2 The importance assigned to DVT is principally due to 4 major outcomes: (1) its acute and devastating potential for fatal PE, (2) less frequent but life or limb-threatening phlegmasia cerulea dolens, (3) chronic limb ailments due to post-thrombotic syndrome (PTS), and (4) chronic pulmonary hypertension. The manifestations of PTS may be variable and at times very severe. Lower-extremity edema, pain, discomfort, throbbing, burning, heaviness, pruritus, paresthesia, and fatigue are among its symptoms. In more severe cases skin discoloration, lipodermatosclerosis, skin ulceration, and venous claudication may occur.3 Conventional recommended treatment with parenteral anticoagulation and vitamin K antagonists (VKA) carries a 25% to 50% risk of PTS at 2 years even if the International Normalized Ratio (INR) is “therapeutic.”4 If the same approach is implemented for symptomatic patients with occlusive DVT of the iliac veins, then the PTS rate rises to 80% at 5 years.5 Additionally, pulmonary hypertension may be seen in over 50% of patients with at least moderate symptomatic PE who are treated with anticoagulation alone at 28 months.6

PTS poses a great financial burden to the health care system by its direct and indirect costs. The latter is mainly due to disability and loss of work days. In 2003 the cost of treatment of severe PTS after hip surgery was estimated at nearly $4,000 in the first year only.7

MEDICAL MANAGEMENT

Over the last 2 to 3 decades and until recently no major improvement in the treatment of DVT was made except for introduction of different forms of low-molecular-weight heparins (LMWH) and their analogues and the finding that compression stockings can reduce PTS.4 The mainstay has been administration of heparin or LMWH+VKA. The American College of Chest Physicians guidelines still places emphasis on the traditional approach with parenteral anticoagulation and VKA.8 These guidelines will undoubtedly change in light of emerging new data.

In the last 5 years new oral anticoagulants have been introduced which can replace VKA in the majority of patients with a superior safety and in some
instances efficacy profiles.9-14 The trials have targeted 3 areas of treatment: (1) primary prevention or prophylaxis, (2) treatment of the acute event, and (3) post or extended treatment (i.e., extension of treatment for secondary prevention). When compared to parenteral anticoagulation and VKA, these studies were designed to show noninferiority and, when against placebo in the extended treatment category, superiority. The new anticoagulants currently available in the United States are rivaroxaban, apixaban (both factor-X inhibitors) and dabigatran (a direct thrombin inhibitor). As of this writing, the former is the only one that has FDA approval for VTE treatment, although approval is expected for the other two drugs in the near future. The following is a brief summary of the outcome of these new anticoagulants in the treatment of DVT.

**NEW ANTICOAGULANTS AND DEEP VENOUS THROMBOSIS**

The major study evaluating the effect of rivaroxaban and DVT was the EINSTEIN-DVT trial.9 This trial led to the approval of this drug by the FDA in November 2012. In that study, 3,449 patients with acute symptomatic DVT were randomized to receive rivaroxaban (1,731 patients) or enoxaparin and VKA. The treatment duration was 3 months to 12 months. Before randomization parenteral anticoagulation was given to 73% of the rivaroxaban group and 70% of VKA group for up to 2 days. Rivaroxaban was given as 15 mg orally twice daily for 3 weeks and 20 mg daily thereafter. The primary efficacy endpoints were recurrent venous thromboembolism (VTE) and bleeding. Recurrent VTE occurred in 2.1% vs 3% (hazard ratio, 0.68; 95% confidence interval [CI], 0.44-1.04; P<.001) of the rivaroxaban and control group. Bleeding occurred in 8.1% of the 2 groups. Noninferiority was thus established for rivaroxaban with respect to VKA.

In parallel with this study, another randomized, double-blind, event-driven superiority study was performed that compared rivaroxaban alone (20 mg once daily in 602 patients) with placebo (594 patients) for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for VTE. Rivaroxaban was found to be superior to placebo in the reduction of recurrent VTE (1.3% vs 7.1% hazard ratio, 0.18; 95% CI, 0.09-0.39; P<.001). Nonfatal major bleeding occurred in 1 patient of the rivaroxaban group vs none in the placebo group (P=.11).

As part of the recently published Hokusai-VTE study, 4,921 patients with DVT were randomized in a double-blind fashion to receive edoxaban at 30 mg or 60 mg daily for 3 months to 12 months vs warfarin.10 However, parenteral anticoagulation for a minimum of 5 days preceded randomization. In the entire population, recurrent VTE developed in 3.2% of the edoxaban group vs 3.5% of the warfarin group (hazard ratio, 0.89; 95% CI, 0.70-1.13; P<.001 for noninferiority). Total bleeding occurred in 8.5% of the edoxaban group and 10.3% of the warfarin group (hazard ratio, 0.81; 95% CI, 0.71-0.94; P=.004 for superiority).10

The AMPLIFY study randomized 5,395 patients with acute VTE (DVT in 74%) to receive apixaban vs enoxaparin and VKA.11 Apixaban was given to 2,609 patients at 10 mg orally twice daily for 1 week followed by 5 mg twice daily for 6 months. The primary efficacy outcome was recurrent symptomatic VTE or death related to VTE, which occurred in 2.3% in the apixaban group compared with 2.7% in the control group (relative risk, 0.84; 95% CI, 0.60-1.18; P<.001 for noninferiority). The composite outcome of major and clinically relevant bleeding occurred in 4.3% of the apixaban group vs 9.7% of the control group (relative risk, 0.44; 95% CI, 0.36-0.55; P<.001).11

Apixaban was also utilized in the “extension” of the previous study, the AMPLIFY-EXT Trial. In this trial 2,846 patients who had completed 6 months to 12 months of conventional treatment were randomized to receive apixaban at 2.5 or 5 mg twice daily or placebo for 12 months.12 Recurrent VTE and death occurred in 8.8% of patients receiving placebo and 1.7% of patients on either a low or high dose of apixaban. The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The study demonstrated that extended anticoagulation with a high or low dose of apixaban reduced the risk of recurrent VTE without increasing the rate of major bleeding.12

The RECOVER study randomized 1274 patients with VTE to dabigatran 150 mg orally twice daily vs 1,265 patients warfarin after a median of 9 days of parenteral anticoagulation.13 Approximately 90% of both groups had symptomatic DVT. The primary outcome was the 6-month incidence of recurrent symptomatic VTE and related deaths, which occurred in 2.4% of the dabigatran and 2.1% of the warfarin groups respectively (95% CI, −0.8-1.5; P<.001 for the prespecified noninferiority.
margin). Major bleeding episodes occurred in 1.6% of dabigatran and 1.9% of warfarin group patients (hazard ratio, 0.82; 95% CI, 0.45-1.48).13

The REMEDY trial randomized 1430 patients who had completed at least 3 months of anticoagulation to dabigatran 15 mg orally twice daily and 1,426 patients to warfarin. Recurrent VTE occurred in 1.8% of the dabigatran vs 1.3% of the warfarin groups (hazard ratio 1.44; 95% CI, 0.78-2.64; \(P=0.01\) for noninferiority). Major bleeding occurred in 0.9% of patients in the dabigatran group and 1.8% of patients in the warfarin group (hazard ratio, 0.52; 95% CI, 0.27-1.02).14 In parallel with the above study, the RESONATE trial randomized 681 VTE patients to dabigatran with the same dose and 662 patients to placebo after completion of a minimum of 3 months of anticoagulation. Recurrent VTE occurred in 0.4% of dabigatran group vs 5.6% of the placebo group (hazard ratio, 0.08; 95% CI, 0.02-0.25; \(P<0.001\)). Major or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran group and 1.8% of patients in the placebo group (hazard ratio, 2.92; 95% CI, 1.52-5.60).14

These two studies demonstrated dabigatran was effective in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.14

The WARFASA study revealed that administration of aspirin in patients with unprovoked VTE after 6 to 18 months of oral anticoagulation reduced the rate of recurrent VTE by about 40%, as compared with placebo with no major bleeding.15

Although the above studies have shown noninferiority to warfarin in reduction of VTE, their effects on PTS have not been investigated. As opposed to VKA, both factor-X and factor-II inhibitors can potentially dissolve clot-bound thrombin and as such may promote earlier clot lysis, less damage to venous architecture and valve function and ultimately less PTS.

These drugs have considerable advantages over VKA. They have a faster onset of action, fewer drug interactions, shorter half lives, and most importantly no need for monitoring.16 Their major potential drawback is absence of an approved reversing agent in case of severe bleeding although administration of prothrombin complex concentrate has been shown to be beneficial.14 In phase 2 proof-of-concept studies, a new recombinant agent, namely Andexanet alfa (PRT4445), has shown promising results in reversing the effects of Factor X inhibitors. Andexanet alfa is a highly specific Factor Xa decoy that effectively targets and sequesters direct and indirect Factor-X inhibitors in the blood, thereby restoring normal hemostasis.17

**PATHOPHYSIOLOGY OF POST-THROMBOTIC SYNDROME**

Intricate and complex cellular and molecular changes occur inside the veins as soon as acute thrombus is formed. Both cellular and humoral factors including cytokines, growth factors, and mitogens are involved and the initial changes are similar to an intense inflammatory reaction. With time chronicity ensues and fibrosis occurs. Some of these humoral factors include platelet-derived growth factor, insulin growth factor 1, transforming growth factor \(\beta\), interleukins 6 and 8, and monocyte chemotactic protein (MCP)-1.18 The ultimate outcome is venous obstruction (whether due to thrombus or resulting fibrosis) or loss of valvular function leading to venous reflux. Ambulatory venous hypertension develops leading to calf pump dysfunction, edema, tissue hypoxia, increased permeability of venules, extravasation of erythrocytes, and other intravascular cellular elements and proteins, fibrosis, and occasionally venous ulceration.19 It stands to reason that removal of the offending etiology, such as thrombus in the early stages, would reduce these changes. Surgical thrombectomy has resulted in a significant long-term reduction in venous pressure, reflux, obstruction, and symptoms.20 Any form of clot removal, be it systemic or catheter-directed thrombolysis (CDT) has led to an up to 50% reduction of PTS at 2 years.3 We do not recommend systemic thrombolysis for the treatment of DVT as there is poor penetration into the occluded thrombus and the flow of administered molecules of the thrombolytic agent (when administered through peripheral vein) is into the heart and lungs and not the lower extremity veins. The dose of systemic thrombolysis is several folds higher than that used in CDT, which can lead to serious bleeding.21

Catheter-directed thrombolysis however leads to very effective thrombus resolution using a fraction of the systemic dose with minimal risk of bleeding. Conversely, systemic thrombolysis through a peripheral vein with a reduced dose, termed “safe-dose thrombolysis,” is very effective for PE as the direction of flow of the thrombolytic agent is uniformly into the lungs no matter from which peripheral vein it is
administered. The lungs are highly sensitive to thrombolysis. They receive the entire cardiac output and are the center of convergence of all venous flow. Hence the thrombolytic agent molecules are not “wasted” elsewhere. Furthermore after the first passage of the thrombolytic agent through the lungs, a repetitious recycle of those molecules occurs by continuously re-entering the lungs after re-entering the venous circulation causing “multiple hits.”

The corollary of this would apply to CDT. As opposed to every other arterial or venous bed with thrombus which benefits from CDT, in the lungs it would not be necessary. We do not dispute the established efficacy of CDT in the treatment of PE but only suggest that a similar result will be obtained by thrombolysis through the peripheral venous circulation using similar low doses.

PERCUTANEOUS ENDOVENOUS INTERVENTION FOR DEEP VENOUS THROMBOSIS

It is clear from the available evidence that severe forms of DVT involving the iliac or femoropopliteal veins will require thromboreductive approaches other than anticoagulation alone. The term PEVI encompasses all modalities that can be employed for the invasive diagnosis and treatment of venous disease when performed through a percutaneous approach, which is the usual practice. It includes CDT, pharmacomechanical thrombectomy, balloon venoplasty, stenting, and imaging with intravascular ultrasound (IVUS). The available catheter devices used to treat DVT include Angiojet (Bayer HealthCare), Trellis (Covidien), Cleaner (Argon Medical Devices), EndoWave (EKOS Corporation), HELIX Clot Buster (ev3), Hydrolyser (Cordis Corporation), AKonya Eliminator (IDEv Technologies), Arrow Trerotola (Teleflex), and AngioVac (Angiodynamics). In our experience with the former two (Angiojet and Trellis catheters), we have not seen superiority of one device over the other.

OLDER RANDOMIZED TRIALS

A Cochrane review of the literature from 1969 through 2002 reported on 668 patients from 12 randomized trials who were treated with systemic or CDT vs systemic anticoagulation alone for DVT within 14 days of onset. The relative risk (RR) for development of clot lysis, PTS, and venous patency was significantly in favor of lysis groups RR = 2.71 (95% CI = 1.84-3.99), 0.66 (95% CI = 0.47-0.94), and 3.26 (95% CI = 2.16-4.92) respectively. A substantially higher bleeding rate was however noted with lysis (10% vs 8% RR = 1.73 (95% CI = 1.04-2.88) and was more seen in the older studies. No benefit in venous function was noted at 6 months. The cumulative patient population was deemed as too small to be able to make valid inferences on mortality and recurrent VTE.

In a pooled analysis of 4 selected papers from 2001 through 2009, Casey et al concluded that CDT as compared to anticoagulation for the treatment of acute DVT lead to a statistically significant reduction in the risk of PTS (RR, 0.19; 95% CI, 0.07-0.48), venous obstruction (RR, 0.38; 95% CI, 0.18-0.37), and a trend for reduction in the risk of venous reflux (RR, 0.39; 95% CI, 0.16-1.00).

CONTEMPORARY RANDOMIZED TRIALS

In the last 3 years the results of 2 of the 3 most contemporary randomized trials comparing PEVI plus anticoagulation to anticoagulation alone have become available. None of these studies used the new oral anticoagulants. In the TORPEDO trial, 183 patients with asymptomatic DVT were randomized to receive PEVI plus anticoagulation vs anticoagulation alone. At 30-month follow up recurrent VTE developed in 4.5% of the PEVI group vs 16% of the control group (P = .02). PTS developed in 6.8% of the PEVI group vs 29.6% of the control group (P < .001).

In the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) trial, which enrolled 209 patients, PTS was noted in 41.1% of the CDT vs 55.6% of the control group at 24 months (P = .047). Ileofemoral patency at 6 months was noted in 65.9% of the CDT vs 47.4% of the control group (P = .012). The ATTRACT trial, a multicenter NHLBI study with the goal of enrolling 694 patients, is ongoing.

VARIATIONS IN VENOGRAPHIC PATTERNS OF DEEP VENOUS THROMBOSIS

DVT has a broad spectrum of presentation based on patients’ signs and symptoms, extent of involvement, chronicity, recurrent venous injuries, and presence of thrombophilic state. Consequently treatment with a “one-size-fits-all” approach is incorrect and management should be individualized. There is also a spectrum in the venographic appearance of DVT with significant clinical implications. On one side of the spectrum is the truly first-time DVT, with preserved...
venous anatomy, which is responsive to CDT or pharmacomechanical thrombectomy (Figure 1). On the other side of the spectrum is distorted venous anatomy with venous stenosis, fibrosis, and minimal thrombus, which is resistant to thrombolysis. Here a “venous conduit” needs to be reconstructed; often times with use of stents. Balloon venoplasty alone is less effective due to the high elastic recoil and perivenous fibrosis. Frequently in-between forms exist, such as acute on chronic DVT.26

**TECHNICAL CONSIDERATIONS**

The preferred access site for PEVI for femoropopliteal and iliac DVT is the popliteal vein (Figure 2). This approach will allow for working in a cephalad direction, in line with the direction of venous valves and avoidance of entry into the side branches. Entry into the popliteal vein should be done using a micro-puncture needle and under ultrasound guidance. Initial venography should be performed through the sheath to delineate the cephalad course of the vein. Segmental venography is then performed by moving a soft-tip 5 Fr catheter cephalad. Following termination of PEVI, the sheath is pulled (even after administration of thrombolysis), manual compression is applied for 10 minutes and the patient made ambulatory after 1 hour of bed rest (Figure 3). This is our routine practice and cannot be over emphasized.26 Early mobility activates the muscle pump and reduces the likelihood of VTE recurrence. Closure devices must be avoided.

**ANTICOAGULATION, THROMBOLYTIC, AND ANTIPLATELET THERAPY**

Patients can undergo PEVI while fully anticoagulated. There is no need to withhold anticoagulation as is usually required when intervening in the arterial system. In our practice tPA is given at 1 mg/hour through the infusion catheter and heparin (via the side port of the popliteal sheath) at 8-12 U/Kg/hour. It is important to modify the “standard heparin protocols” present in many hospitals if overnight CDT is planned.

The byproducts of thrombolytic agents including tPA are thrombogenic and can enhance thrombin generation.29 Consequently simultaneous administration of low-dose heparin is recommended. However the standard heparin protocols are usually associated with intense fluctuations in the partial thromboplastin time (PTT) particularly in the first 1 to 2 days, which in our opinion is one important cause of periprocedural bleeding. The maximum weight considered for heparin dose calculation should not exceed 100 kg even in patients over this weight. Furthermore, bolus administration of heparin should be avoided and if the PTT is low, only the maintenance dose should be increased with...
repeat PTT measurements in 4 hours to 6 hours after each change in heparin dose. The activated partial thromboplastin time of 1.5 times to 2 times the baseline level (or 60 to 100 seconds) should be maintained. With CDT, the duration of thrombolysis should be kept not more than 24 hours to 30 hours, even if some residual thrombus is present at follow-up venography. As long as flow is re-established or channels of flow are created within the occlusive thrombus, there would uniformly be improvement in the clinical status within hours. The objective is not venographic perfection of flow. In truly acute DVT, near total resolution of thrombus occurs within the above timeframe leading to unmasking of any areas of stenosis, which may require stenting. In venosclerotic and chronic DVT, there would almost always be some degree of residual organized thrombus no matter how long CDT continues. Continuation of CDT beyond 24 hours is associated with a higher risk of bleeding. Over 95% of our cases are completed within this time period. Thrombectomy devices alone are sufficient if only one venous segment (femoropopliteal or iliac) is involved with acute DVT. In such cases these devices will lead to shortening of hospitalization and reduction of one day of ICU costs, which ordinarily is required for CDT. Conversely if occlusive thrombus involves 2 or more venous segments, thrombectomy devices alone would not usually be sufficient and CDT is often required. Therefore in such cases, the operator should proceed directly to CDT rather than engaging in a trial of futile mechanical thrombectomy which inevitably will be followed by CDT and raise the cost of the procedure.

Similarly pharmacomechanical thrombectomy should be avoided in chronic DVT with associated venous fibrosis or sclerosis.

Following the procedure, and if not otherwise contraindicated, we administer aspirin at 81 mg daily for 1 month to 6 months in addition to the oral anticoagulant. We have found a favorable response in the reduction of PTS with aspirin. A relative risk reduction of 37% was noted in the PTS rate of patients of the control group who received anticoagulation plus aspirin vs those who did not receive this drug. This is similar to the relative risk reduction of 32% in the rate of recurrent VTE noted in the combined WARFASA and ASPIRE trials where aspirin was administered after completion of anticoagulation with a VKA.

We now administer rivaroxaban at 20 mg daily 2 hours after PEVI. This is less than the 15 mg twice daily oral dose which is given for the first 21 days of treating VTE. The rationale is that patients requiring thrombolysis were excluded from those studies and it makes intuitive sense to use a lower dose when tPA is given. We have had very good success with this dosing regimen. In over 100 patients that we have treated with this approach no bleeding or other complications was observed. We have also used off-label apixaban at 5 mg twice daily or
dabigatran at 150 mg twice daily starting 2 hours after PEVI. We seldom use warfarin because it will increase hospital stay while waiting for the INR to become therapeutic or will require bridging with usually subcutaneous parenteral anticoagulation if outpatient management is contemplated. Continuation of parenteral anticoagulation beyond 24 hours in a patient who has received thrombolysis will increase the risk of bleeding. For patients whose insurance does not cover the new anticoagulants we provide free samples for 1 month. This approach would allow the acute event to subside and an “elective” transition to warfarin to occur at a later date.

During CDT we have also administered intravenous argatroban as a substitute for heparin (with possible superiority) via the side port of the popliteal sheath. Argatroban is a direct thrombin inhibitor and appears to exert a synergistic effect with tPA during CDT. It can also be used in patients with heparin induced thrombocytopenia.

PERIPROCEDURAL BLEEDING

In the current era bleeding complications from PEVI should be very low. In the TORPEDO trial, it was 2/91 (2.2%) and all were minor. Our present experience shows a bleeding rate of <1%. In a retrospective review of 6 case series using thrombectomy devices, the frequency of bleeding requiring transfusion was 7.5%. In the recent CaVenT trial, total bleeding was unacceptably high and at 20%.27

In this trial the anticoagulation protocol was substantially different than our recommendations. The mean duration of CDT was 2.3±1.2 days and in some cases up to 6 days. Parenteral anticoagulation was given for 5 days prior to PEVI, in other words some patients were receiving over 11 days of parenteral anticoagulation and CDT combined, a hospitalization duration which is not acceptable in the current health economy. Furthermore, the anticoagulation was stopped several hours before PEVI and only to be started with bolus administration of 5,000 units of heparin and a maintenance dose of 15 U/kg/hr. One hour after sheaths were pulled, full-dose LMWH was given to a patient who had just received full-dose anticoagulation with heparin. The significant variation in the bleeding rate therefore stems from the differences in the duration and dose of anticoagulation and thrombolysis regimens.

BALLOON VENOPLASTY AND STENTING

The role of balloon venoplasty during PEVI is several fold and includes maceration of thrombus before CDT, sizing of the lesion, initial treatment, postdilatation of venous stents, and, infrequently, cessation of bleeding by endoluminal sealing of the perforation site. For fixed stenoses, however, balloon venoplasty is not sufficient to achieve a durable result and stenting is often required. This is due to the high elastic recoil and perivenous fibrosis, which are frequently present.

Most of the stenting data are from treatment of iliac veins with occasional extension into the IVC and femoral vein. Until recently the result of stenting in the femoropopliteal vein was not reported. The dogma against stenting in this segment is not based on concrete data but individual opinions, hypothetical assumptions and the finding of 4 out of 5 stent thrombosis reported in an old venous registry. In our experience stenting has been safe and effective in the femoropopliteal vein with excellent midterm outcomes comparable to stents placed in the iliac veins.

The natural history of stenting in the venous circulation is fundamentally different than that seen in the arterial system requiring a shift in the paradigm of expectations. Lesions in the order of 50% or less which in the arterial circulation would not require treatment, are often significant enough to cause symptoms and should be treated. An intriguing observation derived from IVUS imaging is the lack of neointimal hyperplasia (NIH) as a cause of stent closure, which is distinctly different from that seen in arterial stents in which NIH is the major etiology. This may be due to the lower venous pressure, oxygen tension, and pH; absence of pulsatile flow and higher compliance of the veins and partial pressure of CO₂.

The thinner media and adventitia and presence of a lower number of inflammatory cells also may be contributing factors. It does not occur independently and is usually an extension of DVT in the adjacent venous segments with high-grade stenosis (inflow or out-flow obstruction). External compression is an important factor in preventing full stent expansion, which is seen in extensive venosclerosis or fibrosis and contributes to stent closure, usually in the presence of some degree of thrombosis, but not NIH. Contrary to its arterial counterpart, stent thrombosis is often asymptomatic or mildly symptomatic. It is not associated with significant sequelae and is amenable to a second PEVI.
INFERIOR VENA CAVA FILTERS DURING PERCUTANEOUS ENDOVENOUS INTERVENTION

The purpose of inferior vena cava (IVC) filter placement is to prevent iatrogenic PE during PEVI. There are diametrically opposed opinions about the necessity of prophylactic IVC filter placement. The prevalence of true or potential PE during PEVI (as judged by objective testing for PE or large entrapped thrombus in the IVC filter) has varied between 0% to 54.1%. In the TORPEDO trial all patients in the PEVI group received a filter. Thrombus entrapment by the IVC filter post-PEVI was seen in 11% of patients.

In a recent randomized trial of patients with DVT who underwent PEVI, the frequency of symptomatic iatrogenic PE was 11.3% in patients without vs 1.4% in those with an IVC filter. We identified the following predictors of PE: PE on admission, involvement of ≥2 adjacent venous segments with fresh thrombus, inflammatory form of DVT, and vein diameter ≥7 mm with preserved architecture.

In patients who only underwent CDT without further instrumentation no PE was observed. A 4.2% rate of transient hemodynamic instability occurred during the procedure in patients with predictors of iatrogenic PE who did not receive a filter. There was no mortality benefit from IVC filter placement. Macroscopic evidence of thrombus and avulsed tissue was seen in up to one-third of filters removed after 1 month (Figure 4). Therefore a selective approach may be exercised in the implantation of IVC filters during PEVI.

ROLE OF INTRAVASCULAR ULTRASOUND

Intravascular ultrasound is an invaluable adjunct during PEVI. It can unmask lesions that are not ordinarily visualized by venography. Intravascular ultrasound can precisely identify areas of external compression, vessel fibrosis, mural wall thickening, endovenous spurs, and trabeculations and chronicity of thrombus. Versions of IVUS catheters such as VisiV F/X (Volcano Corporation) on an S5 imaging platform and newer generations contain additional features of virtual histology and ChromaFluor software packages (Volcano Corporation) which markedly enhance the diagnostic accuracy. It was indeed with utilization of these additional features that we were able to discover absence of NIH as an etiology in venous stent closures as opposed to arterial intimal restenosis wherein NIH is the predominant etiology.

There are some operators who advocate the use of IVUS in almost every case of PEVI. We do not believe that this approach is necessary. It adds to the cost of an already expensive procedure, prolongs the case, and for experienced operators seldom changes major management decisions. Like IVC filters, its use should be individualized. In our current practice, IVUS is used in less than 10% of PEVI cases.

DURATION OF HOSPITALIZATION

Given the prevailing and projected economics surrounding health care, strategies for expeditious and safe treatment of VTE are of paramount importance. Although patients with milder forms of VTE can be managed as outpatients, many symptomatic patients require hospitalization. In the CVenT trial, 5 days of parenteral anticoagulation was followed by another 2.3±1.2 days of CDT. No information on the duration of hospitalization was provided but by inference it must have been long by US standards. In the RE-COVER trial, parenteral anticoagulation was given for a mean of 10 days. In the EINSTEIN-DVT trial, the median duration of hospitalization for the rivaroxaban and control arms were 5 and 8 days respectively. In the TORPEDO and MOPETT trials, hospitalization was considerably shorter and at 2.7±1.1 and 2.2 ± 0.5 days respectively.

FUTURE DIRECTIONS

With the introduction of the new anticoagulants, the current treatment of VTE will change and the guidelines will undergo major revisions. All trials involving these drugs have thus far excluded patients undergoing thrombolysis. We believe that both thrombolysis and new anticoagulants can be safely given together and will have a major role in the treatment of VTE. The key is simply lowering the dose and applying “safe-dose thrombolysis.” The fear of thrombolysis will wane once it becomes accepted that a much lower dose of the thrombolytic agent and anticoagulation regimen (than used in standard practice) is highly effective and safe in the venous circulation.

Our practice currently uses the combination of “safe-dose thrombolysis” and the new anticoagulants: For patients with DVT warranting admission, PEVI is performed with adjunct use of low-dose heparin and tPA and initiation of rivaroxaban 2 hours after PEVI. For patients with moderate and even severe PE, “safe-dose thrombolysis” with...
tPA is given in 2 hours via a peripheral vein, and after 24 hours of modified dose heparin, parenteral anticoagulation is discontinued. Rivaroxaban is given in 2 hours and if stable the patient is discharged the subsequent day.22 We no longer use LMWH in our invasive and thrombolytic strategies. Warfarin is seldom used for the first month after the acute event. This approach of “drip, drug, and discharge” has led to safe and effective treatment of PE and discharge in fewer than 2 days.22 With the mounting economic pressures on health care, this concept will become very appealing, because it will promote safe and effective treatment as well as early discharge.

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