Endovascular
TODAY

Combination Therapy

LYSIS AND DEVICES FOR DVT

Experiences and insights

regarding today's therapeutic

options for treating

venous thrombosis.

Combination Therapy

Lysis and Devices for DVT

Release Date: April 1, 2005   *Expiration Date: April 30, 2006*

STATEMENT OF NEED

Acute deep venous thrombosis (DVT) affects more than 250,000 patients per year. Although up to 50% of patients are asymptomatic, all are at risk for pulmonary embolism (PE).[1-3] Symptomatic PE is the most important acute complication of DVT, with more than 600,000 cases per year in the US responsible for 200,000 deaths. Despite the percentage of asymptomatic patients, the sequelae of DVT can be devastating and lifestyle limiting. DVT and post-thrombotic syndrome can produce edema, pain, muscle fatigue, varicosities, skin hyperpigmentation, subcutaneous fibrosis, venous stasis ulcers, and can result in amputation.

Historically, treatment options have included preventing propagation of thrombus with anticoagulation, inferior vena cava (IVC) filters, surgical thrombectomy, systemic and catheter-directed thrombolysis, and more recently, mechanical thrombolysis techniques. Beginning in the year 2000, more aggressive minimally invasive techniques involving lysis and device combination treatment regimens to address large-volume DVT (caval, iliofemoral, and femoral-popliteal) have been developed. Such "combination therapy" treatments, for example, have included adding thrombolytic agents to the Possis Medical, Inc. (Minneapolis, MN) AngioJet®Rheolytic™ Thrombectomy (RT) Catheter's saline infusion bag, using the RT catheter for Power-Pulse Spray delivery of lytic agent, then, after a short lysis time, using the same RT catheter to perform thrombectomy.[4-6]

TARGET AUDIENCE

This activity is designed for interventional radiologists, vascular surgeons, interventional cardiologists, internists, nurses, angiography suite technicians, and catheterization technicians.

LEARNING OBJECTIVES

After the successful completion of this program, the participant should be able to describe and discuss:
- the various options available for treating DVT.
- combination therapy candidacy and contraindications.
- appropriate ranges of lytic dosing and procedural duration.
- evaluation of combination therapy success.
- embolization considerations and prevention strategies.

METHOD OF INSTRUCTION

Participants should read the learning objectives and monograph in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or higher on the self-assessment test, participants will receive a CME credit letter awarding Accreditation Council for Continuing Medical Education (ACCME) category 1 credit 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity as designed is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with essentials and standards of the ACCME through the joint sponsorship of The Dulaney Foundation and *Endovascular Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing medical education for physicians. The Arizona Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation, has approved this continuing nursing education activity to provide 1.2 contact hours. The Dulaney Foundation designates this educational activity for a maximum of one category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he or she actually spent on the activity. This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required by Anita Cook, RN; Ziv J. Haskal, MD; Alan Matsumoto, MD; Kenneth Ouriel, MD; and Suresh Vedantham, MD.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) any financial interest or other relationships with the manufacturers of any commercial products or devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and (2) the identification of a commercial product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

OFF-LABEL USAGE DISCLOSURE

This activity contains information on applications of thrombolysis and mechanical thrombectomy that are not currently included in the FDA approval of alteplase, tenecteplase, urokinase, reteplase, or the AngioJet RT catheter.

TECHNOLOGY INDICATIONS OVERVIEW

The AngioJet Xpeedior 120 Catheter is intended for use with the AngioJet System in breaking apart and removing thrombus from infrainguinal peripheral arteries ≥3 mm in diameter. The AngioJet Power-Pulse Spray Ancillary Kit is intended for the control and selective infusion of physician-specified fluids, including thrombolytic agents, into the peripheral vascular system using the Xpeedior 120 Catheter and the AngioJet System. All Power-Pulse Spray experience described in this monograph refers to the Xpeedior device.

The AngioJet RT system consists of three components: a single-use catheter, a single-use pump set, and a pump drive unit. The 6-F Xpeedior catheter has a working length of 120 cm, is introduced via a percutaneous approach (6-F sheath), and operates over a 0.035-inch guidewire. The dual-lumen catheter design consists of a stainless steel hypotube that supplies pressurized saline to the distal catheter tip and a second larger lumen that encloses the hypotube, guidewire, and aspirated thrombus debris. The drive unit/pump generates high pressure (~10,000 psi) pulsatile saline flow that exits the catheter tip through multiple retrograde-directed jets. These high-velocity jets create a localized low-pressure zone (Bernoulli effect) for thrombus aspiration and maceration. The jets also provide the driving force for evacuation of thrombus particulate debris through the catheter.

The Xpeedior catheter design also has a means for radially directed low velocity (~7.8 mm/sec) fluid recirculation to assist with thrombus dislodgment from the vessel wall and direction to the catheter tip for evacuation. The Xpeedior catheter works in an isovolumetric manner: the saline infusion flow rate (60 mL/min) is in balance with the evacuation rate of thrombus particulate debris. When used in P-PS
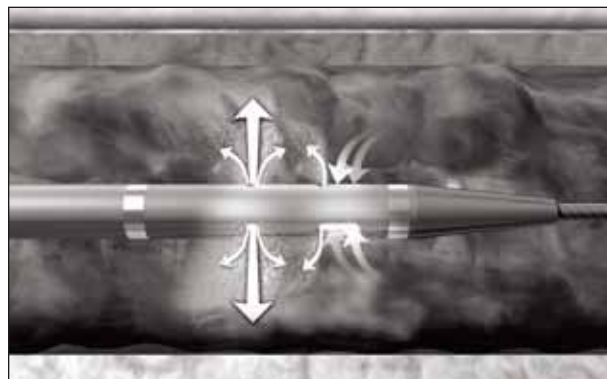
Power-Pulse Spray infusion with the Xpeedior catheter. Fluid is pulsed radially into the thrombus primarily via the small proximal ports at the catheter tip.

mode, the Xpeedior catheter's evacuation is occluded using a stopcock. Thus, all the infused lytic solution is directed radially through the small ports at the catheter tip, at a velocity of approximately 9.2 mm/sec.

Activase® (alteplase, recombinant; [tPA], Genentech, Inc., South San Francisco, CA) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. Alteplase is an enzyme (serine protease) that has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentration, alteplase binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Alteplase is indicated for treatment of acute myocardial infarction, acute massive pulmonary embolism, and acute ischemic stroke. Cathflo Activase is indicated for the treatment of occluded catheters. Alteplase is for intravenous administration only. Extravasation of alteplase infusion can cause ecchymosis and/or inflammation. Management consists of terminating the infusion at that IV site and application of local therapy.

CONTENTS

The Combination Therapy Summit

In February 2005, *Endovascular Today* invited a group of physicians considered to be experts in the treatment of venous and arterial diseases, particularly DVT, to the Combination Therapy Summit to freely discuss and compare their practice patterns regarding the use of RT combined with a lytic agent, a type of procedure termed *combination therapy*. These interventionists varied according to specialty, type and location of institution, practice focus, and volume of patients treated using combination therapy. The goal of this summit was to bring together this heterogeneous group and ask the participants to share their respective data (which when combined total several hundred cases), anecdotal experiences, and beliefs regarding ideal use of the AngioJet RT device and the associated Power-Pulse Spray (P-PS) application, in combination with the lytic agent alteplase, as well as emerging therapeutic options in the field of combination therapy.

The purpose of this CME supplement is to collect these data and experiences, describe in detail those points that were agreed upon and those for which opinions differed and the reasons for each, and provide the educational foundation necessary for both new and experienced users to offer optimal care for patients with DVT and other disorders treatable using combination therapy. Each physician gave a brief presentation on a different element of combination therapy, and these presentations served as starting points for group discussions pertaining to the presenter's topic. The Summit participants agreed that a forum such as this brings to light concepts that might otherwise not be expressed, and that a widely distributed monograph is the ideal vehicle for presenting the collected information to each physician interested in providing this therapeutic option.

The content on the next three pages, previously published by R. Joshua Dym, Darren Fitzpatrick, and Jacob Cynamon, MD, and reprinted with permission, describes some of the options other than combination therapy available for treating DVT.[7] After these descriptions, Drs. David E. Allie and Mark J. Garcia, pioneers in the emerging field of combination therapy, describe their respective techniques, after which we present the insights shared at the Combination Therapy Summit and a treatment algorithm for lower-extremity DVT management.

SUMMIT PARTICIPANTS		
David E. Allie, MD	Cardiovascular Institute of the South	Cardiothoracic/Vascular Surgery
Gary M. Ansel, MD	Mid-Ohio Cardiology and Vascular Consultants	Interventional Cardiology
Michael A. Arata, MD	Pacific Vein Center	Interventional Radiology
Jacob Cynamon, MD	Montefiore Hospital	Interventional Radiology
Mark J. Garcia, MD	Christiana Health Care Services	Interventional Radiology
Ziv J. Haskal, MD	Columbia University Medical Center	Interventional Radiology
Lawrence Hofmann, MD	Johns Hopkins Hospital	Interventional Radiology
David Hunter, MD	University of Minnesota	Interventional Radiology
Peter H. Lin, MD	VA Medical Center	Vascular Surgery
Alan Matsumoto, MD	University of Virginia Health System	Interventional Radiology
Thomas McNamara, MD	UCLA Medical Center	Interventional Radiology
George H. Meier, MD	Vascular & Transplant Specialists	Vascular Surgery
Kenneth Ouriel, MD	The Cleveland Clinic Foundation	Vascular Surgery
Mahmood Razavi, MD	Stanford University Hospital	Interventional Radiology
Suresh Vedantham, MD	Washington University School of Medicine	Interventional Radiology
Anthony Venbrux, MD	George Washington University Hospital	Interventional Radiology

DVT Treatment Options

Material presented on pages 5-7 reprinted with permission from Dym JR, Fitzpatrick D, Cynamon J.[7]

ANTICOAGULATION

Goals of DVT treatment include relief of acute symptoms, prevention of thrombus propagation, embolization and recurrence, and the restoration of venous patency to prevent the future development of venous insufficiency and post-thrombotic syndrome (PTS). Usual therapy centers on anticoagulation, which is the current standard of care. Initial treatment involves anticoagulation with heparin to interfere with the coagulation cascade and to prevent recurrent thrombosis.[8-10] After 24 to 48 hours, oral anticoagulation therapy is initiated with warfarin with a titrated dose to a target INR of 2.0 to 3.0. After 4 to 5 days of total treatment, the heparin is discontinued and the warfarin alone is continued. This overlap is necessary due to warfarin's initial prothrombotic effects. In fact, studies have demonstrated that inadequate or lack of initial heparin therapy may reduce the effectiveness of subsequent oral anticoagulation.[11-13]

The conventional protocol of unfractionated heparin (UFH) followed by warfarin for anticoagulation effectively inhibits the thrombotic process and allows for at least partial clearance of existing thrombus by endogenous plasmin. However, the need for prolonged hospitalization and frequent monitoring while receiving UFH has led to the emergence of subcutaneous low-molecular-weight heparins (LMWHs) as a safe and effective alternative. LMWHs allow for the outpatient treatment of patients with low bleeding risk and no other reason for hospital admission, and thus are significantly more convenient and cost-effective than hospitalization and initial treatment with UFH prior to exclusive oral anticoagulation. Furthermore, several large studies have actually demonstrated an advantage of LMWH over UFH, albeit nonstatistically significant, in terms of venous thromboembolism (VTE) recurrence, hemorrhage and death.[14-16] Other clinical studies have also shown a significant benefit of LMWH over UFH in preventing thrombus progression.[17] Just as LMWH is replacing UFH in many cases, newer designer anticoagulants in development, such as oral direct thrombin inhibitors, may prove to be even more effective and convenient alternatives to the current methods of treatment.

Regardless of the initial anticoagulant agent (UFH/LMWH, or other), current guidelines recommend continuing the oral anticoagulation with warfarin for 3 months if the DVT was due to a merely temporary risk factor. However, if the thrombosis was idiopathic or due to a nonreversible risk factor, at least 6 months of warfarin therapy is generally recommended. In cases of recurrent VTE, patients with hypercoagulable disorders or other permanent risk factors, lifelong anticoagulation may be indicated.[18]

While anticoagulation therapy does fulfill some of the goals of DVT treatment and has been shown to be effective in preventing DVT recurrence,[8] it does not promote lysis to reduce thrombus burden, nor does it restore valve function. Thus, anticoagulation alone does not prevent the future development of PTS, which may occur years after the original thrombotic event.[19] This is especially true for iliofemoral and inferior vena caval thrombosis. Thrombi in these areas, as compared with smaller veins in the calf or leg, have a higher incidence of acute and late morbidity even with proper oral anticoagulation. Two-thirds of patients with iliofemoral DVT develop PTS and 5% will develop leg ulcers.[20] Furthermore, anticoagulation therapy does not eliminate the risk of PE, which can develop in up to 21% of patients with DVT who have received proper anticoagulation.[21]

SURGICAL THROMBECTOMY/SYSTEMIC THROMBOLYSIS

It has been demonstrated that prevention of PTS and acute or delayed embolization often necessitates the removal of the thrombus from the vein. One method that is effective in adequately removing thrombus is surgical thrombectomy. While originally associated with a high rate of recurrence and mediocre clinical results,[22] refinement in the surgical technique with creation of a temporary arteriovenous fistula has been shown to minimize operative mortality and improve late patency to approximately 80%.[23,24]

VENOUS THROMBOSIS RISK FACTORS AND PATHOPHYSIOLOGY

- Virchow first identified a triad of factors important in the development of venous thrombosis: venous endothelial damage, hypercoagulability, and venous stasis.[25]
- Hereditary risk factors generally involve deficiencies or elevations of certain blood factors and other proteins involved in the coagulation cascade.
- Acquired risk factors include malignancy, estrogen therapy, pregnancy, antiphospholipid antibody syndrome, and immobility related to myocardial infarction, stroke, limb fractures, paralysis, air travel, or a long operative procedure.[26]
- Major general surgery, particularly orthopedic surgery, is considered to be an important risk factor for DVT.[27-29]

Nevertheless, surgical thrombectomy has not been widely accepted as a method for thrombus removal.

Systemic thrombolytic therapy was instead advanced as a less invasive option that can adequately remove the thrombus through lysis, thereby promptly restoring venous patency and valve function. As compared to standard anticoagulation, it is believed that thrombolytic therapy reduces the risk of future PTS.[30,31] However, several studies have shown that the benefits of systemic thrombolysis for DVT therapy come with a cost. One study demonstrated that while it was three times more effective in removing clot when compared with conventional oral anticoagulation, bleeding risk increased four-fold in systemic thrombolysis patients.[32] Another study showed that although systemic thrombolytic therapy was associated with significant venographic improvement and improved physical findings associated with PTS (pain, swelling, hyperpigmentation), it was also associated with a higher frequency of bleeding and suspected PE on the first day of treatment.[35] As the risks of bleeding and PE outweigh the benefits of treatment, systemic thrombolysis is not a currently accepted treatment modality for DVT.

CATHETER-DIRECTED THROMBOLYSIS

Aside from the added risk of systemic thrombolysis, the effectiveness of the lytic agent may be significantly reduced since the drug may not reach the clot. In order to reach a concentration in the area of thrombosis that is high enough to achieve lysis, large doses of the thrombolytic must be administered. Catheter-directed thrombolysis (CDT) was proposed as a means to gain the benefits of thrombolytics while minimizing the potential systemic side effects by focusing delivery of the agent directly to the thrombus, thereby reducing the total drug dose as well as the amount of drug that enters the systemic circulation. In this technique, a catheter (end-hole or multi-side-hole) is positioned with its tip in the thrombus, and heparin and the lytic agent of choice (usually alteplase or urokinase) is administered [Editor's Note: the lytic agent is administered directly into the clot so as to activate the clot-bound plasminogen while the patient receives heparin systemically]. Lysis of thrombus can be monitored by repeated injection of contrast while repositioning the catheter as needed. Furthermore, intervention for treatment of DVT with associated venography also allows for the identification of predisposing lesions in the venous system that can be treated with angioplasty and stenting following removal of the thrombus.

An early report of this technique seemed very promising, finding that it produced complete lysis in 72% of patients.[34] Subsequently, a prospective multicenter registry, the National Venous Thrombolysis Registry, was established in order to collect and analyze data for a large number of patients with lower-extremity DVT treated with CDT.[35] It was hoped that the results of this study would lay the foundation for the development of controlled, randomized clinical trials that would provide firm support for the efficacy of CDT. The study included 63 sites with a total of 473 patients; 287 of whom had adequate data for analysis. Of those cases, 83% achieved at least 50% thrombolysis (measured initially by venography), with complete lysis in 31% of cases. Primary patency rates (assessed by ultrasound) were 65% and 60% at 6 and 12 months, respectively. Long-term patency seems to have been dependent on two factors—the degree of initial lysis, and whether or not stents had been placed. At 12 months, 79% of limbs with initially complete lysis remained patent, as compared to only 32% of limbs with an initial lysis of less than 50%. Of limbs treated with stents, 74% were patent at 1 year compared with 33% of limbs that did not receive stents.

The Venous Registry also demonstrated that CDT was less effective for patients with chronic DVT and/or a prior history of DVT, with both groups demonstrating decreased degrees of thrombolysis. Acute cases of DVT (≤10 days) achieved complete lysis almost twice as often as patients with chronic DVT (>10 days), independent of thrombus location. Of patients with no prior history of DVT, 36% achieved complete lysis compared with only 20% of patients with such a previous history. Patients with previous DVT also had a higher rate of minimal (<50%) lysis. Nevertheless, the findings do demonstrate that CDT is a very effective therapy in the specific group of patients with no prior history of DVT that present with an acute [iliofemoral] DVT.

The authors of the Venous Registry proposed that CDT is theoretically a better option for the long-term management of DVT, citing that systemic anticoagulation, the current standard of care, neither promotes lysis nor the restoration of valve function necessary for the prevention of PTS. Because CDT quickly restores venous flow, it results in prompt resolution of symptoms and may prevent damage to the venous valves caused by the presence of the thrombus. Although there are no studies assessing the incidence of chronic venous insufficiency in these patients, early lysis is expected to preserve venous function by preventing incompetence of venous valves resulting both from chronic venous hypertension due to obstruction, as well as from fibrotic changes secondary to the presence of clot. Furthermore, patients treated with thrombolysis assessed by an 80-item quality-of-life questionnaire reported improved overall physical function and fewer postthrombotic symptoms than patients treated with only anticoagulation.[36]

Recently, a single-center randomized study with 35 patients compared CDT using streptokinase to standard anticoagulation in patients with iliofemoral DVT.[37] It demon-

strated a significantly better patency rate at 6 months for the patients treated with thrombolysis than those treated with anticoagulation, 72% versus 12% respectively. However, while this study helps validate the findings of the prior retrospective studies, the use of CDT has still remained limited due to the lack of any large multicenter randomized trials such as there are for UFH and LMWH. Other barriers to the widespread use of CDT are the high cost of thrombolytics and the fact that no thrombolytic agents are as of yet FDA-approved for CDT.[38]

Another impediment to CDT is the increased risk of hemorrhagic complications. While it is important to note that heparin is not without side effects, with significant bleeding occurring in 7% to 30% of patients on IV UFH,[39] the shift to LMWH markedly lowers bleeding complications, with a major hemorrhage rate of only 1.5% with LMWH therapy.[14] In contrast, in the National Multicenter Venous Registry, major bleeding complications requiring transfusion were found in 11% of the cases, and an additional 16% of patients suffered from minor bleeding complications. Two major intracranial bleeding complications occurred, one of them resulting in death. PE occurred in 1% (6/473) of the patient population in the registry, one of which was fatal. It is unclear if the risk of PE after CDT is greater than the risk of PE on oral anticoagulation.

Perhaps the greatest obstacle to interventionalists performing CDT is that success with this procedure comes at a great cost. It is labor intensive and involves multiple visits to the angiography suite with long infusion times that may be difficult for a patient to endure. It also requires observation in a monitored setting such as an intensive care or step-down unit. Compelling evidence from prospective, randomized clinical trials would certainly help to justify the significant additional effort that CDT entails.

PERCUTANEOUS MECHANICAL THROMBECTOMY

In an effort to produce more rapid lysis and limit trips to the angiography suite, percutaneous mechanical thrombectomy (PMT) has evolved as a possible alternative or adjunct to CDT for the treatment of DVT. Several PMT devices have been approved by the FDA for use in treatment of hemodialysis graft thrombosis; these devices have subsequently been applied to the treatment of DVT. The only such device that is approved for native vessels, specifically for use in infrainguinal peripheral arteries, is the AngioJet rheolytic thrombectomy system (Possis Medical, Inc., Minneapolis, MN). It consists of an Xpeedior rheolytic catheter (0.035-inch guidewire compatible), a pump set, and a drive unit. The pump set and drive unit produce a high-velocity saline jet, which results in an area of low pressure (-1 atm) at the catheter tip (called the *gap zone*). The low pressure leads to fragmentation and

aspiration of the clot through the effluent lumen. Subsequent thrombolysis can also be administered if necessary.

The AngioJet system and other such devices are particularly useful in patients with contraindications to pharmacologic thrombolysis. Furthermore, while the Venous Registry study demonstrated that CDT had its best results in patients with acute DVT, mechanical thrombectomy may potentially have more success in patients with subacute or chronic DVT where lytic agents have difficulty penetrating the organized thrombus.[35] Once the clot is removed, venous lesions predisposing to thrombus formation can be treated as part of the intervention with angioplasty or stenting as needed.

A study examining the efficacy of the AngioJet device found that mechanical thrombectomy alone achieved greater than 90% thrombus removal in 24% of patients with DVT and 50% to 90% removal in 35%.[40] However, after CDT was utilized as an adjunct in the remaining patients without contraindications, the overall clinical success was 82%. Thus, this study demonstrates that while mechanical thrombectomy may be an effective alternative to CDT, the combination of both therapies is even more powerful. It is believed that the use of mechanical thrombectomy improves outcomes because it initially reduces the thrombus burden and, similar to balloon maceration, it exposes a greater area of the thrombus surface to the lytic agent, allowing the drugs to work more effectively and at lower doses. Thus, the potential advantages of using both pharmacological and mechanical thrombolysis are the decreased dose and infusion time of thrombolytic drugs, with fewer bleeding complications and comparable procedure success to CDT alone.

A retrospective study comparing CDT alone to "pharmacomechanical" therapy (PMT and CDT) confirmed the success of this combination technique.[41,42] The study found that the results of mechanical thrombectomy were greatly improved if prior CDT was also performed (62% vs 26% success rate). Furthermore, the study confirmed that adjunctive PMT greatly reduced both time of lysis (40% reduction) and lytic drug dose (60% reduction).

It should be noted that the clot displacement caused by PMT produces an inherent risk of PE as a complication. As temporary "retrievable" inferior vena cava filters have recently been approved by the FDA, it is reasonable to consider utilizing such a device.[42] One study of PE occurrence in dogs subsequent to PMT indicated that temporary filtration may be indicated during such a procedure.[43] However, several smaller studies with humans have not demonstrated clear evidence that temporary filtration is needed.[41] Further investigation into this area is necessary to elucidate whether the theoretical increased risk for PE warrants the utilization of filtration devices.

Combination Therapy

During the Summit, several approaches to combination therapy were discussed, and most participants had unique perspectives based on their respective experiences. The following are descriptions of the two primary combination therapy options discussed, the Power-Pulse Spray (P-PS) Technique and the Rapid Lysis Technique, each summarized by the physicians who first introduced them. Further analysis and commentary regarding variations and individual user experiences from the Summit appear in the pages that follow.

THE POWER-PULSE SPRAY TECHNIQUE
By David E. Allie, MD

The total or subtotal iliofemoral vein segment thrombotic occlusion is crossed using standard techniques with a .035-inch Glidewire (Terumo Medical Corporation, distributed by Boston Scientific Corporation, Natick, MA). This crossing is often facilitated with a 5-F Terumo Glidecatheter. Initially, the AngioJet RT system is set up and primed in its thrombectomy mode with normal saline (NS). A lytic bag (using either 10-20 mg of alteplase; 10 mg of tenecteplase; or 1,000,000 IU urokinase [Abbokinase, Abbott Laboratories, Inc., Abbott Park, IL]; in 50 mL NS) is then exchanged for the saline prime, and a stopcock is added to the outflow port RT catheter manifold, converting the RT system to its P-PS mode. It is important to advance the RT catheter through the entire thrombosed segment such that the volume of lytic is distributed throughout the clot.

The RT system using the Xpeedior catheter is set to deliver a 0.6-mL volume of the concentrated lytic solution per each pedal pump/pulse. The infused volume meter on the device unit console is set at zero at the initiation of the P-PS mode, therefore allowing calculation of the total lytic volume and dose. A typical iliofemoral DVT will consume a 50-mL bag with a single antegrade and retrograde pass covering approximately 1 cm to 2 cm with each pump stroke. The concentrated pulsed lytic is allowed to lyse for 20 to 30 minutes. The RT system is then converted back to its thrombectomy mode. It is important to withdraw the residual 12-mL lytic solution outside the patient to avoid infusing additional lytic. In most cases, thrombectomy is required after P-PS. The RT catheter is then reintroduced with a single antegrade and retrograde pass followed by venography. Flow-limiting lesions, which are amenable to usual treatments such as stenting, are often uncovered at this point.

THE RAPID LYSIS TECHNIQUE
By Mark J. Garcia, MD

If the patient has no contraindications to lytic therapy, either 25 mg alteplase or 10 U reteplase (Retavase, ESP Pharma, Inc., Edison, NJ) is added directly to a 1,000 mL NS (heparin is not added directly to the solution, because it precipitates the lytic agent, rendering it inactive). If lytic therapy is contraindicated, we use 5,000 U of heparin in a 1,000-mL NS bag while the patient continues to receive systemic anticoagulation.

Once access is confirmed, a short 8-F sheath is placed over a Bentson wire (Cook Incorporated, Bloomington, IN), followed by coaxial placement of an angled catheter (eg, Berenstein). The catheter is advanced carefully through the clot with segmental venography performed along the way. Once a full popliteal-to-cava venogram is completed, the 4-F Berenstein catheter (Cordis Corporation, a Johnson & Johnson company, Miami, FL) is negotiated through the clot beyond the most central aspect of the DVT. The catheter is then exchanged over a stiff wire (eg, Amplatz, Cook Incorporated) for an 8-F, angled (eg, Hockey Stick, Cordis Corporation) guiding catheter, placed to the central portion of the clot burden. Coaxially, the RT catheter is advanced over the wire, placed such that its tip is 2 cm to 3 cm beyond the tip of the guiding catheter. The wire is then removed* to allow the RT catheter to take the shape of the guiding catheter, which allows for better wall-to-wall apposition of the RT catheter, enhancing clot removal.

We work from the central to the peripheral thrombus, keeping the tip of the RT catheter just beyond the guiding catheter as we rotate the guide in a 360° circle, slowly but continuously retracting the system through the entire clot burden. This spiraling technique is continued from the central to peripheral portions of the clot with frequent venograms performed at each segment through the outflow port without removal of either catheter. Once resolution of the thrombus has occurred, evaluation for venous intervention (angioplasty or stenting) may proceed. Upon completion, the catheter and sheath are removed with a "ball" of 4 X 4 dressings placed on the puncture site and pressure dressing (microfoam tape) applied in a complete circumference around the knee.

*AngioJet product labeling contains the following warning: Do not inject fluids through the Catheter Outflow lumen. During the procedure, do not retract the guide wire into the Catheter. If retraction of the guide wire into the Catheter occurs, remove both the Catheter and guide wire from the patient in order to back-load the Catheter over the guide wire. The Catheter should always be back-loaded onto the guide wire to prevent the wire tip from exiting and binding in the Catheter windows.

Insights From the Combination Therapy Summit Roundtable

During the Combination Therapy Summit, the participants focused on several issues integral to the treatment of venous thrombosis, such as treatment procedures and protocols and the benefit-versus-risk considerations associated with each option. Although there was not unanimous consensus on every issue raised, the roundtable discussions illustrated those points where practice trends converged, as well as those for which further discussion at a future date is necessary. The following summarizes the panel members' discussions regarding their experiences and perspectives with respect to patient selection, associated vessel wall injury, drug integrity, dosage and volume, duration of procedure, technical considerations, advantages of P-PS therapy over traditional RT, embolization risks, filter use, and appropriate use of anticoagulation.

VESSEL WALL INJURY CONSIDERATIONS: COMPARISON OF ANGIOJET P-PS AND ANGIOJET RT IN A PORCINE MODEL

By Peter H. Lin, MD; Ruth L. Bush, MD; and Alan Lumsden, MD

To evaluate the effects of RT and P-PS/RT treatment in normal vessels, animal studies were performed in both acute and chronic porcine arterial models. In each experiment, the degree of vessel injury observed during treatment with the RT catheter alone (RT group) was compared to treatment with the AngioJet P-PS technique followed by RT (P-PS group). For acute studies, six juvenile 45 to 55 kg pigs were used. The degree of acute injury in arteries was assessed by histopathologic analysis performed 4 days after treatment. Treated blood vessels included bilateral carotid,

THE POWER-PULSE SPRAY TECHNIQUE

1. Cross thrombotic occlusion with .035-inch Glidewire.
   Preparation of the AngioJet RT Catheter
2. Set up and prime 6-F RT catheter in its thrombectomy mode as per instructions for use. Prime system using 12 mL NS.
3. Exchange saline priming bag for 10 to 20 mg alteplase in 50 mL NS ("lytic bag").
4. Activate the RT catheter to prime with lytic (infuse 12 mL).
5. Reset Infused Volume meter to Zero on Drive Unit console.
6. Attach 3-way stopcock to outflow port on the RT catheter manifold.
7. Close the stopcock to occlude outflow.
   P-PS Technique
8. Advance the RT catheter through the entire thrombosed segment such that the volume of lytic is distributed throughout the clot.
9. Each foot pedal pump/pulse delivers 0.6 mL lytic solution.
10. Continue advancing and pulsing lytic until entire occlusion has been crossed.
11. Repeat P-PS in retrograde direction and remove catheter (1 pedal tap/1 mm withdrawal). The Infused Volume meter calculates total solution (convertible to total lytic dose).
12. Allow pulsed lytic to lyse for 30 minutes.
    Normal Thrombectomy Mode
13. OPEN STOPCOCK.
14. Exchange lytic bag with priming NS bag.
15. Evacuate 12 mL lytic residual.
16. Reintroduce RT catheter in thrombectomy mode.
17. Make a single antegrade and retrograde pass with RT catheter.
18. Obtain postthrombectomy angiogram.
19. Further treatment at discretion of clinician (unmasked culprit lesion, PTA/stent).

SOLUTION INFUSION PER PUMP STROKE

AngioJet Xpeedior 120 infuses 0.63 mL/pump stroke

25 mg alteplase in 500 mL NS:	20 mg alteplase in 50 mL NS:	5 mg alteplase in 50 mL NS:
0.05 mg/mL = 0.032 mg/pump stroke	0.4 mg/mL = 0.25 mg/pump stroke	0.1 mg/mL = 0.063 mg/pump stroke

femoral, and iliac arteries (n=6 vessels per animal, total treated vessels=36). For chronic studies, a similar group of 6 juvenile pigs were used, and vessel injury was assessed at 1 month after treatment. Blood vessels that were treated in the chronic group included carotid, femoral, and iliac arteries (n=6 vessels per animal, total treated vessels=36). Vessels were randomized to either RT or P-PS group treatment types. RT (n=18) was performed by operating the RT catheter for 30 seconds at a rate of 1 mm/s from distal to proximal over a length of 30 mm. P-PS (n=18) was performed using alteplase at a concentration of 40 mg per 1 L saline.

There were no significant procedural complications and both treatment types were well-tolerated. No difference in the severity of vessel spasm during treatment was observed in either group. At the conclusion of each experiment, animals were euthanized and vessels were explanted, fixed in buffered formalin, and forwarded for analysis by an independent pathologist who was blinded to the treatment assignment. Samples were assessed according to a prespecified injury scale that included evidence of endothelial cell denudation, fracture in the internal elastic lamina, extent of injury to the vascular media, presence of mural thrombus, and intimal hyperplasia (chronic studies). Histological studies indicated that there was an increased trend of vessel injury in the P-PS group; however, this difference did not reach statistical significance in this study, when compared to the RT cohort. The increased trend for vessel injury in the P-PS group may possibly be related to these vessels being instrumented twice (for P-PS, then for RT), versus only one instrumentation in RT vessels. No significant difference in vessel wall injury was found in the chronic group when comparing the P-PS and RT groups. In either group, no perforations or deep dissections were observed in either treatment cohorts. These results suggest that P-PS treatment may result in similar vessel injury to the vessel wall compared to the RT treatment group, based on histological analysis at 4 days and 1 month. Further studies are planned to assess the clinical and histopathologic effects of treatment with the P-PS technique in animal models of DVT.

DRUG INTEGRITY

A recent study conducted by Charles Semba, MD, et al, and presented at the Summit by Mahmood Razavi, MD, sought to determine the viability of alteplase solutions after propulsion through rheolytic (eg, AngioJet Xpeedior catheter) or high-speed maceration thrombectomy devices.[44] Two experiments were performed for each device type (N=4); the first used undiluted (1 mg/mL) freshly reconstituted alteplase, and the second used a concentration diluted in NS (.05 mg/mL). The fluids were collected in

---

COMBINATION THERAPY PATIENT SELECTION

Ideal Cases
- Symptomatic iliofemoral or deep vein thromboses
- Clot age <7 days, although most present between 14 and 28 days and are commonly treated successfully

Relative or Possible Contraindications
- Contraindications to lysis or anticoagulation
- History of ischemic stroke (<1 year)
- Recent history of cerebral trauma
- Pregnancy
- Infected clot
- Impaired renal function
- History of hemorrhagic stroke
- Recognized potential for death from hematoma
- Pulmonary hypertension
- History of intracranial aneurysm

All possible contraindications must be evaluated on a case-by-case basis. In cases of extreme need or desire for clot removal, therapeutic benefits may outweigh risks. Proper evaluation, risk assessment, and informed consent are necessary.

---

glass vials at ambient temperature and were assayed for color/clarity (inspection for particulate matter), UV spectrophotometry (protein concentration), native size exclusion chromatography (percent monomer, determines "clumping"), and in vitro clot lysis (bioactivity).

These experiments showed no loss of enzymatic activity by alteplase after passing through the rheolytic system. Dr. Razavi noted that this confirms the clinical observations that alteplase maintains its clinical activity when used in combination with mechanical thrombectomy devices such as the AngioJet.

PATIENT SELECTION

The participants acknowledged the difficulty in precisely determining a clot's age, an issue that is compounded by the fact that clot age is not the sole predictive factor of procedural success or associated risk; patient symptoms must also be analyzed. Based on the relative nature of these factors, the Summit participants emphasize that all clots should be evaluated on an individual basis, with all elements of the patient's condition and the nature of the clot taken into consideration before deciding on the best course of action.

The most common indications for combination therapy are symptomatic iliofemoral or femoral deep vein thromboses. Most Summit participants have used combination

therapy in other anatomic locations, but discussion was limited to this indication, as it is the most common treated. Bleeding complications have been shown to correlate with increasing age, but most operators reported success in patients across broad age ranges.

Relative Contraindications

It is currently unclear to what extent combination therapy will enable safe treatment of patients with relative contraindications to traditional CDT, but the panelists did believe that P-PS has the potential to do so. The group listed the following as their criteria for notable and perhaps absolute contraindications (depending on other patient-related factors): clot infection; history of hemorrhagic stroke, regardless when the stroke occurred; contraindications involving anticoagulation and/or thrombolysis; recognized active bleeding; pulmonary hypertension; poor renal function; and history of intracranial aneurysm. It was stated that in cases of extreme need or desire for clot removal, combination therapy may still be the best treatment option available for a particular patient exhibiting one or more of these contraindications. The need for proper informed consent with acknowledgement of the potential for negative outcomes, including death, associated with any procedural option was emphasized.

Role of Clot Age/Nature and Determining the Potential for Treatment Success

The consensus of the group was that, in general, the shorter the duration of the symptoms and the more acute the clot, the higher the likelihood of a successful, uneventful treatment (ie, success rates correlate inversely with thrombus age). Although treatment within 7 days of clot formation is considered ideal, the participants agreed that practice patterns indicate that most patients present when their clot is between 14 and 28 days old. Clots within this age range are, however, routinely treated with acceptable rates of success, but the clinicians must take into consideration that success in these more chronic or more organized clots may require longer procedure times, increased lytic doses, increased systemic impact and associated conditions, and in some cases, additional procedures using RT and/or combination therapy, or use of other therapeutic options. Many clinicians have also treated chronic clots and seen excellent results.

In cases during which the clot is determined to be chronic to the degree that treatment will likely be unsuccessful based on the standards outlined previously, it is recommended that the clinician first determine if there is an acute or subacute element that has caused the symptoms that have resulted in the patient's presentation. Such elements often exist in addition to the chronic clot, which may not be symptomatic. Some participants described successful cases during which they first treated the acute, symptomatic elements using combination therapy, and subsequently treated the chronic elements using another means. Some observers have also found value in using combination therapy in chronic cases as a means of determining the necessity or value of prolonged lytic infusions.

In clots that are chronic to the degree that a guidewire cannot be passed, other interventional/endovascular options should be considered.

Defining Procedural Success

Data defining anatomic success in venous thrombosis cases is limited but has previously been defined as (1) restoration of flow with any residual stenosis treated and (2) >50% clot removal.[45] However, the summit participants noted that there has been no definitive proof of which anatomic results directly correlate with clinically meaningful, successful outcomes. The consensus of this group was that completely successful procedures utilizing combination therapy should be defined as >90% clot lysis/removal, with restoration of rapid antegrade flow. In some cases, depending on the individual patient considerations, achieving complete success may not be possible, and procedural success goals must be adjusted accordingly; the overall consensus was that partial procedural success can be defined as 50% to 90% clot lysis/removal with flow restoration.

LYSIS DOSAGE: VOLUME AND DURATION

Investigators reported using a range of lytic agent dosing regimens, which vary according to their procedural timing needs and operator-specific techniques. Arguably, the range of dose concentrations and volumes administered reflects the heterogeneity of patients treated and the need for dose-ranging prospective studies.

During P-PS procedures, most participants routinely use total infusion volumes of between 25 mL and 125 mL. The average total volume delivered ranged from 40% to 100% of the total. Most physicians used nearly all of the infusate, depending upon the extent, chronicity, and volume of clot

PROCEDURAL SUCCESS	
Complete success	>90% clot lysis/removal and flow restoration
Partial success	50% to 90% clot lysis/removal flow restoration
Unsuccessful	<50% clot lysis/removal and/or lack of flow restoration

to be addressed. In rare cases, some investigators reported exceeding 500 mL or more. Presumably, risks of hemolysis would increase with the increased activation of the device, and preventative measures (eg, hydration, etc.) would be important. Most participants reported lytic dwell times of 15 to 30 minutes before aspiration using the RT catheter.

THE POTENTIAL ADVANTAGES OF COMBINATION THERAPY

Long-term follow-up is currently ongoing. However, anecdotal experiences indicate that immediately postprocedure, at 6 months, and at 1 year indicate improvement over more conservative strategies. This is particularly the case with younger patients.

The majority of the Summit participants agreed that in terms of thrombus removal efficacy and duration of treatment, traditional RT has, in their experience, demonstrated an improvement over CDT alone. Combination therapy, however, whether incorporating the P-PS technique or the Rapid Lysis technique, was believed by most of the participants to be of even further benefit regarding efficacy and duration of acute-clot treatment than traditional RT procedures. Many participants also agreed that the duration of thrombolysis necessary is on average longer with CDT than has been observed with combination therapy techniques.

Some of the physicians present stated that, in their experience, combination therapy also facilitated successful pro-

DOSING EXPERIENCE OF SUMMIT PARTICIPANTS			
	Alteplase (mg)	Saline (mL)	Concentration (%)
Low	2	100	2
	25	1,000	3
	25	500	5
Mid	5	50	10
	25	125	20
	10	50	20
High	5	100	25
	10	25	40
	25	25	100

cedural completion within a single setting versus either RT or CDT alone. Individual definitions of procedural success varied, but the majority agreed with this premise. However, several participants, although not necessarily in disagreement, said further data were necessary to prove or disprove this hypothesis, and that individual practice and facility considerations would make definitively drawing such a conclusion problematic.

EMBOLIZATION CONSIDERATIONS

Although there were isolated cases in which embolization occurred, use of the P-PS or Rapid Lysis techniques has, in the experience of those present, not been associated with significantly increased likelihood of causing embolization versus traditional RT. These experiences reflect previously published data that showed no incidence of clinically significant PE associated with the AngioJet RT catheter. Opinions differed regarding whether procedures using either combination therapy or traditional RT and aspiration are more likely to cause embolization than CDT, with a few users citing anecdotal experiences to this effect. To limit the risk of embolization, some RT/combination-therapy users incorporate prevention strategies, each of which focus on individualized care relative to the specific patient and clot being treated, as well as the interventionist's preferences regarding technique and use of retrievable IVC filters.

Procedural Anticoagulation

The majority of participants routinely incorporate full periprocedural anticoagulation with heparin or a direct thrombin inhibitor during combination therapy procedures; those who do not anticoagulate fully routinely administer subtherapeutic dosing. Some participants also utilize antiplatelet agents periprocedurally, most notably when complex intervention is anticipated. If anticoagulation is contraindicated for a particular patient, combination therapy and RT should be avoided.

ADDRESSING EMBOLIZATION

Most Summit participants reported using a combination of several methods for preventing embolization when performing combination therapy procedures. One or more of the following are routinely incorporated:
• Full periprocedural anticoagulation*
• Periprocedural antiplatelet administration
• Discretionary use of retrievable/temporary filters**
• Technique modification involving leaving the superior "cap" intact until after the P-PS infusion and wait time are complete (the group was divided regarding this technique; many participants routinely infuse the entire clot length without leaving the superior "cap" intact)
• Postprocedural anticoagulation for at least 9 to 12 months

*If contraindicated, the patient is likely not a combination therapy/RT candidate.
**Routine use of retrievable/temporary filters is not recommended in combination therapy/RT procedures, nor is any use of permanent filters.

Postprocedural Pharmacology

After the combination therapy procedure is complete, many participants recommended that all patients should proceed to a hematology consultation and hypercoagulation work-up. However, some noted that such testing is only mandatory in cases for which one or more of the following exist: unprovoked or recurrent DVT, age <50 years, DVT at an unusual site, DVT during pregnancy or first year of hormonal usage, unexplained recurrent fetal loss, and family history of DVT.[46]

In most cases, patients are placed on anticoagulation for at least 9 to 12 months, although some users reported stopping anticoagulation at 6 months. In most cases during which a stent is placed, the majority of participants also put the patient on an antiplatelet agent; a minority prescribe antiplatelets routinely, regardless of stent placement.

Filter Use

Based on anecdotal experiences and previous data[47] linking the use of IVC filters to recurrent DVT or postthrombotic syndrome, each participant agreed that permanent embolic protection filters should not be used in conjunction with RT or combination therapy procedures unless otherwise required due to another indication. Routine use of retrievable or temporary filters was not advocated, but the group acknowledged having successfully used these devices on a case-by-case basis, such as in cases of known significant embolization risk (eg, those involving free-floating thrombus, excessively large clots, poor cardiopulmonary reserve, etc.).

Technique Modification

One embolization–risk-reduction strategy routinely

PERIPROCEDURAL CARE

By Mark J. Garcia, MD

Pre- and postprocedure protocols varied among the participants. We have summarized the procedural trends they reported in the text on these pages. In addition, we provide one physician's specific protocol for periprocedural care.

Preprocedure Care

All patients undergo preprocedural venous duplex examination, hypercoagulability work-up, and blood work (CBC, DIC screen, BUN, and creatinine), and hydration with IV fluids as tolerated. Either a Foley (C.R. Bard, Inc., Murray Hill, NJ) or a Texas catheter (Kendall External Catheters) is used to monitor urine output and degree of postprocedure hemoglobinuria. Patients with a contrast allergy are appropriately premedicated with standard steroid and diphenhydramine prep. A hematology consultation is requested for all patients, and a nephrology consultation is requested for patients with renal issues. Prior to the procedure, the patient is started on therapeutic doses of heparin with the PTT goal of 80. Once full anticoagulation is achieved, the procedure is performed with heparin infusion continued throughout. We do not routinely place vena cava filters prior to lysis.

Postprocedure Care

Patients return to an unmonitored floor bed unless catheter-directed lysis is needed, necessitating transfer to the Intensive Care Unit (rare). Full anticoagulation is continued with the patient at bed rest for the remainder of the day. Vigorous hydration (3 L NS) and furosemide (usually 40 mg IV) are given. Postprocedure labs include creatinine. We no longer routinely order CBC, DIC screens unless the patient has had extensive rheolysis (>2 L solution) or has other clinical indications.

Discharge anticoagulation is maintained with warfarin or enoxaparin; the choice in our institution is left to the discretion of the hematologist. A postprocedural venous Doppler exam is obtained prior to discharge. If there is massive swelling of the extremity, it is wrapped with an Ace bandage from the toes to the groin and elevated above the level of the heart for several days to enhance edema resolution. Follow-up Doppler examinations are obtained at 1-, 3-, 6-, and 12-month intervals, and yearly thereafter, unless clinically indicated. Evaluation for insufficiency is performed on follow-up exams. Note: Color Doppler evaluation is imperative, because wall thickening is commonly seen and should not be mistaken for recurrence of DVT.

Clinical Issues and Lessons Learned

• Our early experience showed that unless a PTT of >70 was obtained prior to treatment, early rethrombosis occurred.

• Gross hemoglobinuria is expected and is usually resolved within 48 to 72 hours. We are uncertain of the use of renoprotective agents (eg, acetylcysteine) in this setting, as we have used them but have no long-term or scientific data to date.

• Bradycardia and hypotension are seen occasionally and are usually transient and resolve with discontinuation of the rheolysis (ie, standard AngioJet RT) until the vital signs return to baseline (usually within 1 minute). Rarely have we had to give atropine, which rapidly corrects the situation and allows for further treatment as needed. We have not placed temporary pacers, but their use could be an option.

• Anecdotally, we have had some success on lysis of chronic DVT, which we describe as greater than 4 to 6 weeks old, with a "harder" feel compared to fresh, or acute, clots. This is attempted only in extenuating circumstances.

employed by some of the participants involves leaving the superior "cap" intact during the initial RT or combination therapy passes, clearing the "cap" after the P-PS infusion and wait period to complete treatment of the entire clot length. Advocates of this strategy believe that it also helps to minimize negative systemic effects such as the degree of hemolysis. Those who routinely infuse the entire length of the clot without leaving the superior "cap" do so to establish complete antegrade flow more rapidly, and have not seen evidence that doing so results in a higher risk of embolization.

The potential for embolization is considered to be significantly lower in patients with an obstruction of the top end of the vein, such as is the case with May-Thurner syndrome patients. As a result, most Summit participants reported using RT or combination therapy procedures with somewhat less trepidation in these patients.

THE ADVENTT TRIAL

The ADVENTT Trial (Accelerated Deep Venous Thrombolysis and Thrombectomy) is the first multicenter, prospective US trial underway intended to validate combined use of chemical thrombolysis using alteplase and AngioJet RT for the treatment of symptomatic lower-extremity DVT. For the first half of the cohort, alteplase is mixed into the pump solution, but outflow is not occluded (akin to techniques described by Dr. Mark J. Garcia). P-PS may play a role in the latter half of the trial. The endpoints include rapid completion of therapy, safety, and, later, quality-of-life outcomes. The trial is a physician-sponsored IND under the supervision of the FDA; it is funded with grants from Possis Medical and Genentech. Dr. Ziv J. Haskal of Columbia University is the IND sponsor, trial designer, and national Principal Investigator.

1. Coon WW, Willis PW, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh Community Health Study. Circulation. 1973;48:839-846.
2. Anderson FA, Wheeler HB, Goldberg RJ, et al. A population based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch Intern Med. 1991;151:933-938.
3. Patel NH. DVT-incidence, pathogenesis, clinical features and current systemic therapy. SIR 2003. Categorical Course.
4. Allie D, Lirtzman M, Wyatt C, et al. Novel combination thrombolytic therapy in limb salvage: mechanical thrombectomy (rheolytic thrombectomy with AngioJet) and chemical thrombolysis (tenecteplase) "power-pulse spray" technique. Am J Cardiol. 2002;90:108H.
5. Allie DE, Hebert CJ, et al. Novel simultaneous combination chemical thrombolysis/rheolytic thrombectomy therapy for acute critical limb ischemia: the power-pulse spray technique. Cathet Cardiovasc Intervent. 2004;63:512-522.
6. Uppot R, Garcia M, Roe C, et al. Management of deep venous thrombosis using the AngioJet rheolytic thrombectomy system. J Vasc Interven Radiol. 2003;14:S116
7. Dym RJ, Fitzpatrick D, Cynamon J. Management of deep vein thrombosis: review and description of the power pulse technique. Albert Einstein College of Medicine and Montefiore Medical Center. November 2004:1-16.
8. Hull R, Delmore T, Genton E, et al. Warfarin sodium versus low dose heparin in long-term treatment of venous thrombosis. N Engl J Med. 1979;301:855-858.
9. Coon WW, Willis PW. Recurrence of venous thromboembolism. Surgery. 1973;73:823-827.
10. Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA. 1998;279:458-462.
11. Brandejes DPM, Heijboer H; Buller HR; et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal vein thrombosis. N Engl J Med. 1992;327:1485-1489.

12. Hull RD, Raskob G, Brant RF, et al. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. Arch Intern Med. 1997;157:2317-2321.
13. Hull RD, Raskob G, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for DVT. Arch Intern Med. 1997;157:2562-2568.
14. Dolovich, LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparin with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160:181-188.
15. Leizorovicz A, Simonneau G, Decousus H, et al. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep vein thrombosis: A meta-analysis. BMJ. 1994;309:299-304.
16. Lensing AW, Prins MH, Davidson BL, et al. Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis. Arch Intern Med. 1995;155:601-607.
17. Breddin HK, Hach-Wunderle V, Nakov R, et al. CORTES Investigators. Clivarin: Assessment of Regression of Thrombosis, Efficacy, and Safety. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. N Engl J Med. 2001;344:626-631.
18. Deitelzweig S, Jaff MR. Medical management of venous thromboembolic disease. Tech Vasc Interv Radiol. 2004;7(2):63-67.
19. O'Donnell TF, Browse NL, Burnard KG, Thomas ML. The socioeconomic effects of iliofemoral thrombosis. J Surg Res. 1977;22:483-488.
20. Strandness DE Jr, Langlois Y, Cramer M, et al. Long-term sequelae of acute venous thrombosis, JAMA. 1983;250:1289-1292.
21. Plate G, Ohiin P, Eklof B. Pulmonary embolism in acute iliofemoral venous thrombosis. Br J Surg. 1985;160:1288-1290.
22. Lansing AM, Davis WM. Five-year follow-up study of iliofemoral venous thrombectomy. Am Surg. 1988;168:620-628.
23. Eklof B, Juhan C. Revival of thrombectomy in the management of acute iliofemoral venous thrombosis. Contemp Surg. 1992:40:21-30.
24. Juhan C, Alimi Y, Barthelemy P. Late results of iliofemoral venous thrombectomy. J Vasc Surg. 1997;25:417-422.
25. Virchow R. Uber die Erweiterung kleinerer Gefasse. Arch Path Anat. 1851;3:427.
26. Mitchell RN, Cotran RS. Hemodynamic disorders, thrombosis, and shock. In: Cotran RS, Kumar V, Collins T, eds. Robbins pathologic basis of disease. 5th ed. Philadelphia: W.B. Saunders. 1999;113-138.
27. Heit JA, Silverstein MD; Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160:809-815.
28. Hyers TM; Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolic disease. Chest. 1986;89(suppl 2):26S-35S.
29. Stulberg BN, Insall JN; Williams GW, et al. Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. J Bone Joint Surg Am. 1984;66:194-201.
30. Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. Br J Surg. 1979;66:838-843.
31. Turpie AGG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Chest. 1990;97:172S-175S.
32. Hirsh J, Lensing A. Thrombolytic therapy for deep vein thrombosis. Int Angiol. 1996;5:S22-S25.
33. Schweizer J, Kirch W, Koch R, et al. Short- and long-term results after thrombolytic treatment of deep vein thrombosis. J Am Coll Cardiol. 2000:36:1336-1343.
34. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. Radiology. 1994;191:487-494.
35. Mewissen MW, Seabrook GR; Meissner MH, Cynamon J, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a National Multicenter Registry. Radiology. 1999;191:487-494.
36. Comerota AJ, Throm RC, Mathias SD, et al. Catheter-directed thrombolysis for iliofemoral deep vein thrombosis improves health-related quality of life. J Vasc Surg. 2000;32:130-137.
37. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomized clinical trial. Eur J Vasc Endovasc Surg. 2002;24:209-214.
38. Semba CP, Razavi MK, Kee ST, et al. Thrombolysis for lower extremity deep venous thrombosis. Tech Vasc Interv Radiol. 2004;7:68-78.
39. Hirsh J, Dalen JE, Deykin D, et al. Heparin: mechanism of action, pharmaco kinetics, dosing considerations, monitoring, efficacy, and safety. Chest. 1992;102(suppl):337S-351S.
40. Kasirajan K, Gray B, Ouriel, K. Percutaneous AngioJet thrombectomy in the management of extensive deep venous thrombosis. J Vasc Interv Radiol. 2001;12:179-185.
41. Vedantham S, Vesely TM, Parti N, et al. Lower extremity venous thrombolysis with adjunctive mechanical thrombectomy. J Vasc Interv Radiol. 2002;13:1001-1008.
42. Murphy KD. Mechanical thrombectomy for DVT. Tech Vasc Interv Radiol. 2004;7(2):79-85.
43. Trerotola SO; McLennan G, Davidson D, et al. Preclinical in vivo testing of the Arrow-Trerotola percutaneous thrombolytic device for venous thrombosis. J Vasc Interv Radiol. 2001;12:95-103.
44. Semba CP, Weck S, Razavi MK, Setum CM, Patapoff T: Characterization of alteplase (tPA) following delivery through the AngioJet rheolytic catheter. J Endovasc Ther. 2005;12:123–128.
45. Vedantham S, et al. Quality improvement guidelines for endovascular treatment of lower extremity deep vein thrombosis. J Vasc Interv Radiol. 2005, submitted.
46. Hirsh J, Lee AYY. How we diagnose and treat deep vein thrombosis. Blood. 2002;99:3102-3110.
47. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Grp. N Eng J Med. 1998;338:409-415.

Case Study

Treatment of Chronic Iliofemoral DVT Using Power-Pulse Spray Thrombolysis, Rheolytic Thrombectomy, and Stenting

By Michael Arata, MD

A 48-year-old female developed pain and swelling in the left lower extremity after an airline flight. Medical evaluation included a venous ultrasound demonstrating occlusive DVT. Anticoagulation and compression therapy was initiated. Her symptoms, however, continued despite adequate conservative care. Vascular medicine evaluation was sought, and she was found to be heterozygous for Factor II (prothrombin 22210A). Follow-up ultrasound demonstrated persistent occlusive DVT, and venography was performed, suggesting May-Thurner syndrome. Her pain was severe enough to require narcotic analgesia. Due to her continued symptoms, she was referred to our center for evaluation and more aggressive treatment of chronic DVT approximately 1 year after her initial symptom onset.

PROCEDURE

After informed consent, the patient was sterilely prepped and draped in the angiography suite. Ultrasound of the popliteal fossa was performed, demonstrating a patent popliteal vein. One percent lidocaine local anesthesia was administered and under direct ultrasound visualization, the popliteal vein was accessed using micropuncture technique. An 8-F sheath was exchanged over a wire. A venogram of the left lower extremity was obtained, showing complete occlusion of the popliteal vein just prior to its confluence with the femoral vein. Collaterals reconstituted the common femoral vein, which abruptly occluded at the external iliac level (Figure 1A). A pelvic venogram confirmed the complete occlusion of the proximal external iliac vein with collateral reconstitution in the IVC (Figure 1B).

A guide catheter was negotiated through the occlusion with a buckled Glidewire, and IVC access was obtained. After diagnostic examination, RT was undertaken using the Xpeedior catheter, resulting in partial thrombus removal and significant residual thrombus. P-PS thrombolysis was performed utilizing 25 mg of tenecteplase (TNKase; Genentech, Inc.; when utilizing alteplase, I use 10 mg*) diluted in 50 mL of saline and delivered via the RT catheter (Figure 1C). A 15-minute dwell time was allowed, during which angioplasty with 9-mm and 10-mm balloons was performed in the femoral vein to macerate the thrombus, facilitating the effect of the thrombolytic agent. Venography was performed after maceration, demonstrating some reduction in the thrombus burden; however, significant thrombus remained. After the P-PS lytic infusion, repeat thrombectomy was performed, and the majority of thrombus was removed. Underlying stenoses were evident in the femoral and iliac veins. Angioplasty with a 10-mm balloon was then performed in the femoral/popliteal segments, and a 12-mm balloon was used in the common femoral segment (Figure 1D). Self-expanding nitinol stents (Smart; Cordis Corporation) were then deployed from the confluence with the IVC through the common femoral region and dilated to 12 mm. Postdilatation venography was performed, demonstrating an excellent result (Figure 1E).

FOLLOW-UP

Immediately postprocedure, the patient had resolution of edema and significant reduction of pain. Due to persistent pain, venous ultrasound was performed 2 weeks postprocedure. The ultrasound documented venous patency with no evidence of rethrombosis. Her pain gradually resolved over the subsequent weeks and may have been secondary to venous dilation from angioplasty or stenting. Anticoagulation was continued due to her elevated Factor II level.
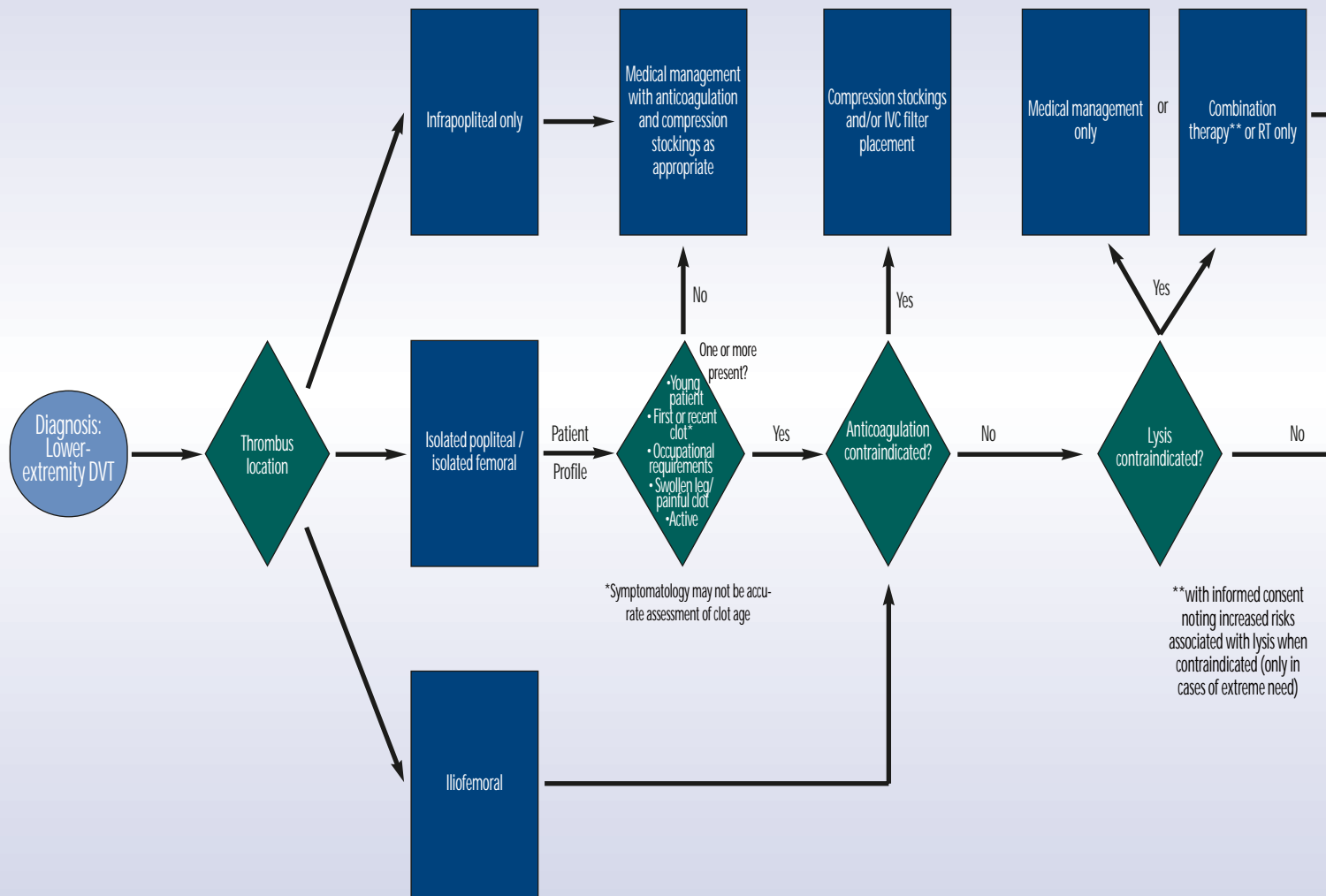

Figure 1. Pretreatment venogram via popliteal sheath demonstrating occluded femoral vein with collaterals (A). Pretreatment venogram via injection of the common femoral vein demonstrating complete iliac vein occlusion with pelvic collaterals (B). Rheolytic catheter used for P-PS spray thrombolysis infusion (C). Recanulated femoral vein following treatment with P-PS thrombolysis, RT, and balloon angioplasty (D). Final result: pelvic venogram following treatment with P-PS and stenting (E).

TREATMENT ALGORITHM FOR LOWER-

Based on experiences shared at

Diagnosis: Lower-extremity DVT

Thrombus location

Infrapopliteal only

Medical management with anticoagulation and compression stockings as appropriate

Isolated popliteal / isolated femoral

Patient Profile

One or more present?
• Young patient
• First or recent clot*
• Occupational requirements
• Swollen leg/ painful clot
• Active

No

Yes

*Symptomatology may not be accurate assessment of clot age

Anticoagulation contraindicated?

Yes

No

Compression stockings and/or IVC filter placement

Medical management only or **Combination therapy** or RT only**

Yes

Lysis contraindicated?

No

Iliofemoral

**with informed consent noting increased risks associated with lysis when contraindicated (only in cases of extreme need)

-EXTREMITY DVT MANAGEMENT

the Combination Therapy Summit

Consider surgical bypass

Repeat procedure

No

Venogram

Guidewire able to pass through clot?

No

Yes

Combination therapy treatment options:
• Lytic infusion, then RT
• Power-Pulse Spray
• Rapid Lysis
(see protocol descriptions on pages 8-14)

>90% thrombus removal?

No

Yes

Treat unmasked lesion

No

Drip infusion
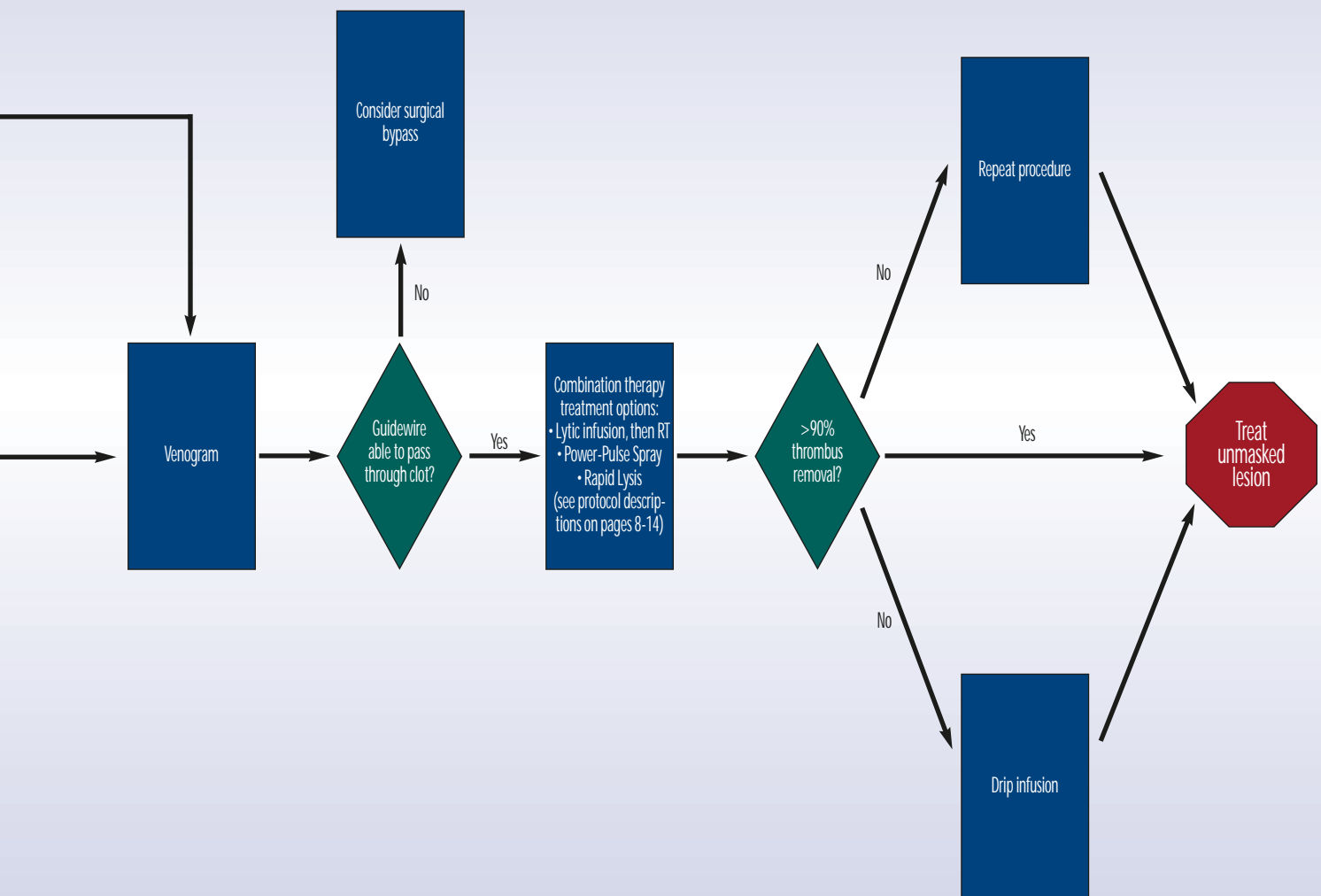
CME QUESTIONS

Circle the most appropriate answer in the ANSWER SECTION on the following page.

1. Approximately how many US patients are affected by acute DVT each year?
A. 100,000
B. 250,000
C. 600,000
D. 1 million

2. DVT and postthrombotic syndrome are known to produce each of the following sequelae except:
A. varicosities
B. amputation
C. venous dissection
D. edema

3. The aggressive minimally invasive combination therapy for treatment of DVT described in this monograph refers to:
A. anticoagulation combined with antiplatelet therapy
B. anticoagulation combined with placement of an IVC filter
C. mechanical thrombectomy combined with intraprocedural thrombolytic infusion
D. mechanical thrombectomy combined with postprocedural thrombolytic infusion

4. Which of the following has been recognized as the most common indication for combination therapy?
A. prior unsuccessful mechanical/rheolytic thrombectomy
B. symptomatic iliofemoral or femoral DVT
C. symptomatic IVC thrombosis
D. suspicion of elevated risk of embolization

5. Which of the following was not listed as a relative contraindication for combination therapy procedures?
A. pulmonary hypertension
B. presence of infected clot
C. presence of symptoms exceeding 3 weeks
D. history of hemorrhagic stroke

6. Bleeding complications were described as having been shown to correlate with which of the following?
A. increasing patient age
B. duration of symptoms
C. decreasing creatinine level
D. sedentary lifestyle

7. The likelihood of procedural success using combination therapy was said to correlate:
A. with total volume delivered
B. with amount of lytic agent infused
C. inversely with clot age

8. Power-Pulse Spray procedural length depends on all of the following except:
A. patient age
B. length and age/nature of clot
C. volume being infused
D. device advancement pace

9. On average, most P-PS users reported allowing the solution to remain in the vessel for how long?
A. 5-10 minutes
B. 10-15 minutes
C. 15-30 minutes
D. 30-40 minutes

10. Which of the following technique modifications was not recommended as an option for preventing embolization in most combination therapy candidates?
A. leaving the superior cap intact during the initial device passes, clearing the cap after the P-PS infusion and wait time
B. routine use of temporary or retrievable embolic protection devices
C. full periprocedural anticoagulation
D. routinely infusing the entire length of the clot

11. Which of the following periprocedural measures is not necessarily recommended for every combination therapy candidate?
A. preprocedural hypercoagulability work-up
B. preprocedural hydration with IV fluids as tolerated
C. vigorous postprocedural hydration
D. postprocedural transfer to the ICU

12. Summit participants defined complete procedural success as:
A. >80% clot lysis/removal and flow restoration
B. >85% clot lysis/removal and flow restoration
C. >90% clot lysis/removal and flow restoration
D. 100% clot lysis/removal and flow restoration

REGISTRATION/EVALUATION FORM: COMBINATION THERAPY

To obtain AMA/PRA category 1 credit, you must:
• Read the learning objectives and the CME article and complete the self-assessment test.
• Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
• Send the Registration/Evaluation form to **The Dulaney Foundation, 7102 Blackwell's Hollow Road, Crozet, VA 22932, or fax to (434) 978-4943.**
• Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION
Circle the best answer for each question on page 18.

1. A B C D	2. A B C D	3. A B C D	4. A B C D	5. A B C D	6. A B C D
7. A B C	8. A B C D	9. A B C D	10.A B C D	11.A B C D	12.A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD, RN) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an unrestricted educational grant from Genentech, Inc., and Possis Medical, Inc.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until April 30, 2006.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES
After successful completion of this program, you should be able to:

• Describe the various options available for treating DVT.	5	4	3	2	1
• Discuss combination therapy patient candidacy and contraindications.	5	4	3	2	1
• Describe appropriate ranges of lytic dosing and procedural duration.	5	4	3	2	1
• Discuss evaluation of combination therapy procedural success.	5	4	3	2	1
• Discuss embolization considerations and prevention strategies.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
• The information presented will influence how I practice.	5	4	3	2	1
• The information presented will help me improve patient care.	5	4	3	2	1
• The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
• The program was educationally sound and scientifically balanced.	5	4	3	2	1
• The program avoided commercial bias or influence.	5	4	3	2	1
• Overall, the program met my expectations.	5	4	3	2	1
• I would recommend this program to my colleagues.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____
_____

• Please list any topics you would like to see addressed in future educational activities: _____
_____