

Endovascular Therapy for Acute Limb Ischemia

Current and future trends in percutaneous intervention for limb salvage.

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Acute limb ischemia (ALI) is caused by a sudden decrease in limb perfusion, usually producing new or worsening symptoms and signs, threatening limb viability, and can lead to death if revascularization is not performed promptly.¹ Devastating systemic effects include severe electrolyte disturbances resulting in a potentially fatal acid-base imbalance. The incidence of ALI has been reported to be approximately 0.014% per year in the United States.²

Current treatment modalities include open surgical interventions, pharmacologic catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT), and percutaneous aspiration thrombectomy (PAT). Open surgical options include balloon catheter thrombectomy, endarterectomy with or without patch angioplasty, and intraoperative isolated limb thrombolysis. Unfortunately, ALI carries 9% and 15% in-hospital and 30-day mortality, respectively, and 15% and 25% amputation rates at discharge and 30 days, respectively.^{2,3} The 5-year survival rate after ALI caused by thrombosis approximates 45%.⁴ The basic treatment principle is restoration of uninterrupted pulsatile flow with a strategy that will provide the most complete revascularization with the lowest procedural risk. It has been suggested to consider computed tomographic angiography in patients with Rutherford class 1 or 2A ALI presentations, but this is associated with a potential major drawback of large volume contrast load, putting patients at high risk of contrast-induced nephropathy, especially if percutaneous treatment is chosen.¹ Where the expertise for endovascular treatment strategy exists, it would be more

judicious to resort to diagnostic invasive angiography in order to save valuable time and muscle in selected patients with limb-threatening ischemia.

Regardless of the technique, careful postprocedure follow-up is crucial, because ignoring compartment syndrome can lead to permanent nerve injury, paresis, or even death. Simple physical inspection, palpation of pulses with handheld Doppler confirmation, neurological exam of the affected limb, and assessment of pain with passive movement is generally effective. Pain that is out of proportion to the physical exam often denotes an early warning. Furthermore, judicious use of antiplatelet and anticoagulation drugs plays a pivotal role, not only in preventing further progression of disease, but especially in patients with cancer, atrial fibrillation, and hypercoagulable states. Use of aspirin, clopidogrel, warfarin, and cilostazol should be evaluated and tailored per each patient's indications.

CATHETER-DIRECTED THROMBOLYSIS

Catheter-directed, locally administered thrombolytic agents were the first successful nonsurgical treatment approach for ALI. CDT remains an initial treatment option for patients presenting with Rutherford category I or 2 ALI (Table 1).⁵ Thrombolytic therapy is administered through an intra-arterial catheter placed within the thrombus to achieve regional thrombus dissolution with relatively less systemic fibrinolysis compared to what would occur with systemically administered thrombolysis. However, time to achieve reperfusion with thrombolytics can be as high as 1.5 days and may still eventually lead to limb loss.^{3,6,7} Moreover,

TABLE 1. RUTHERFORD CLINICAL CLASSIFICATION OF ALI

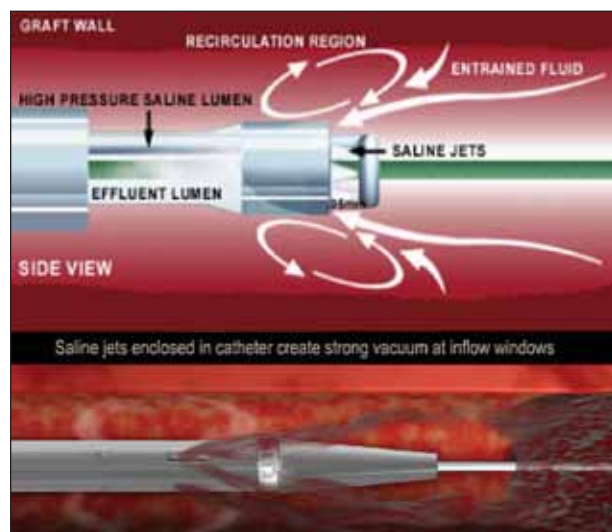
Class	Category	Prognosis	Sensory Loss	Muscle Weakness	Arterial Doppler	Venous Doppler
1	Viable	No immediate limb threat	None	None	Audible	Audible
2A	Threatened: marginal	Salvageable if treated promptly	Minimal-none	None	+/- Audible	Audible
2B	Threatened: immediate	Salvageable if treated immediately	More than just toes	Mild-moderate	Rare audible	Audible
3	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

Adapted from Rutherford RB et al. *J Vasc Surg.* (1997;26:517).⁵

thrombolytics are also associated with 5% to 15% risk of systemic bleeding complications including major intracranial hemorrhage.^{3,6-8} The Rochester trial showed a significant mortality benefit at 1 year, with thrombolysis mostly due to decreased complications compared to an open operative procedure,⁶ and the STILE (Surgery versus Thrombolysis for Ischemia of the Lower Extremity) trial showed modest amputation-free survival with CDT compared with surgery⁷ but the largest of the three, TOPAS, failed to reveal any mortality benefit over open embolectomy at 1-year follow-up.³ Although no statistical difference was noted in the rate of amputation between the two groups in these three trials, CDT did avoid the need for open surgery and can treat smaller distal vessels. Drawbacks include increased overall cost due to the need for prolonged infusion times combined with intensive care requirements and possible repeat catheterization procedures.

PERCUTANEOUS MECHANICAL THROMBECTOMY

Percutaneous removal of a thrombus today is a well-established modality and is often used as first-line therapy for ALI patients. There are several percutaneous devices that can remove thrombus from peripheral arteries using a rapid stream of fluid and hydrodynamic forces. The AngioJet rheolytic thrombectomy system (Medrad Interventional/Possis, Minneapolis, MN) (Figure 1) is a US Food and Drug Administration–approved device for infrainguinal arterial interventions in the United States. It is a dual-lumen catheter, one lumen of which accommodates either a 0.014- to 0.035-inch guidewire depending on model, and the smaller lumen delivers a high-velocity, pulsatile saline flow to the catheter tip via a high-pressure stainless steel hypotube connected to an external piston pump and drive unit. The hypotube forms a closed loop at the catheter tip, which contains multiple jets aimed retrograde into the larger effluent lumen that is used for both guidewire passage and evacuation of thrombus debris. The jets fragment and dislodge the thrombus, creating a localized low-pressure



(Courtesy of Medrad Interventional)

Figure 1. AngioJet LF140 rheolytic thrombectomy (PMT) catheter with demonstration of intravascular Bernoulli principle. The 5-F catheter is delivered and operated over a 0.014- or 0.018-inch guidewire.

zone (Bernoulli/Venturi effect) that draws the thrombus into the catheter tip and then out of the vessel through the catheter's effluent lumen (Figure 1).^{9,10} The catheter, in theory, works isovolumetrically; that is, the volume of saline infused via the jets is approximately equal to the volume of thrombus debris evacuated from the catheter.¹¹

The AngioJet catheter has been reported to aspirate more than 75% of the thrombus in patients presenting with ALI involving native vessels and grafts.¹⁰ A multicenter registry of 99 patients treated with rheolytic thrombectomy reported 70% substantial or complete revascularization (< 50% residual defect) and < 5% in-hospital and 30-day mortality related to limb ischemia.¹¹ Primary patency rates of 74% and 69% have been reported at 3 months and 1 year respectively.⁹ Another approach with the AngioJet catheter is called the *power-pulse spray technique* and has been reported to have

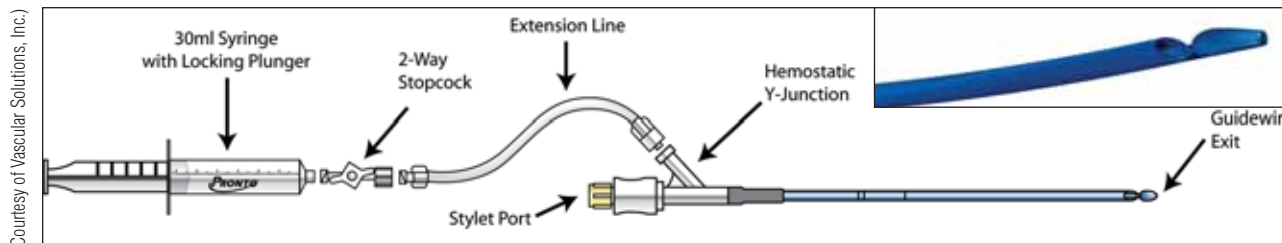


Figure 2. Pronto (PAT) catheter system with the soft Silva-tip located distal to the thrombus aspiration port to prevent vessel wall damage.

90% success rates.¹⁰ This technique involves thrombolytic drug infusion through the PMT catheter while occluding the outflow port and is followed by thrombus aspiration.

An important consideration is the potential to induce distal embolization.¹⁰ The efficacy of the device is limited by the size of the effluent lumen, a property that is dependent on the size of the device. This limitation, however, must be balanced by the convenience of placing the device through a relatively small-bore sheath, as well as the increased safety associated with the use of a smaller device in the tibial vessels. Another limitation is that a significant amount of red blood cell hemolysis resulting in hemoglobinemia and hemoglobinuria can occur with repeated passes of the device with fatal consequences, especially in patients with renal insufficiency.^{9,11} This, along with potential for fluid overload due to intravascular irrigation, is a concern because on an average, four passes with a PMT catheter have been reported to be required to achieve good results.¹¹ Although volume overload and hemolysis have not been reported to be a problem in preliminary clinical trials, we have witnessed fatalities from hyperkalemia and recommend caution in children and patients with chronic renal failure. Other potential pitfalls are early and late recurrent thrombosis resulting from vessel wall damage.¹¹

PERCUTANEOUS ASPIRATION THROMBECTOMY

PAT is based on the simple concept of applying suction by a syringe to a specially designed aspiration catheter in order to achieve thrombus aspiration. The Pronto extraction catheter (Vascular Solutions, Inc., Minneapolis, MN) (Figure 2) is a low-profile, dual-lumen, rapid-exchange aspiration thrombectomy catheter compatible with a 6-F guiding catheter and a 0.014-inch wire. It has an atraumatic spherical distal tip and sloped extraction lumen designed to protect the vessel wall while advancing the catheter during aspiration, which is completed by 30-mL locking vacuum syringes that are provided.¹⁰ It has a 0.053-inch crossing profile for vessels as small as 1.5 mm and a hydrophilic coating for smooth navigation. Although the efficiency and volume of thrombus extracted with these catheters are not equivalent to those of rheolytic catheters, the advantages

of these catheters include ease of use and deliverability to small-caliber distal vasculature. PAT has been reported to be a successful and safe aid during coronary interventions for acute myocardial infarction and for mesenteric arterial interventions due to its flexibility.^{12,13} The Pronto catheter's success in ALI has mostly been anecdotal, limiting its application in primarily managing embolization during peripheral interventions.¹⁴

The apparent benefits of the device are minimal risk for distal embolization, the ability to intervene within smaller-caliber vessels, quick set up, and no evidence of hemolysis to date. However, prospective data on rapidity of thrombus removal, native vessel injury, distal embolization, blood loss, flexibility, maneuverability, ease of operation, primary patency rates, impact on total fluoroscopy time and complications in regards to the Pronto catheter are limited in the medical literature. The Export catheter (Medtronic, Inc., Minneapolis, MN) is a similar catheter, but we are unaware of published reports of its use in ALI. Our experience with the Pronto catheter in 16 patients with ALI revealed 6% mortality (one patient died due to severe mechanical valve thrombosis resulting in severe heart failure) and a 12% amputation rate at 30 days. Although approximately 75% achieved complete or substantial response, more than 65% of the patients required additional use of rheolytic thrombectomy, and most of them required either angioplasty or stenting for residual defects.

SIMULTANEOUS ANGIOPLASTY WITH THROMBOLYTIC IRRIGATION

Mostly used as a bailout technique after failed/inadequate PMT or PAT, simultaneous angioplasty with thrombolytic irrigation (SATI) combines a low-pressure (2 atm) balloon angioplasty with simultaneous in situ thrombolysis using the Clearway irrigation balloon (Atrium Medical Corporation, Hudson, NH). The balloon creates a fluid layer over its surface, allowing local delivery of thrombolytics while a low-atmosphere angioplasty is accomplished (Figure 3). We have reported three cases of ALI treated with SATI as a bailout.¹⁵ Only one of those required additional CDT and none had any hemorrhagic complications. Drawbacks

(Courtesy of Atrium Medical Corporation)



Figure 3. Clearway irrigation balloon catheter depicting micropores through which thrombolytics are delivered locally.

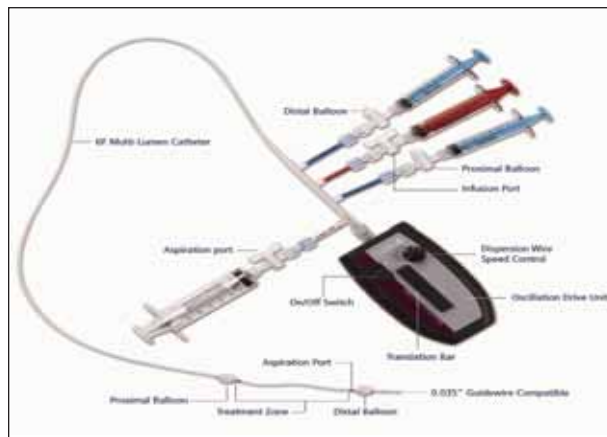
include a relatively large profile, requiring a 7- or 8-F sheath, increasing the risk of vascular access complications, and a small balloon length requiring several balloon inflations in case of large thrombus distribution; however, recent availability of 50-mm-length balloons should improve its applicability. Hopefully, the ongoing randomized trial comparing SATI to PMT (Use of Clearway Balloon vs. Mechanical Thrombectomy as Initial Treatment for Acute Limb Ischemia) will further define its role.

ISOLATED PHARMACOMECHANICAL THROMBOLYSIS-THROMBECTOMY SYSTEM

In our practice, a relatively novel device has proven extremely useful in urgent management of patients presenting with ALI. In some subgroups, CDT, PMT, and PAT systems show modest improvements in mortality compared to surgery but with important disadvantages of major bleeding, distal embolization, recurrent thrombosis, prolonged thrombolytic infusion, and increased overall cost. Prolonged infusion times combined with intensive care requirement and possible repeat catheterization procedure are the main factor in the increased cost.

The relatively novel, isolated (site-specific) pharmacomechanical thrombolysis-thrombectomy (IPMT) system, Trellis (Covidien, Mansfield, MA) (Figure 4), is designed to improve on the shortcomings of both mechanical thrombectomy and catheter-based thrombolysis. The Trellis PIS is a 510(k) Food and Drug Administration–approved device. This hybrid catheter device uniquely isolates the thrombolytic agent between two balloons (diameter, 3–10 mm) inflated proximal and distal to the thrombotic lesion. For arterial use, it is available in a 6-F multilumen catheter that is passed over a 0.035-inch guidewire with treatment zone lengths (length between two balloons for isolation of the desired lesion from systemic circulation) of 10 and 30 cm (Figure 5).

When inflated (distal balloon is inflated first using a 3:1 ratio of saline to angiographic contrast), the balloons isolate the treatment zone and maintain the concentration of the thrombolytic agent in the affected area. Next, a battery-powered, flexible sinusoidal wire is inserted through the catheter (replacing the guidewire) and produces oscillations at 500 to 3,000 rpm only in the isolated zone (Figure 6). This



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Figure 4. The Trellis peripheral infusion system (PIS) has five ports adjacent to the external oscillation unit. Two ports are used to inflate the balloons on the proximal and distal side of the treatment segment, which can measure 10 or 30 cm. A thrombolytic agent is infused through one port into the isolated treatment segment. A sinusoidal wire oscillates to fragment the clot and disperse the drug. The clot aspiration ports allow aspiration of the drug and of the dissolved thrombus before/as the balloons are deflated.

process mechanically mixes the clot with the thrombolytic agent (typically 1 mg recombinant tissue plasminogen activator per minute to a total of 10 mg) and enhances rapid dissolution of the thrombus by increasing the surface area of clot exposed to the lytic agent. Lysed thrombus is then aspirated via an integral port as the proximal balloon is deflated while the inflated distal balloon prevents distal embolization. This reduces systemic dispersion of the thrombolytic agent, thereby also reducing bleeding complications while achieving rapid revascularization and avoiding prolonged infusions.

Trellis PIS has been extensively described in treating deep venous thrombosis,¹⁶ and there are reports for treatment of either de novo suprainguinal arterial lesions or infrainguinal peripheral arterial bypass graft occlusion.¹⁷⁻¹⁹ Initial case studies on Trellis PIS have been extremely successful, with 97% 30-day survival and no reports of major hemorrhage or death, even though more than half of the patients presented with ALI (15 out of 26 patients).¹⁷ The distal embolization rate was less than 10%, while 15% of patients required an adjunctive surgical procedure, and 54% required an adjunctive interventional procedure (angioplasty with or without stenting).¹⁷ The aspiration mechanism of the device has been changed to enable aspiration of larger thrombotic debris since then.

Cost analysis of using Trellis PIS has been found to be 0.7 times less expensive than using CDT and is driven by decreased hospital/intensive care unit monitoring,

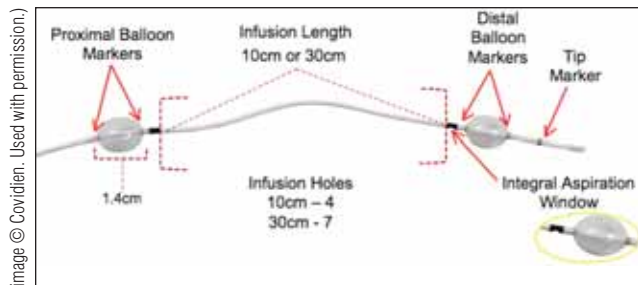


Figure 5. The size of the distal and proximal lumen occluding balloons, treatment zones, and infusion and aspiration ports. All distal and proximal references are in relation to the oscillation drive unit.



Figure 7. Angiogram of a patient presenting with ALI from mid-distal SFA complete occlusion (arrow) (A). Activated Trellis device's vibrating diversion wire (top arrow) with visible distal balloon (bottom arrow) (B). Postprocedure angiogram showing excellent three-vessel run-off to the leg (C). Aspirated thrombotic debris from the lesion (D).

decreased angiographic suite time, lower dose of thrombolytic agent used, and less bleeding complications.¹⁷ Combining the known benefits of local lytic infusion with mechanical fragmentation, the Trellis PIS allows rapid revascularization, a significant advantage over the standard multi-hour thrombolytic infusion protocols. Hemolysis and hyperkalemia have not been reported to be a problem even in the larger deep vein thrombosis treatment registries. At present, the Trellis PIS is the only device that has the ability to isolate lytic infusion in combination with mechanical thrombus fragmentation while preventing major bleeding, prolonged intensive care unit stay, and distal embolization.

The availability of the 6-F Trellis PIS with treatment lengths of 10 and 30 cm has increased its utilization in arterial occlusions. Our experience with the Trellis PIS is growing rapidly and has revealed excellent results in native (both de novo and pretreated) suprainguinal (Figure 6) and infrainguinal arteries (Figure 7). We have also reported one of the first cases with successful utilization of the Trellis PIS for aortofemoral graft thrombosis presenting with ALI.²⁰ We have had excellent outcomes with the Trellis PIS in 34 vessels in 20 patients treated with ALI, with 19 out of 20 patients experiencing successful results.²¹ Only one patient required additional CDT, and none experienced distal embolization.

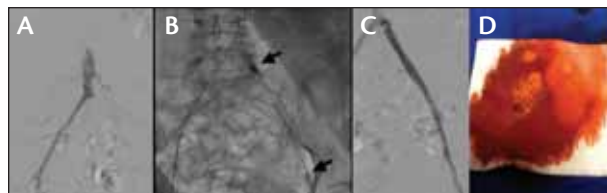


Figure 6. Angiogram of a patient presenting with acute limb ischemia from left external iliac occlusion (A). Activated Trellis device with visible proximal (top arrow) and distal balloon (bottom arrow) (B). Postprocedure angiogram depicting brisk luminal and distal flow (C). Aspirated thrombotic debris from the lesion (D).



Figure 8. Proposed management algorithm for the treatment of ALI (modified from the Inter-Society Consensus [TASC] working group).

CONCLUSION

Percutaneous intervention can offer limb-salvage success rates that rival those for surgical management for ALI, and a strong consideration for endovascular management of ALI can be made where the skilled personnel and facilities exist (Figure 8). IPMT is an indispensable tool in the current armamentarium for endovascular treatment of ALI (includes CDT, PMT, PAT) with successful clinical outcomes achievable in up to 95% of cases. Successful endovascular treatment of ALI also requires careful postprocedure observation for compartment syndrome or any other complications and a patient-centered approach toward discharge medications guided by etiology and treatment technique remain important milestones of management. ■

Raghav Gupta, MD, is from the Cardiovascular Section, University of Oklahoma in Oklahoma City. Dr. Gupta has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

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the Local Paclitaxel Delivery for SFA Disease (IRRITAX) trial, and that he receives grant/research funding from Atrium Medical Corporation, Medtronic, and Bristol-Myers Squibb. He further disclosed that he is coprincipal investigator of the trial Use of Clearway Balloon vs. Mechanical Thrombectomy as Initial Treatment for Acute Limb Ischemia trial. In both trials, Atrium Medical Corporation provides the Clearway angioplasty and in situ thrombolysis balloon. Other financial disclosures of Dr. Hennebry include that he is a proctor for carotid stenting for Abbott Vascular. He is also an investigator for the CHOICE carotid stent registry sponsored by Abbott Vascular and for the ORION study for iliac stents sponsored by Boston Scientific Corporation. Dr. Hennebry may be reached at (405) 271-4742; thomas-hennebry@ouhsc.edu.

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* 2007;45(suppl S):S5-67.
2. Dormandy J, Heeck L, Vig S. Acute limb ischemia. *Semin Vasc Surg.* 1999;12:148-153.
3. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med.* 1998;338:1105-1111.
4. Aunes S, Trippestad A. Operative mortality and long-term survival of patients operated on for acute lower limb ischemia. *Eur J Vasc Endovasc Surg.* 1998;15:143-146.
5. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26:517.
6. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg.* 1994;19:1021-1030.
7. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg.* 1994;220:251-266.
8. Earnshaw JJ, Whitman B, Foy C. National audit of thrombolysis for acute leg ischemia (NATALI): clinical factors associated with early outcome. *J Vasc Surg.* 2004;39:1018-1025.
9. Wagner HJ, Muller-Hulsbeck S, Pitton MB, et al. Rapid thrombectomy with a hydrodynamic catheter: results from a prospective, multicenter trial. *Radiology.* 1997;205:675-681.
10. Rogers JH, Laird JR. Overview of new technologies for lower extremity revascularization. *Circulation.* 2007;116:2072-2085.
11. Ansel GM, George BS, Botti CF, et al. Rheolytic thrombectomy in the management of limb ischemia: 30-day results from a multicenter registry. *J Endovasc Ther.* 2002;9:395-402.
12. De Luca G, Dudek D, Sardella G, et al. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. *Eur Heart J.* 2008;29:3002-3010.
13. Gupta R, Chimpiri AR, Saucedo JF. Superior mesenteric artery thrombosis managed percutaneously by timely combining aspiration thrombectomy with angioplasty and stents. *J Thromb Thrombolysis.* 2010;29:105-107.
14. Zafar N, Prasad A, Mahmud E. Utilization of an aspiration thrombectomy catheter (Pronto) to treat acute atherothrombotic embolization during percutaneous revascularization of the lower extremity. *Catheter Cardiovasc Interv.* 2008;71:972-975.
15. Rathi S, Latif F, Exaire JE, Hennebry TA. Use of simultaneous angioplasty and in situ thrombolysis with a specialized balloon catheter for peripheral interventions. *J Thromb Thrombolysis.* 2009;28:77-82.
16. Arko FR, Davis CM III, Murphy EH, et al. Aggressive percutaneous mechanical thrombectomy of deep venous thrombosis: early clinical results. *Arch Surg.* 2007;142:513-518; discussion 518-519.
17. Sarac TP, Hillerman D, Arko FR, et al. Clinical and economic evaluation of the Trellis thrombectomy device for arterial occlusions: preliminary analysis. *J Vasc Surg.* 2004;39:556-559.
18. Kasirajan K, Ramaiah VG, Diethrich EB. The Trellis thrombectomy system in the treatment of acute limb ischemia. *J Endovasc Ther.* 2003;10:317-321.
19. Vena RF, Benetti F, Vrsalovic F, et al. Percutaneous infusion system for in situ thrombolysis in the abdominal aorta and iliac arteries. *J Endovasc Ther.* 2002;9:932-935.
20. Hanna EB, Gupta R, Hennebry TA. Use of trellis thrombectomy system in acute aortofemoral graft occlusion. *Catheter Cardiovasc Interv.* 2010;75:838-842.
21. Hennebry TA. Treatment of acute limb ischemia using isolated pharmaco-mechanical thrombolysis—the Trellis system. Oral abstract presented at: New Cardiovascular Horizons; June 2-5, 2010; New Orleans, LA.