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CLINICAL APPLICATIONS OF THROMBOLYTIC THERAPY FOR ARTERIAL AND GRAFT OCCLUSION

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BACKGROUND

Operative thromboembolectomy and bypass procedures are the standard methods of reconstruction for ischemic extremities. Although it is well accepted that thrombosis is the cause of bypass graft failure, it is not uniformly appreciated that thrombosis is the final common pathway causing ischemia due to chronic arterial occlusive disease. Intra-arterial catheter-directed thrombolysis has been used to restore perfusion to occluded native arteries and bypass grafts and allow arteriographic evaluation and correction of the culprit lesion.

Our understanding of arterial and graft occlusion, coupled with advances in techniques of operative and catheter-based therapy, allows the informed physician to evaluate individual patients and develop a treatment strategy appropriate to the problem at hand. Operative and catheter-based techniques should no longer be viewed as competitive ("either-or") treatment modalities. Rather, the advantages of both can be offered and, we hope, the disadvantages of each recognized and minimized.

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The first attempt at regional delivery of thrombolytic agents was made over 30 years ago; however, only during the 1980s did catheter-directed thrombolysis become a commonly accepted therapeutic alternative.* The therapy has evolved and improved because of growing interest in fibrinolytic agents, improved understanding of the technique of delivery, and continuing technical advances on the part of treating physicians and catheter delivery systems. Techniques for the intra-arterial delivery of lytic agents have been refined to the point where arterial occlusion can be assessed at the time of arteriography to predict the likelihood of clot lysis and ensure the most efficient delivery of the lytic agent to the occluding thrombus.[23]

The basic principle underlying catheter-directed thrombolytic therapy is the activation of fibrin-bound plasminogen.[1] The fibrin bond of the plasminogen contained within the thrombus makes the plasminogen molecule particularly susceptible to activation by the delivered plasminogen activator. The goal of regional clot dissolution without a systemic fibrinolytic response generally can be achieved only with a short duration of a regional infusion. Although intravenous infusion for acute arterial occlusion has been suggested, it is minimally effective and usually not recommended because the plasminogen activator delivered intravenously would have minimal surface contact with the occluding thrombus. The potential for effective thrombus dissolution in this setting is minimal.

When fibrin-bound plasminogen is activated, a high concentration of plasmin is generated within the thrombus. Intrathrombus infusion protects the plasminogen activator and plasmin from circulating inhibitors. If systemic activation of plasminogen occurs, breakdown of fibrinogen, clotting factors, and other plasma proteins follows.

Several major categories of pharmacologic plasminogen activators are available for thrombolytic therapy. These plasminogen activators have evolved from relatively impure and highly antigenic substances to pure, less antigenic, and increasingly fibrin-specific agents.[18] Whether a high degree of fibrin selectivity is advantageous in patients receiving catheter-directed thrombolysis has not been proved.

The most commonly used plasminogen activators are streptokinase (SK), urokinase (UK), recombinant tissue plasminogen activator (rt-PA), prourokinase (proUK) (single-chain UK plasminogen activator), and acylated SK.

Streptokinase

Streptokinase was first discovered in 1933 and was the first thrombolytic agent approved for clinical use.[70] It is a protein containing 415 amino acids and has a molecular weight of 437 daltons. SK is produced by group C β-hemolytic streptococci.[46] SK alone is incapable of con-

*References 4–7, 17, 21, 25–31, 41–44, 50–54, 56, 60, 65, 71–76, 79

verting plasminogen to plasmin directly and is not an enzyme. SK activates plasminogen by forming a 1:1 complex with human plasminogen. The SK-plasminogen complex formed causes a conformational change of the plasminogen molecule that exposes the active site. The SK-plasminogen complex can then convert other plasminogen molecules to plasmin.

Streptokinase has many systemic effects on the coagulation system. Circulating levels of plasminogen and fibrinogen are markedly decreased during SK therapy. An increase in fibrin split products occurs as a result of accelerated breakdown of fibrinogen. Plasmin causes a reduction in clotting factors V and VIII. These reductions alter normal hemostasis and explain the hemorrhagic complications. Effective SK therapy usually results in a plasminolytic state that includes a decrease in plasma plasminogen, a decrease in whole blood clotting time, a decrease in fibrinogen, and the appearance of serum fibrin and fibrinogen degradation products with a slower coagulation time.

Streptokinase is an effective thrombolytic agent but has a number of disadvantages. It is rapidly cleared from the plasma and requires the presence of a cofactor plasminogen for its activation. It is highly antigenic and has significant systemic fibrinolytic effects, even delivered intra-arterially.[18]

Urokinase

Urokinase is a human plasminogen activator produced by the kidney.[47, 78] It is generally accepted that UK is a double-chain polypeptide with a molecular weight of 54,000 to 57,000 daltons; however, several investigators contend that UK could exist in several molecular weights of approximately 22,000, 33,000, and 54,000 daltons. The complete primary amino acid sequence of UK has been determined.[33] Plasmin and kallikrein cleave proUK at position 156, which then produces UK in its two-chain form. The two chains are held together by a disulfide bond important to the enzyme's fibrinolytic activity.

Urokinase was originally extracted from human urine and required enormous amounts of urine; for example, 1500 L are required to produce enough enzyme to treat one patient. The tissue culture techniques of Bernik and Kwaan demonstrated that improved production of UK could be achieved, and the best fibrinolytic activity is obtained using cells taken from 26- to 32-week-old fetuses.[8] UK is now produced by cultured human fetal kidney cells.

Urokinase converts the inactive forms of plasminogen to plasmin with a greater affinity for the fibrin-bound lysplasminogen. This conversion is due to the cleavage of a single amino acid bond (arginine 560–valine 561).[63] Activation of fibrin-bound plasminogen allows fibrinolysis to occur in a relatively inhibitor-free environment because there are no competing substrates for fibrin-bound plasmin.

Urokinase is rapidly cleared by the liver, and 3% to 5% is cleared

by the kidneys. Its half-life is about 16 minutes but might be prolonged in patients with hepatic dysfunction.

Although UK induces clotting defects that persist after discontinuation of the drug's infusion (similar to those mentioned for SK), coagulation variables do not deteriorate as much and normalize more rapidly with UK than with SK.[16] Because of its increased production costs, the price of UK is five to eight times that of SK for the treatment of an individual patient.

Tissue Plasminogen Activator

When t-PA was able to be extracted from human vascular endothelium, fibrin-specific plasminogen activators became possible.[2, 18] The endothelial extract was found to induce highly specific clot lysis compared with SK or UK.[35]

Tissue plasminogen activator is a single-chain polypeptide serine protease with a molecular weight of approximately 68,000 daltons. It was first extracted from Bowes melanoma cells and other mammalian tissue but is now prepared by recombinant DNA techniques. The principal site of in vivo synthesis is the endothelial cell.

Structurally, t-PA exists as a single chain easily converted to a double chain by cleavage of the peptide bond arginine 275–isoleucine 276. In the absence of fibrin, t-PA is a weak activator of plasminogen. The presence of fibrin causes a 500- to 1000-fold increase in activation.[39] This effect is a result of specific binding of t-PA with fibrin and plasminogen with fibrin. The half-life of t-PA is 2 to 6 minutes owing to binding by the rapid t-PA inhibitors and clearance by the liver. The agent exists in plasma in a free state and complexed with plasma serine proteinase inhibitors.

Tissue plasminogen activator is fibrin specific and can induce thrombolysis without causing systemic lytic effects.[13, 45] Local or regional infusions also cause more effective lysis than systemic infusion.[13] Early use of t-PA in acute myocardial infarction from acute coronary thrombosis likewise resulted in high thrombolytic rates without systemic fibrinogenolytic effects.

With the development of recombinant DNA technology, larger quantities of t-PA could be produced from *Escherichia coli* cells. The properties of rt-PA are similar to those of t-PA derived from melanoma cell lines. Recombinant t-PA has been evaluated extensively in clinical trials for myocardial infarction, with lesser enthusiasm for acute stroke, pulmonary embolus, and arterial and graft occlusion.

Prourokinase

In 1979, a single-chain precursor to high-molecular-weight UK, named proUK, was isolated from urine.[40] Because of its configuration, it is also called single-chain UK plasminogen activator (scu-PA).

Prourokinase has been identified in human plasma, cultures of endothelial cells, explants of fetal organs, and various malignant cell lines.[34] This proenzyme is derived from human urine or genetically manipulated *E. coli* and has a molecular weight of about 54,000 daltons.

Prourokinase is converted to high-molecular-weight UK by hydrolysis of the lysine 158–isoleucine 159 peptide bond. The cleavage converts proUK into its two-chain structure and increases its activity 500- to 1000-fold.[37] proUK differs from UK in several ways—mainly its higher fibrin affinity, lower specific activity, and stability in plasma. In vitro, proUK is nonreactive due to circulating competitive inhibitors. Because of these inhibitors, proUK has several hundred–fold higher plasminogen activating power than plasmin. The fibrin specificity of proUK does not depend on actual fibrin binding as does that of t-PA; thus, the method of clot lysis of the two agents differs.[37]

Studies in which proUK was used in rabbits, dogs, and baboons demonstrated fibrin-selective clot lysis without fibrinogenolytic effects or hemorrhagic complications.[4–9] Testing in dogs also showed that, although proUK had superior fibrin specificity, it was equal to UK in efficacy.[14]

The agent was first used in humans to treat acute myocardial infarction. A pilot study followed a multicenter study of acute myocardial infarction that demonstrated a reperfusion rate of 60% in patients with proven coronary artery thrombosis. The dose given was 50 mg of proUK, and mean time to lysis was about 55 minutes. Increasing the dose to 70 to 80 mg increased reperfusion to almost 70%; however, time to lysis was prolonged and several patients developed fibrinogenolysis.[34] No hemorrhagic effects were noted. Combining UK with proUK, as well as t-PA and proUK, produces a synergistic response because of complementary mechanisms of action.[36]

Acylated Plasminogen–Streptokinase Activator Complex

Streptokinase has significant fibrinogenolytic effects reflecting the wide-ranging proteolysis resulting from its use. Modifying its molecular structure by adding an acyl group produced a more efficient agent with greater fibrin specificity. Furthermore, the acyl group blocked the binding site of antistreptococcal antibodies, thereby eliminating its inactivation in plasma by circulating inhibitors.[49, 66] The acylated SK molecule is essentially inert and does not activate plasminogen to plasmin in vitro; however, in clinics, APSAC has been observed to behave similarly to SK.

INTRA-ARTERIAL THROMBOLYTIC THERAPY

Objectives

The primary objectives of the infusion of the fibrinolytic agent are to dissolve the occluding thrombus, restore perfusion, and allow

evaluation of the underlying cause of the arterial or graft thrombosis. Additional advantages of thrombolytic therapy include the following:

1. Convert an urgent surgical procedure into an elective procedure.
2. Gain patency of an occluded but nondiseased inflow source for subsequent bypass.
3. Lyse thrombi in the distal vasculature, thereby regaining patency of the outflow tract.
4. Convert a major vascular reconstruction into a limited, less extensive procedure.
5. Prevent arterial intimal injury from balloon catheter thrombectomy.
6. Restore the patency of branch vessels inaccessible to mechanical thrombectomy.
7. Reduce the extent of amputation in patients in whom complete success (limb salvage) cannot be achieved.

Although these are admirable goals, the likelihood of achieving them depends on a precise understanding of the patient's underlying disease, knowledge of the risks and benefits of alternative therapeutic options, and a familiarity with the techniques and potential complications of intra-arterial thrombolytic therapy.

Patient Selection

Proper selection of the appropriate patients is critical to successful therapy. If one determines that elimination of the occluding thrombus will benefit the patient, the first step in patient selection is accomplished. We now know that long segments of the vascular tree can be obliterated by acute thrombus precipitated by severe but relatively segmental atherosclerotic disease. Also, failure of a bypass graft is often due to a segmental pathologic condition, either anastomotic or within the graft, with the remainder of the graft being a potentially well-functioning conduit. This is particularly true for bypass grafts functioning for 1 year or more before thrombosis. In these clinical scenarios, the ability to eliminate the thrombus and identify and correct the segmental disorder is an important advantage of fibrinolytic therapy.

Patients diagnosed with clear-cut acute embolic occlusion of large arteries easily accessible by a limited incision under local or regional anesthesia can be treated quickly and efficiently with standard operative embolectomy. Intra-arterial fibrinolytic therapy is an adjunct to what can be achieved operatively; some patients should not be offered fibrinolytic therapy, either because risk of complications is excessively high or because the operative alternative is more efficient. Patients who are good candidates for lytic therapy are contrasted with those who are less favorable candidates in Table 1.

Patients with thrombosis of a bypass graft in the postoperative period should not be treated with intra-arterial thrombolysis for several

Table 1. FACTORS PREDICTIVE OF THE SUCCESS OF CATHETER-DIRECTED INTRA-ARTERIAL THROMBOSIS

Factor	Likelihood of Successful Lysis	
	High	Low
Guidewire	Passes into clot	Cannot pass
Duration of occlusion	Short (hours or days)	Long (weeks)
Location of occlusion	Proximal	Distal
Distal vessels (by arteriogram)	Visualized	Not visualized
Distal Doppler signals	Audible	None
Relative contraindications	None/few	Some/many

reasons. Early postoperative thrombosis usually represents a technical error or poor patient selection for the revascularization procedure. For the former problem, operative thrombectomy with concurrent correction of the technical problem is recommended. For the latter situation, recurrent thrombosis is certain after mechanical or pharmacologic thrombectomy, and the limits of revascularization should be accepted.

Patients who have thrombosed knitted Dacron grafts treated with lytic agents have an increased risk of transgraft hemorrhage.[23] Transgraft extravasation does not appear to be a problem with grafts having an external covering or through woven Dacron or polytetrafluorethylene (PTFE) grafts. The presence of a knitted Dacron graft in a central location is a strong relative contraindication to lytic therapy.

Patients with modest ischemia who have tolerable intermittent claudication are not offered arteriography or operative intervention. This group of patients should not be offered intra-arterial lytic therapy for the same reason bypass procedures are not considered, because the natural history of their disease is favorable. Although the likelihood of early success with any intervention in claudicants is high, finite complication and amputation rates exist, and each patient should be fully aware of such risks and participate in sharing the responsibility for the choice of treatment. The attitude of "let's treat the lesion and see what happens because we have nothing to lose" should be avoided.

Patients who have acute thrombosis of a proximal artery causing significant ischemia are considered candidates for thrombolysis, assuming no contraindications to therapy exist. Patients who have acute thrombosis of a popliteal aneurysm causing profound ischemia are also good candidates for lytic therapy.[68] This severe degree of ischemia occurs more frequently when the popliteal trifurcation is involved. Emergent operative reconstruction in these patients is associated with an excessive amputation rate.[10] Re-establishing patency of infrapopliteal vessels by the regional delivery of a fibrinolytic agent eliminates the severe ischemia, frequently opens the occluded outflow tract, and allows an elective operation. This approach increases the chance of limb salvage and successful aneurysm repair. If the patient has thrombosis of a popliteal

aneurysm but the limb is not threatened, vascular reconstruction (if indicated) should be planned without prior thrombolysis.

Patients with acute occlusion of a saphenous vein bypass, either in situ or reversed, can have their graft salvaged by intragraft infusion by fibrinolytic agents.[67] Operative thrombectomy is associated with poor long-term results.[32] Thrombosed femorotibial grafts likewise carry a high operative failure rate, as does any bypass in which the runoff vessels are involved. Patients who have undergone multiple previous reconstructive procedures with acute thrombosis are at high risk for an unsuccessful operative reconstruction. Numerous reasons exist for graft failure in such patients, and it is often difficult to define accurately the cause and perform appropriate correction at the time of emergency thrombectomy.

Patients who have acute embolic occlusion of vessels inaccessible to mechanical thrombectomy, and those with wound complications in whom another wound would carry significant morbidity, should be considered potential candidates for intra-arterial fibrinolytic therapy.

Technique

To ensure a more favorable outcome, intra-arterial lytic therapy should be considered as a treatment alternative before angiography. The approach is usually from the contralateral femoral artery, threading the catheter around the aortic bifurcation. Vessels considered for thrombolysis should have an attempt at guide wire penetration of the occlusion. If a guide wire can be passed well into or through the thrombus, successful thrombolysis is likely. If a guide wire cannot be passed through the occlusion, either atherosclerotic disease, neointimal fibroplasia, or highly organized and calcified thrombus is present that will not respond to a lytic agent; therefore, primary operative reconstruction is generally recommended.

If guide wire passage is successful, the infusion catheter should be embedded well into the occluded vessel. After catheters are positioned appropriately, either UK or rt-PA is the recommended agent. Our prior experience with SK resulted in an unacceptably high rate of bleeding complications. The initial dose of UK is usually a 500,000-unit bolus followed by 4000 units/min until recanalization is achieved, at which point the dose can be reduced to 1000 to 2000 units/min. If rt-PA is chosen, a dose of 0.05 mg/kg/h is used for a period of up to 12 h. These generic recommendations can be modified by using higher dosages if more rapid lysis is required. Patients are given broad-spectrum antibiotics intravenously while the catheter is in place. Routine blood studies are performed before and during treatment and include a complete coagulation profile. A guaiac test on a stool specimen is performed before treatment for documentation. All patients remain at absolute bedrest, most of them in the Intensive Care Unit. Puncture sites are observed frequently, and the circulatory status of the infused extremity is clinically monitored and ankle pressures measured when either improvement or deterioration is observed.

Periodic arteriography is performed to follow the therapeutic response and guide positioning of the catheter. The initial 2 to 4 h of infusion is generally performed in the radiology suite. Catheters are then advanced into the thrombus as required, realizing that inappropriate catheter position frequently leads to failure.

If one is confronted with multisegment occlusion and infusion guide wires can be advanced into the distal segment, infusion of lytic agents is performed through a coaxial system. The dose of the lytic agent is then split between the catheters, with relatively higher doses delivered to the distal occlusion.

The concurrent administration of heparin with SK has been associated with excessively high hemorrhagic complication rates. The severity of bleeding complications by infusing heparin during UK administration has not been similarly observed; however, most agree that the concurrent use of heparin with all thrombolytic agents tends to increase the risk of bleeding. Heparin is used to reduce the risk of pericatheter thrombosis. If a catheter is placed into a long static arterial segment or if the catheter traverses a high-grade stenosis to reach the occluding thrombus, higher doses of heparin are given to achieve adequate anticoagulation.

The systemic lytic effect is evaluated by monitoring the fibrinogen level, prothrombin time, partial thromboplastin time, and fibrin degradation products during infusion. Although bleeding can occur in any patient receiving lytic therapy, those with significant hypofibrinogenemia appear to be at greatest risk of a serious hemorrhagic complication. If the fibrinogen level is below 100 mg/dL, the infusion is slowed or stopped to allow the restoration of circulating fibrinogen and clotting factors. On rare occasions, fresh frozen plasma or cryoprecipitate can be given.

After successful infusion, an arteriogram is performed and blood studies are repeated. The catheter is removed when the fibrinogen level is 100 mg/dL. After successful lysis, the underlying cause of the occlusion should be identified and corrected immediately by means of standard intervention techniques. If percutaneous correction is not possible, systemic anticoagulation is continued until the definitive operative procedure is completed.

The technique selected to repair the underlying lesion may have substantial impact on long-term success. In general, operative repair is more durable than percutaneous techniques. This has been demonstrated by several studies evaluating the threatened femoropopliteal/tibial saphenous vein bypass graft (Table 2).[3, 12, 59] Because neointimal fibroplasia is important in the development of prosthetic graft failure, operative revision is recommended.

Intraoperative Intra-arterial Thrombolytic Therapy

The goal of intraoperative intra-arterial thrombolytic therapy is to deliver a plasminogen activator at a high concentration to the thrombus,

Table 2. THE THREATENED FEMOROPOPLITEAL/TIBIAL AUTOGENOUS BYPASS: COMPARISON OF DURABILITY OF TECHNIQUES OF GRAFT REVISION

Author	Five-Year Durability	
	Balloon Dilation	Operative Revision
Bandyk et al, 1991[3]	50% (9/18)	86% (55/64)
Perler et al, 1990[59]	22% (4/18)*	62% (5/19)
Cohen et al, 1985[12]	43% (3/7)	82% (18/22)

*Three-year durability

thereby providing regional thrombolysis with minimal effects on plasma fibrinogen or clotting factors and with a low risk of bleeding complications.

An early report on the use of intraoperative SK dampened the enthusiasm of many surgeons for intraoperative thrombolysis. Cohen and colleagues[12] treated 12 patients with SK in doses from 25,000 to 250,000 IU using a repeated bolus technique over 30 to 150 minutes of inflow occlusion. A 42% mortality rate was reported, and 42% of the patients suffered bleeding complications. It is likely in this early study that patient selection, choice of lytic agent, and method of infusion contributed to the high complication rate.

Norem and colleagues[55] found that after balloon catheter thromboembolectomy, additional thrombus can be retrieved following intraoperative infusion of SK. In 19 patients having thromboembolectomy for acute arterial ischemia, intra-arterial SK was infused in the operating room. After a relatively short waiting period, repeat balloon catheter thrombectomy retrieved additional thrombus, and all patients demonstrated angiographic improvement. Similar findings occurred with the use of intraoperative UK infusion.

Comerota and Rao[19] performed a prospective, randomized, blinded, and placebo-controlled study to evaluate the regional and systemic effects on plasma fibrinogen and the fibrinolytic system of intraoperative intra-arterial UK infusion, and whether a dose-response relationship exists. Safety issues were also specifically addressed.

One hundred and thirty-four patients were prospectively randomized to receive one of three doses of UK infusion or a saline placebo infusion into the distal arterial circulation during routine infrainguinal lower-extremity revascularization for chronic limb ischemia. The results indicated that up to 500,000 units of UK given as a bolus infusion into the distal circulation produced no significant fibrinogen breakdown compared with the placebo. A dose-related increase in plasma fibrinogen degradation products and in plasma D-dimer was reported. No increase in operative blood loss, blood replaced, or wound hematoma occurred. Interestingly, an unexpected reduction was reported in the UK group compared with the placebo group ($P = 0.033$).

Table 3. COMPLICATIONS OF INTRA-ARTERIAL LYTIC THERAPY

Drug-associated complications	**Technique-associated complications**
Hemorrhage	Pericatheter thrombosis
Due to lysis of hemostatic fibrin	Catheter-induced thrombosis
Due to the reduced coagulopathy	Toxic complications of contrast
Distal emboli	Pseudoaneurysm of puncture site
Allergic reaction	Arteriogram complication
Pyretic reaction	
Serum sickness (SK)	
Transgraft extravasation (hemorrhage)	

COMPLICATIONS OF THROMBOLYTIC THERAPY

Complications encountered with catheter-directed delivery of thrombolytic agents can be categorized as those secondary to the drug and its subsequent effects on the fibrinolytic and coagulation system and those mechanical (arteriographic) complications associated with the technique (Table 3).

Allergic Reactions

Because bacteria are the source of SK, a foreign protein from the cell wall of the bacteria accounts for the allergic and pyretic side effects observed in up to 30% of the patients. If SK infusion is anticipated, pretreatment with 100 mg of hydrocortisone and administration of acetaminophen every 6 hours reduces the allergic response. Allergic reactions are rare with UK, so pretreatment with steroids is unnecessary. Some patients have developed low-grade fevers with UK infusion and are treated with oral acetaminophen.

Hemorrhage

Bleeding is the most common and most feared complication of thrombolytic therapy. Bleeding usually occurs as a result of the active lytic state resulting from dissolution of "hemostatis" thrombus but can also be due to the induced coagulopathy (fibrinogen and clotting factor depletion) caused by the lytic agent used. It was often difficult to distinguish the incidence of major bleeding complications from less serious bleeding complications in many reports. Major bleeding complications should be defined as those that cause permanent disability, prolong hospital stay, or require blood transfusions.

Patients who have major invasive procedures, especially arterial cannulation, have higher rates of bleeding complications than those who do not, which has been observed in myocardial infarction trials in which patients with arterial interventions had a 30% bleeding complication rate

compared with 5% or less in those without.[24] Intracerebral bleeding is the most dreaded of all hemorrhagic events, and its incidence is probably an inescapable 1% to 2%. Data have been gathered from several myocardial infarction trials that demonstrate the risk of intracerebral bleeding is increased by age, hypertension, low body weight, coincident head injury, previous cerebrovascular accident, and previous warfarin anticoagulation.[24]

The mechanisms for bleeding during thrombolytic therapy can be characterized as (1) lysis of hemostatic thrombi, (2) consequences of clotting factor and fibrinogen depletion, and (3) continued anticoagulation. Most of the bleeding during the infusion of the lytic agents was not caused by biochemical changes created by the lytic agents, but rather by the lysis of hemostatic clot. Patients treated with lytic agents who have complete vascular integrity have a smooth therapeutic course, without bleeding complications.

Most bleeding occurs as a result of the trauma of invasive diagnostic or therapeutic procedures. By definition, invasive procedures are required for catheter-directed thrombolysis; therefore, an unavoidable minimal number of bleeding complications occur. However, if lytic therapy is anticipated before diagnostic arteriography, the appropriate entry site can be chosen using a single wall puncture technique, permitting appropriate catheter or sheath placement with minimal or additional trauma.

The purpose of laboratory monitoring of thrombolytic therapy is to accurately document that the thrombolytic agent chosen is effectively producing a lytic state. However, although this is a necessary part of systemic thrombolysis, the efficacy of catheter-directed thrombolysis is evaluated clinically and angiographically and does not depend on laboratory markers of systemic fibrinolysis. In general, laboratory values do not correlate with hemorrhagic complications or efficacy of lysis.

It has been found that the importance of fibrinogen depletion, as stressed early in the clinical experience with thrombolysis, was probably overrated. Subsequent analyses have demonstrated that no correlation existed with bleeding complications.[48] However, the majority of these observations were made in patients treated for venous thromboembolism or acute myocardial infarction. On the other hand, the clinical experience with catheter-directed thrombolysis for peripheral arterial and graft occlusion suggested that fibrinogen depletion was linked to the incidence of serious bleeding complications. A number of factors are relevant to these observations:

1. Patients treated for peripheral arterial or graft occlusion require arterial puncture and prolonged cannulation.
2. The duration of therapy extends far beyond that needed for myocardial infarction and may exceed that required for venous thromboembolism.
3. The fibrinogen concentration measured may detect hemostatically ineffective fibrinogen.[62]
4. Certain patients with low fibrinogen concentrations (those treated

with thrombolytic agents and those with hereditary afibrinogenemias) do not uniformly have hemorrhagic complications.[64]

5. The fibrinogen associated with platelets may be as important hemostatically as circulating fibrinogen.[15]

Transgraft Extravasation

Extravasation of contrast material and blood has been reported in patients treated with SK or UK who have prostheses in place.[38, 61] Extravasation has been observed mostly through knitted Dacron grafts. The larger mesh of the knitted graft is the likely explanation for this observation. Plasmin lyses the fibrin seal of the graft, which opens the interstices, allowing subsequent extravasation of dye and blood. Reports of extravasation from grafts in place for more than 1 year indicate that the fibrin meshwork is continually susceptible to lysis despite a long graft implant time. Therefore, patients with knitted prostheses have a major added hemorrhagic potential when treated with lytic agents. In our opinion, these patients may be considered to have a relative contraindication to thrombolytic therapy. In the event of a knitted prosthesis in a central location (chest or abdomen), if hemorrhage occurs it can be life threatening; therefore, alternative therapy is suggested. Because many patients with aortic aneurysmal and occlusive disease subsequently suffer myocardial infarction and because high-dose fibrinolytic therapy can benefit many patients with myocardial infarction, we suggest that knitted Dacron grafts not be used in the chest or abdomen.

Distal Emboli

Embolic complications distal to the occluded artery or graft can occur during intra-arterial thrombolysis—usually the result of either partial lysis of thrombus—with fragments carried distally during reperfusion or, less frequently, a mechanical complication due to catheter manipulation or volume of infusate.

In our experience, distal embolic occlusion is observed infrequently during treatment of thrombosed native arteries or saphenous vein grafts. It has been observed occasionally during treatment of acute arterial emboli and more frequently during treatment of thrombosed PTFE grafts with patent runoff vessels.

Appropriate treatment of distal emboli that occur during catheter-directed thrombolysis is catheter advancement and continued infusion, perhaps at a higher dose. Although this tends to lyse distal emboli, occasionally, occlusions of the smaller arteries are resistant to lysis. If lysis does not occur in the presence of progressive ischemia, the risk of irreversible ischemic damage escalates rapidly, and clinical judgment as to the appropriate treatment can be difficult.

Technical Complications

Technique-related complications are those associated with arteriography and catheter placement. Intimal dissection, thrombosis, allergic and toxic reactions to contrast agents, and femoral neuropathy have been reported.

In terms of pericatheter thrombosis, it should be noted that whenever the catheter passes through a stenosis to treat an occlusion, the risk of thrombosis increases and concurrent anticoagulation should be given. Repeat arteriography may lead to a large contrast dye load and subsequent renal failure.

REVIEW OF RANDOMIZED TRIALS

The efficacy and safety of thrombolytic therapy for arterial and bypass graft occlusion have been studied in a number of well-performed, prospective randomized trials. Patient selection has varied somewhat and endpoint analysis has not been consistent; therefore, the reader must examine these studies carefully to determine the appropriate application to individual clinical scenarios.

Berridge and colleagues[9] addressed the important issue of systemic thrombolysis versus catheter-directed thrombolysis for acute arterial occlusion while at the same time investigating whether catheter-directed SK was equivalent to catheter-directed t-PA. The results of this study indicated that catheter-directed thrombolysis was significantly more effective than systemic thrombolysis for acute arterial thrombotic and embolic occlusion, and that catheter-directed t-PA was more effective than catheter-directed SK.

Ouriel and associates[57] performed a prospective randomized study to evaluate the efficacy and safety of intra-arterial catheter-directed UK for acute limb ischemia (< 7 days) compared with a standard operative revascularization. One hundred and fourteen patients who had acute limb ischemia of less than 7 days' duration were randomized to either catheter-directed UK infusion or surgical revascularization. Patients enrolled in this study included those with embolic and thrombotic occlusion, as well as native arterial occlusion and bypass graft occlusion (autogenous bypass and prosthetic bypass grafts). Seventy percent of the patients randomized to catheter-directed UK achieved arteriographically successful thrombolysis. An underlying lesion responsible for the arterial or graft occlusion was identified in only 37%, and each patient had a correction of the underlying lesion by percutaneous balloon dilation or operative revision. The cumulative limb salvage was similar for the two treatment groups (82% at 12 months); however, the cumulative survival rate was improved significantly in patients randomized to thrombolysis (84% versus 58% at 12 months, $P = 0.01$).

Interestingly, no difference was noted in limb salvage in those patients with acute limb ischemia who were treated; however, a signifi-

Table 4. MORTALITY REDUCTION ASSOCIATED WITH ARTERIAL UROKINASE IN TWO PROSPECTIVE RANDOMIZED STUDIES

Author	Number of Patients	Method	Mortality*
Ouriel et al, 1994[57]	114	Percutaneous catheter-directed	16% vs 42% ($P < 0.02$)
Comerota et al, 1993[20]	134	Intraoperative	2% vs 12% ($P = 0.034$)

*Incidental observation—not a primary endpoint

cant reduction in mortality occurred in those randomized to thrombolysis, similar to the observation mentioned previously in the intraoperative UK study (Table 4).[3] Although the authors attributed the high mortality in the surgical group to in-hospital cardiopulmonary complications as a consequence of the operative procedure, there may be other beneficial effects of lytic therapy that were not readily apparent.

The first large prospective randomized multicenter trial evaluating catheter-directed thrombolysis versus surgical revascularization for the ischemic lower extremity was the surgery versus thrombolysis for ischemia of the lower extremity (STILE) trial.[69] The stated purpose of this trial was to evaluate the role of catheter-directed thrombolysis compared with routine operative revascularization in management of the spectrum of patients with nonembolic limb ischemia. This study was designed as all-inclusive of nonembolic limb ischemia and entered patients into the trial who had progression of ischemic symptoms within the prior 6 months. Randomization followed arteriographic documentation of obstruction of either a native artery or bypass graft. Patients were randomized to either rt-PA or UK infusion or operative revascularization. The primary endpoint was a composite clinical outcome consisting of death, amputation, ongoing or recurrent ischemia, or defined major morbidity. Results indicated that overall, lower-limb ischemia was treated more effectively with operative revascularization than with catheter-directed thrombolysis. However, when the outcome was stratified by duration of ischemia, it became apparent that acutely ischemic patients (< 14 days of ischemia) had a significantly better outcome when treated with catheter-directed thrombolysis than those randomized to operative revascularization.

Two large groups of patients treated in the STILE study were those with native arterial occlusion and those with occluded lower-extremity bypass grafts. It is important to separate these two groups because the treatment outcome may be different. Two separate publications reviewed the details of each.

Comerota and colleagues[20] reviewed the results of randomizing patients with occluded lower-extremity bypass grafts to catheter-directed thrombolysis versus operative revascularization. Interestingly, the average duration of graft occlusion was 34 days. Catheter placement proved to be a problem, in that 39% randomized to lysis failed to have the

catheter positioned properly and, therefore, reverted to surgical revascularization. However, following successful catheter placement, patency was restored in 84%, and overall, 42% had a major reduction in their planned operation. In these patients, 1-year results of successful lysis compared favorably with the best surgical procedure, which was new graft placement. Acutely ischemic patients (0 to 14 days) randomized to lysis showed a trend toward a lower major amputation rate at 30 days ($P = 0.07$) and significantly at 1 year ($P = 0.026$) compared with surgical patients. However, those with more than 14 days of ischemia showed no difference in limb salvage, but a higher ongoing recurrent ischemia rate in lytic patients ($P < 0.001$). Patients who had occluded prosthetic grafts had greater major morbidity than those with occluded autogenous grafts ($P < 0.02$) (Table 5).[22]

In an analysis evaluating surgical revascularization versus thrombolysis for nonembolic lower-extremity native artery occlusions, Weaver and co-workers[77] reviewed the results obtained in 237 patients with native artery occlusion who were prospectively randomized to either catheter-directed thrombolysis or surgical revascularization. The results indicated that 78% of the patients could have the catheter positioned properly and a lytic agent infused. This led to a reduction in the predetermined surgical procedure in 56% of the patients. Although lysis time was shorter with rt-PA than with UK (8 versus 24 hours; $P < 0.05$), no difference was seen in efficacy or safety. At one year, the incidence of recurrent ischemia and major amputation was increased in patients randomized to lysis. Of interest was the outcome in the diabetic cohort

Table 5. COMPOSITE CLINICAL OUTCOME AT ONE-YEAR SURGERY VERSUS THROMBOLYSIS BY DURATION OF ISCHEMIA (INTENT TO TREAT)[22]

	Surgery		Lysis		
	Number	Percent	Number	Percent	*P* Value
Duration of ischemia 0–14 days					
Count*	23		35		
Composite clinical outcome	17	74	27	77	0.780
Death	0	0	2	6	0.247
Major amputation	11	48	7	20	0.026
Ongoing/recurrent ischemia	14	61	23	66	0.709
Major morbidity	4	17	9	26	0.46
Duration of ischemia >14 days					
Count*	22		42		
Composite clinical outcome	10	46	34	81	0.0003
Death	0	0	3	7	0.202
Major amputation	3	14	7	17	0.753
Ongoing/recurrent ischemia	9	41	34	81	0.001
Major morbidity	3	14	8	19	0.588

*Duration of ischemia uncertain in two patients

From Comerota AJ, Weaver FA, Hoskins JD, et al: Results of a prospective randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. Am J Surg 172:105, 1996; with permission.

of patients who had infrainguinal occlusive disease. In those diabetics randomized to surgery, a 32% mortality rate was present at 1 year compared with a 7.5% mortality rate in diabetics randomized to catheter-directed thrombolysis (Tables 6 and 7).[22, 77]

The final, large, prospective, randomized multicenter trial to be published was that of Ouriel and colleagues. They reported the efficacy of three intra-arterial doses of recombinant UK (rUK) versus surgery in the initial treatment of limb-threatening lower-extremity arterial ischemia of 0 to 14 days' duration. Two hundred and thirteen patients were randomized to receive one of three doses of rUK versus surgical revascularization. The results indicated no difference in outcome with rUK surgical revascularization. Sixty-six percent of the patients randomized to rUK had successful thrombolysis. In the lytic group, a significant reduction was seen in the magnitude of the surgical procedure ultimately required in those patients. Overall, limb-salvage rates and patient survival rates were similar in the two groups.

Current Clinical Applications

All who have participated in randomized trials such as those described above appreciate that patients may meet entry criteria and be randomized, yet not represent the patient the experienced clinician would choose to treat initially with the method identified by randomization. Currently, patients with acute limb ischemia due to thrombosed lower-extremity bypass grafts are treated preferentially with catheter-directed thrombolysis. This is especially true if the graft has been functional for an extended period of time after insertion (Fig. 1). After a guide wire and catheter are positioned appropriately, one can anticipate a high likelihood of success. Critical to long-term benefit are the identification and correction of an underlying lesion that may lead to graft failure.

Acute embolic occlusion, especially if multiple vessels are involved, is well treated with catheter-directed thrombolysis. It has been our experience that embolic occlusions lyse relatively rapidly, and the infusion of UK did not cause additional embolic events. Acute native artery thrombosis can be treated successfully if a guide wire can be advanced through the occluded segment and if a catheter can be positioned appropriately (Fig. 2). One must use considerable clinical judgment, however, because long segments of diseased vessels ultimately require surgical intervention. It may not be prudent to subject the patient to prolonged lytic infusions if the final operation cannot be avoided.

Intraoperative intra-arterial infusions of UK and t-PA have been useful. We now routinely infuse lytic agents in the distal circulation in all patients when thrombus is removed. It has been shown that complete mechanical removal is the exception rather than the rule, and residual distal thrombolic material can undergo accelerated lysis with intraoperative intra-arterial infusions.

Text continued on page 670

Table 6. PER-PROTOCOL ANALYSIS: PATIENTS WHO RECEIVED RANDOMIZED TREATMENT, MAJOR AMPUTATION, OR DIED AT ONE-YEAR FOLLOW UP, BY INITIAL PATENCY[22]

	Ischemia 0–14 Days					Ischemia > 14 Days				
	Surgery		Lysis			Surgery		Lysis		
Outcome	Number	Percent	Number	Percent	*P* Value	Number	Percent	Number	Percent	*P* Value
Patent	13		22			19		16		
Death	0	0	0	0	0.99	0	0	3	19	0.09
Amputation	4	31	3	14	0.38	2	11	2	13	0.99
Not patent	6		4			1		13		
Death	0	0	1	25	0.40	0	0	0	0	—
Amputation	5	83	1	25	0.19	1	100	4	31	0.36
Overall	19		26			20		29		
Death	0	0	1	4	0.99	0	0	3	10	0.26
Amputation	9	47	4	15	0.05	3	15	6	21	0.72

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Table 7. CATHETER-DIRECTED THROMBOLYSIS VERSUS SURGERY FOR NATIVE ARTERY OCCLUSION: COMPOSITE CLINICAL OUTCOME AT 30 DAYS, 6 MONTHS, AND 1 YEAR (INTENT TO TREAT)[77]

	Surgery (n = 87)						Thrombolysis (n = 150)					
	30 Days		6 Months		1 Year		30 Days		6 Months		1 Year	
Event	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Count	87	—	87	—	87	—	150	—	150	—	150	—
Composite clinical outcome	29	33.3*	38	43.7*	43	49.4*	91	60.7	104	69.3	107	71.3
Death	7	8	11	12.6*	13	14.9	6	4.0	11	7.3	15	10.7
Major amputation	0	0	0	0	0	0	4	2.7	10	6.7	15	10.8
Ongoing ischemia	20	23*	26	29.9*	30	34.5*	79	52.7	94	62.7	96	64
Major morbidity	15	17.2	16	18.4	17	19.5	35	23.3	37	24.7	39	25.3

*$P < 0.05$; surgery versus thrombolysis

From Weaver FA, Comerota AJ, Youngblood M, et al: Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: Results of a prospective randomized trial. J Vasc Surg 24:513, 1996; with permission.

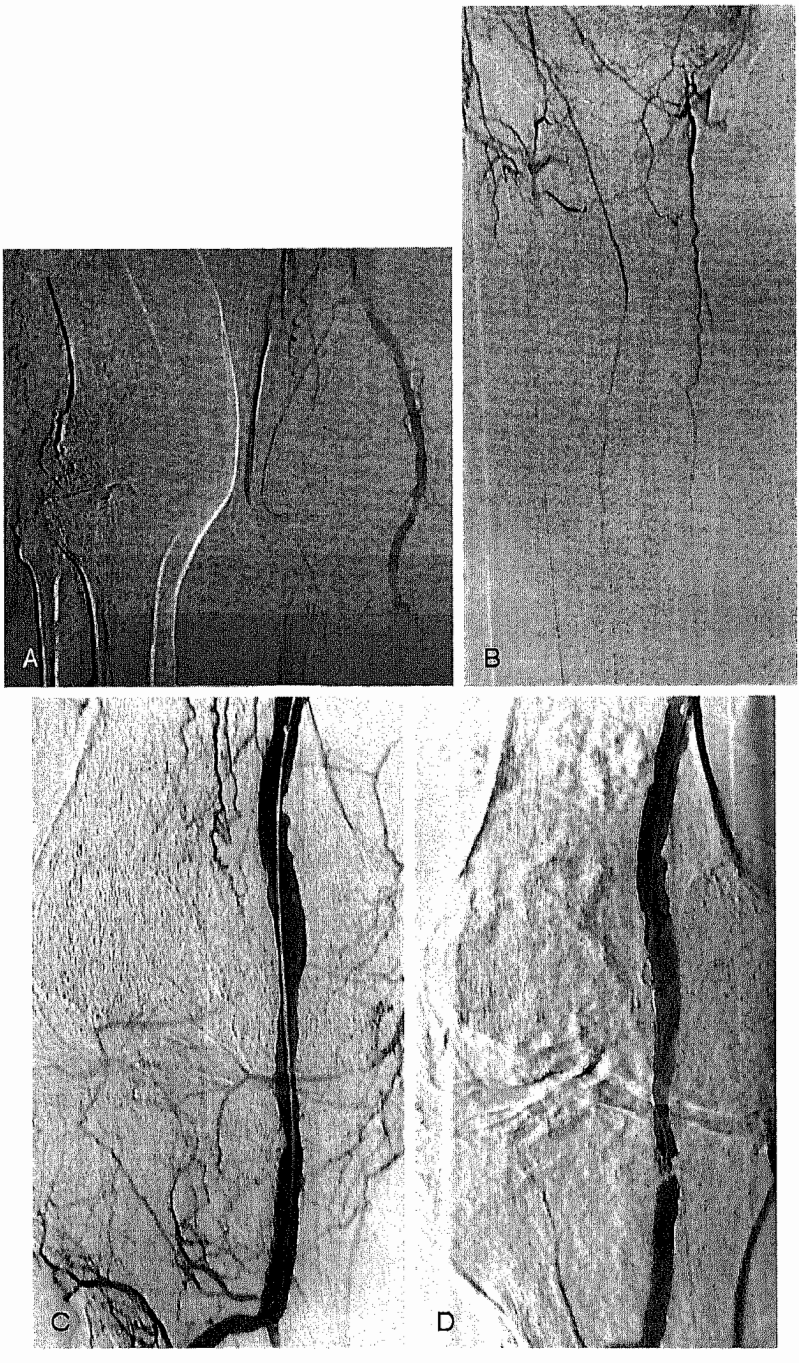

Figure 1. *See legend on opposite page*

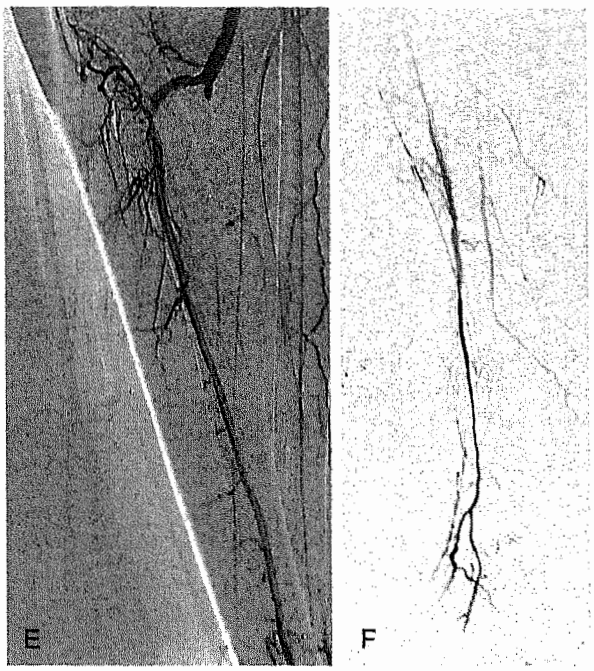

Figure 1. This case illustrates the utility of catheter-directed thrombolysis for acute, native artery thrombolysis. The patient is an 84-year-old man who was admitted to the hospital with a 5-day history of a cold, painful right foot. *A*, Arteriogram demonstrates occlusion of the right popliteal. *B*, Poor distal runoff with no named artery visible below the knee. *C*, The catheter was positioned proximal to the occlusion of the popliteal artery. After 24 hours of infusion of urokinase, the popliteal artery is open and a short focal stenosis is disclosed. *D*, Correction of the stenosis of the popliteal artery was achieved with balloon angioplasty. *E*, Patency was restored to the anterior tibial artery with continued runoff *(F)* into the foot.

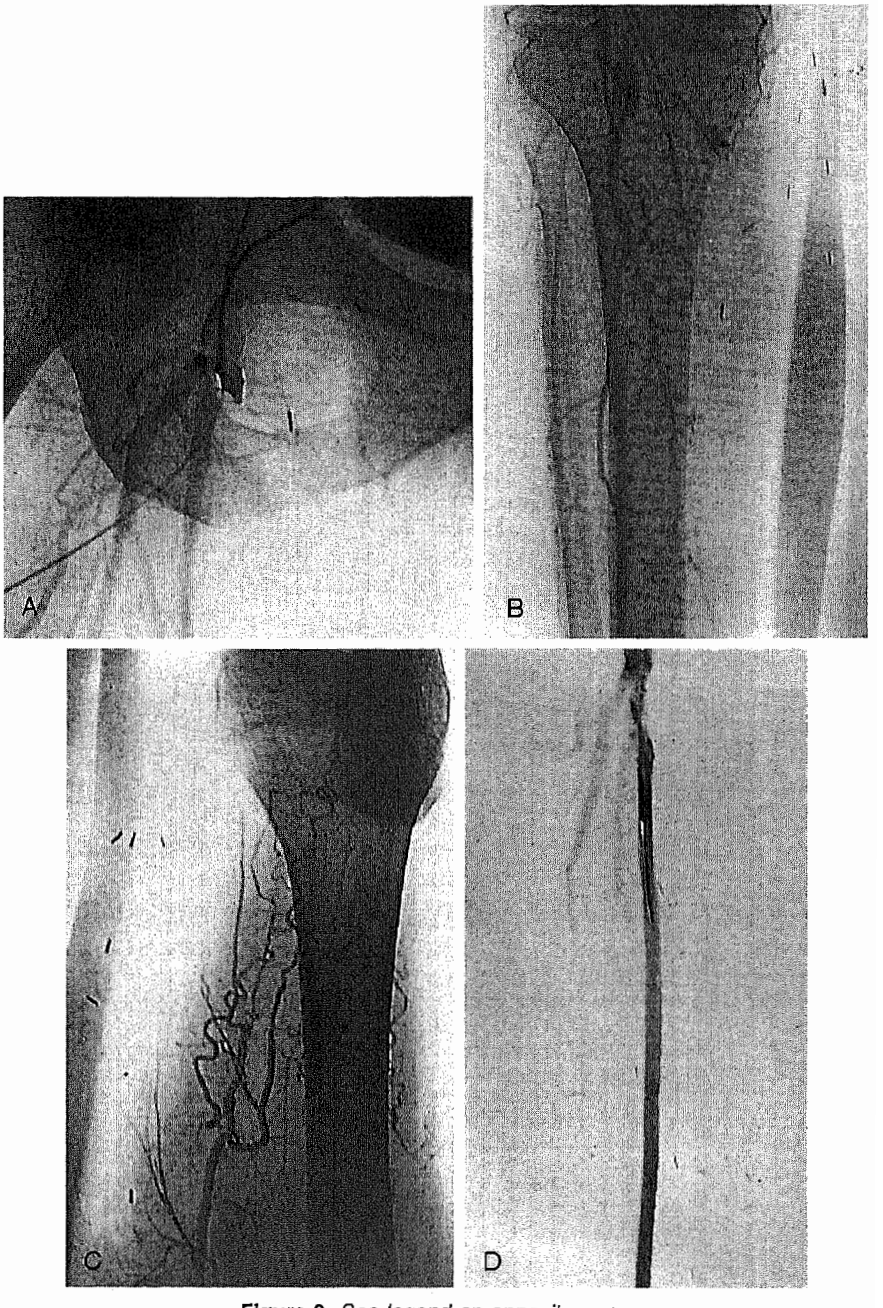

Figure 2. *See legend on opposite page*

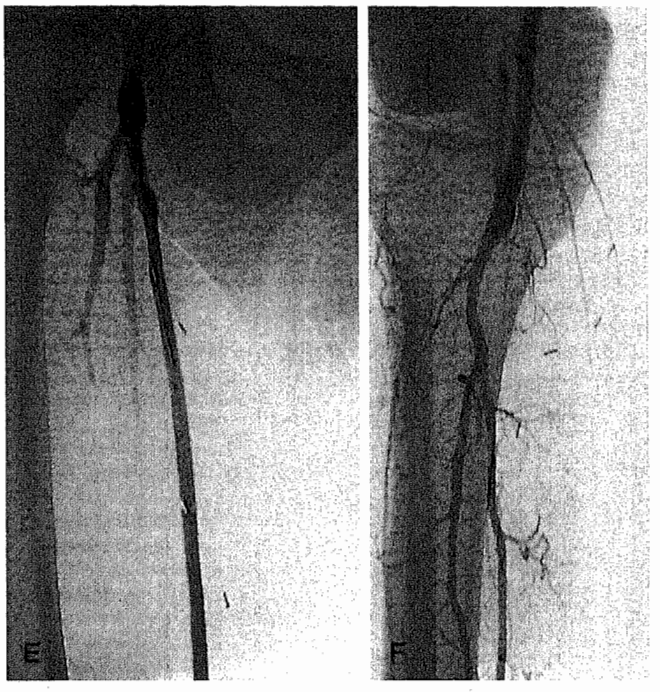

Figure 2. This case demonstrates the utility of regional delivery of thrombolytic therapy for occluded autogenous bypass grafts. The patient is a 65-year-old man who is 2½ years status post femoral-to-popliteal bypass graft with reversed saphenous vein. The patient presented with a 1-week history of pain and numbness in his right foot. *A*, The arteriogram demonstrates occlusion of the proximal vein graft. *B*, Arteriogram demonstrating distal anastomosis. *C*, Occlusion of the midportion of the graft. *D*, Catheter was positioned into the graft. The graft was laced with 250,000 units of urokinase. The catheter was positioned and infused with urokinase initially at 200,000 units/hour for 4 hours, then at 100,000 units/hour for 20 hours. Graft patency was restored; however, a stenosis is demonstrated at the proximal anastomosis. *E*, The stenosis in the proximal graft was corrected with balloon angioplasty. *F*, A completion arteriogram in the proximal graft demonstrates a normal caliber graft with good distal runoff.

SUMMARY

Catheter-directed thrombolysis and intraoperative intra-arterial thrombolysis are important adjuncts to how we care for patients with acute arterial and bypass graft occlusions. Of importance is that intra-arterial thrombolysis not be thought of as a competitor to operative revascularization, but rather as an adjunct to what can be accomplished, which enables the responsible physician to offer the best care for these patients.

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