

Thrombolysis in the Management of Lower Limb Peripheral Arterial Occlusion—A Consensus Document*

Working Party on Thrombolysis in the Management of Limb Ischemia†

The aim of this paper is to develop an intercontinental consensus on the use of thrombolytic therapy in occlusive peripheral arterial disease affecting lower limbs. A working party of self-designated angiologists, hematologists, interventional radiologists, and vascular surgeons of Europe and North America convened at 4 closed meetings. All published data known to any of the participants was entered into discussion. The working party discussed the topics outlined in this paper and a first draft was prepared in segments by members of the working party, discussed, and further revised into an interim report. It was then circulated to a number of Societies for their input. A final meeting of the Working Party together with delegates of the Societies collaborated on the definitive version of the text. The Party appreciates that in many areas the scientific evidence is not yet available. Nevertheless, it was felt that enough practical and scientific data were available to establish recommendations for clinical practice as well as for reporting results of thrombolytic therapy, which could be updated as later evidence became available. The guidelines apply only to drugs currently available for clinical use. The data are also considered to be sufficiently cogent that regulatory agencies should move to approve thrombolytic agents for intra-arterial therapy of acute lower extremity ischemia.

J Vasc Interv Radiol 2003; 7:S337–S349

DEFINITION AND OBJECTIVE OF THROMBOLYTIC TREATMENT

The principal objective of thrombolytic therapy is to remove pathologic thromboemboli and to facilitate restoration of vascular patency. In the con-

text of this paper, therapeutic thrombolysis is defined as enzymatically induced or accelerated thromboembolus dissolution. In most patients, thrombolysis is identified as an underlying lesion that subsequently requires endovascular or surgical treatment. There should be a multidisciplinary approach to thrombolytic therapy, which should involve angiologists, hematologists, interventional radiologists, and vascular surgeons (1).

End Points: It is imperative that the end points that define success or failure of thrombolytic therapeutic intervention be clearly defined. In addition to anatomic and physiologic and/or physical outcome measures, clinical end points should be emphasized. Furthermore, cognizance should be taken of whether the outcome to be evaluated is “early” (e.g., <30 days) or “late” (e.g., 6 or 12 months). In scientific studies, end point selection depends on trial structure and the aim of the study (e.g., dose ranges vs clinical efficacy studies). Nevertheless, most drug licensing agencies recognize only death and/or amputation as primary end points for studies in patients with severe leg ischemia.

Recommendation 1: The primary end point in reporting results of thrombolytic therapy in lower limb ischemia is amputation-free survival of the patient.

Recommendation 2: The secondary assessment of an individual patient following thrombolytic therapy should include patency of the artery thrombolized, substantiated by any objective imaging modality.

Other secondary end points should also be clearly defined (e.g., decreased requirement for surgery, a reduction in the magnitude of the surgical procedure, the replacement of surgery by an endovascular procedure, restoration of useful limb function, and relief of painful ischemic symptoms).

Recommendation 3: Complication rates should be documented and reported.

Clinical Presentation: DURATION OF HISTORY: While it can be difficult to be certain of the duration of history in all cases, patients can usually relate their deterioration of symptoms to a particular time period, whether or not there has been a history consistent with peripheral vascular disease. Acute thromboses or emboli presenting within 24 hours should prove more amenable to thrombolytic therapy. However, some emboli may consist of old thrombus and atherosclerotic plaque, and thus be less amenable to thrombolysis. Furthermore, recent randomized studies (2,3) have discussed a relation between the time interval of thrombosis and thrombolysis and concluded that du-

Reprinted from Am J Cardiol 1998; 81:207–218, ©1998 Excerpta Medica, Inc. with permission from Elsevier.

This study was supported in part by Abbott Laboratories, Abbott Park, Illinois; Behringwerke AG, Marburg, Germany; Boehringer Ingelheim UK, Bracknell, Berkshire, United Kingdom; Boehringer Mannheim AG, Mannheim, Germany; Genentech, Inc., South San Francisco, California; and Knoll AG, Ludwigshafen, Germany. This study was endorsed by the Cardiovascular and Interventional Radiological Society of Europe, Brussels, Belgium; the European Society for Vascular Surgery, Milan, Italy; the Internal Society for Thrombosis and Hemostasis, Chapel Hill, North Carolina; the International Union of Angiology, Lisbon, Portugal; and the Society of Interventional Radiology, Fairfax, Virginia. **Address for reprints:** Marc Verstraete, MD, Center for Molecular and Vascular Biology, Herestraat, 49, B-3000 Leuven, Belgium.

*Disclaimer: This Consensus Document deals with the use of thrombolytic therapy in the management of lower limb ischemia. Much of the discussion centers on published data. However, it is recognized that in clinical practice each case must be considered on its own merits, and that there may be good clinical reasons for adopting a different approach from those included in these guidelines. Participating societies and individuals wish to emphasize that the comments and recommendations in this Document should be taken as a whole and do not necessarily represent the only correct approach to the treatment of individual patients.

†A list of participants and collaborators appears in Appendix B.

Table 1
Severity of Acute Leg Ischemia

Category	Description	Capillary Return	Muscle Paralysis	Sensory Loss	Doppler Signals		
					Arterial	Venous	
I	Viable	Not immediately threatened	Intact	None	None	Audible	Audible
IIa	Threatened	Salvageable if treated	Intact/slow	None	Partial	Inaudible	Audible
IIb	Threatened	Salvageable if treated as emergency	Slow/absent	Partial	Partial	Inaudible	Audible
III	Irreversible	Primary amputation frequently required	Absent	Complete	Complete	Inaudible	Inaudible

Modified from Rutherford et al (4), with permission.

ration seems important and should be reported.

Recommendation 4: Ischemia duration should be clearly documented.

SEVERITY OF ISCHEMIA: *Recommendation 5:* The severity of ischemia to be treated must be clearly defined.

High dose, bolus, or pulse-spray methods (see further) may be used to treat the severely ischemic leg. However, caution should be exercised if a surgical option can achieve a more favorable outcome in a shorter period of time (e.g., the white limb secondary to a large proximal embolus), a situation with usually a very rapid and successful outcome if treated by standard surgical techniques.

We have adapted the Ad Hoc Committee's Classification of arterial disease (4) to promote more accurate reporting of the type of patients subjected to thrombolysis. We have broadened category II into a and b (Table 1) and believe that the current proposal is a useful example. Patients should be allocated to the category of their worst clinical finding (except venous Doppler signal).

Terms and Methods: **DEFINITION OF TERMS:** Initial technical success of thrombolytic therapy is defined here as the restoration of antegrade flow with complete or near complete lysis of the thrombus. The British Thrombolysis Study Group distinguishes complete lysis from clinically useful lysis, lysis but no runoff, and failure of lysis (5).

Systemic intravenous infusion: Intravenous administration of a thrombolytic agent through a peripheral vein (for example, the current method used for thrombolytic therapy of coronary artery thrombosis and pulmonary embolism). It must be recognized, however, that high-dose intra-arterial infusions will also elevate the systemic

action of the agent. Therefore "systemic infusion" refers to the site of infusion, not to the patients' response to the plasminogen activator. Systemic intravenous infusion for limb artery occlusion was investigated in the 1960s and 1970s but has been almost completely abandoned: it is inferior to intra-arterial infusion for leg arterial occlusion because the initial lytic success rates are lower and the complication rates higher (6,7).

Regional intra-arterial infusion: With nonselective intra-arterial catheter-directed infusion of the thrombolytic agent, the catheter is positioned proximal to the occluded vessel. With selective intra-arterial infusion, the distal end of the intra-arterial catheter is positioned within the occluded artery, but its tip is proximal to the thrombus.

The results (higher initial lytic success rates and fewer complications) with intra-arterial thrombolytic therapy improved as procedural difficulties were surmounted and gradual changes in infusion methods were introduced (8–10).

Guidewire traversal test: A guidewire is passed through the length of the thrombus before the initiation of prolonged infusion with the catheter embedded in the proximal thrombus. If a nonhydrophilic guidewire is passed, initial successful lysis of "acute" thrombi (<7 days old) was thought to be more likely (10,11).

Intrathrombus infusion: The thrombolytic agent is delivered by an intra-arterial catheter embedded within the thrombus. This serves to maximize the concentration of the drug within the thrombus and directly delivers the agent to the vicinity of thrombus-bound plasminogen. The inability to embed a catheter in the proximal thrombus may be predictive of failure of lysis (3,11).

Intrathrombus "bolusing" or "lacing": The term "bolusing" has been used interchangeably with "lacing" to refer to the initial intrathrombic delivery of a concentrated lytic agent with a view toward saturating the thrombus with the plasminogen activator. (In other contexts bolus treatment may have a different meaning.) During this portion of the procedure, a catheter (either one with an end hole or one with multiple side orifices with or without a tip occluding wire) is positioned in the most distal part of the thrombus. It is retracted proximally as the thrombolytic agent is delivered along the entire length of the thrombus. A retrospective study by Sullivan et al (12) suggested that a high-dose intrathrombus bolus infusion before the initiation of a slow continuous infusion of urokinase shortens the duration of lytic therapy for peripheral arterial occlusions. A more recent prospective randomized study (13) comparing high-bolus tissue plasminogen activator (t-PA) plus infusion with infusion without bolus supports this claim.

INFUSION METHODS: *Stepwise infusion* consists of placing the tip of the catheter within the proximal thrombus and infusing a fixed dose of lytic agent over a short period of time. As the thrombus dissolves, the catheter is advanced and the process is repeated until all of the thrombus has dissolved. This method is labor intensive and requires the patient to be confined to the angiography suite during the entire treatment (14).

Continuous infusion refers to the conventional means of infusing the lytic agent using a constant (steady flow) infusion pump. This is the standard method used for catheter-directed intrathrombus infusion. This may or may not be preceded by intrathrombus lacing.

Graded infusion refers to a protocol in which there is a periodic tapering of the infusion rates with the highest doses given within the first few hours. Mc-Namara and Fischer (10) and Traugher et al (15) were among the first to demonstrate a shortening of the duration of lytic therapy with the use of the graded infusion technique.

Forced periodic (e.g., pulse-spray) infusion refers to the technique of forcefully injecting the thrombolytic agent into the thrombus to fragment it and increase the surface area available for enzymatic action by the plasminogen activator. This technique was developed for the potential of accelerating lysis and shortening treatment time. Once brisk antegrade flow has been established in the treated conduit, there appears to be no continued benefit from pulse-spray infusion over slow continuous infusion (16–18).

Pharmacomechanic thrombolysis is the combination of mechanical thrombus disruption with concomitant infiltration of a lytic agent. Disruption may be achieved by the use of pulse-spray catheters, or of microporous and other balloons designed for local drug delivery.

Catheter systems: There are several catheter systems designed specifically for infusion of thrombolytic agents. Most of these are of $\leq 5\text{Fr}$ caliber. Clearly, any standard catheter that can be properly positioned may be used for end hole infusion. However, many catheters are available that have distal side orifices for more equal distribution of a thrombolytic agent. These orifices may be side holes over a certain length of the distal portion of the catheter ("infusion length" = 5, 10, 20 cm, etc.) and, depending on the design, these catheters may or may not require an end hole occluding wire. Other catheters need end hole occlusion and have side slits that open simultaneously when a threshold catheter lumen pressure is reached. This latter design results in a more even distribution of the lytic agent than the side hole design in which most of the fluid is emitted through the proximal holes. One recent design incorporates a 1-way valve at the distal end so that a tip-occluding wire is not needed during pulse-spray infusion. Two catheters may be used coaxially (e.g., 5Fr outer and 3Fr or an infusion guidewire inner) to bathe a long segment evenly;

this also allows the infusion length to be changed as thrombolysis progresses. So far, there is no convincing clinical evidence that any catheter system or infusion technique is superior to another.

ADJUNCTIVE TECHNIQUES AND PROCEDURES: The speed and long-term efficacy of intra-arterial thrombolysis can be enhanced utilizing adjunctive techniques. These techniques have 2 roles: (1) they may be used with thrombolysis to remove insoluble material or to debulk thrombus to accelerate the restoration of flow, and (2) they may be used to correct underlying lesions at the time of lysis or in the periprocedural period.

Techniques used in conjunction with thrombolysis to remove clots are catheter suction thromboembolectomy and mechanical thromboembolectomy. The latter uses a variety of systems, including saline jet spray with an associated Venturi and an additional external suction or a high-speed rotating impeller. Simple catheter aspiration is well established in many centers as an important adjunct to thrombolysis (19). Mechanical techniques must still be considered experimental (20–22).

Once flow has been restored, complete angiography should be performed to define the vascular anatomy and areas of disease that may require treatment. Other useful adjunctive modalities to investigate anatomy and function are duplex ultrasound, intravascular ultrasound, invasive intraluminal pressure recordings ("pull-back pressure") and segmental noninvasive pressure measurements. In most cases a causative lesion will be identified, and this should be managed by the most appropriate endovascular or conventional surgical procedure. Failure to detect and rectify an underlying lesion is associated with poor long-term patency (23–29).

THROMBOLYTIC AGENTS (SEE ALSO APPENDIX A)

Clinical Use: Thrombolytic drugs in clinical use for leg arterial occlusion are streptokinase (SK), produced by cultures of Lancefield group C. β -hemolytic streptococci, urokinase (UK), extracted from human urine or from long-term cultures of human neonatal kidney cells, and recombinant human

tissue-type plasminogen activator (rt-PA, alteplase). Anistreplase, an equimolar complex of SK and paraneisoylated human lys-plasminogen (APSAC), and reteplase, a mutant of human rt-PA (deletion of kringle 1, finger and growth factor domains) are currently not being used for leg arterial occlusion.

Future Developments: Several new thrombolytic agents are under clinical development (for review: 30). At present, clinical studies in leg arterial occlusion have been reported for recombinant human UK (31) recombinant glycosylated pro-UK (32), and recombinant staphylokinase (33–35). Although the available data are limited, the latter 2 agents have been shown to be effective without inducing fibrinogen depletion, in contrast to currently available agents. Because fibrinogen depletion has been shown to be significantly ($p < 0.01$) correlated with hemorrhagic complications of UK and t-PA (3), fibrin specificity would appear to be an important refinement of therapeutic thrombolysis in leg arterial occlusion. In vivo ultrasound significantly augments fibrinolysis with plasminogen activator (36–38), but the technique requires further development before it can be safely tested in clinical applications.

Dose and Choice of Lytic Agent (see also Table 2): In the early days of catheter thrombolysis, SK was the most widely used agent. Hess et al (14) originally proposed repeated intra-thrombus injection of small amounts of SK (1,000 to 3,000 IU every 5 to 15 minutes) with step-by-step advancement of the catheter between 2 injections (stepwise infusion). This regimen was soon replaced by a low-dose continuous infusion with the aid of an arterial infusion pump: 5,000 IU/hour was selected as 1/20th of the commonly used intravenous maintenance dose of 100,000 IU/hour (9,39). In recent years, UK and rt-PA have largely superseded SK as preferred agents in clinical use. For UK, dosage schemes varied initially, but the low-dose concept was gradually abandoned in favor of higher doses. Popular schemes are 240,000 IU/hour for 2 hours or until restoration of antegrade flow, reduced to 120,000 IU/hour for another 2 hours, and 60,000 IU/hour until lysis is complete (2,10). Phase I of the Thrombolysis or Peripheral Arte-

Table 2
Reported Dosage Schemes in Catheter Thrombolysis

Agent	Scheme	Selected References
Stepwise infusion:		
SK	1,000–3,000 IU every 2, 3, 5–15 min	14, 95, 96
UK	3,000–4,000 IU every 3–5 min	96–98
Continuous infusion:		
SK	5000 IU/h (rarely with initial loading dose of 20,000 or 40,000 IU over 20 min) 10,000 IU/h	Many reports in the 1980s; 7, 99–102 99, 101, 103
UK		
Low-dose technique	Variable schemes up to 100,000 IU/h (occasionally with variable loading dose)	104–108
High-dose technique	Mainly graded infusion (see below)	
rt-PA	0.25, 0.5, 1, or 2.5 mg/h 0.5 mg/h 0.5, 1, 3, or 10 mg/h 3, 5, or 10 mg/h 10 mg/h (max. 30 mg) 0.025 or 0.05 mg/kg/h 0.05 mg/kg/h 0.05 or 0.1 mg/kg/h	42, 109 7, 43, 100, 101 110 41 52 111 3 40, 112
Graded infusion:		
UK	4,000 IU/min up to antegrade flow 1,000 IU/min up to complete lysis	10
Modifications	4,000 IU/min up to antegrade flow 1,000 to 2,000 IU/min to complete lysis 4,000 IU/min for 2 h 2,000 IU/min for next 2 h 1,000 IU/min for remainder 250,000 IU followed by 4,000 IU/min for 4 h and 2,000 IU/min up to 36 h 4,000 IU/min for 4 h 2,000 IU/min for up to 48 h	113 2 3 31
Intrathrombus bolusing or lacing		
UK	120,000 to 250,000 IU lacing dose 60,000 IU lacing dose followed by McNamara's scheme 250,000 IU lacing dose followed by 50,000 IU/h	12 44, 70 114
rt-PA	3 × 5 mg (5–10 min interval) followed by 0.05 mg/kg/h 0.33 mg/ml 0.2 ml every 15 s for 15 min every 30 s thereafter	115, 116 117
Forced periodic (pulse spray) infusion		
UK	25,000 IU/ml 0.2 ml every 30 s for 20 min every 60 s thereafter 20,000 IU/cm occlusion length (microhole balloon catheter) 25,000 IU/10 cm thrombus followed by graded infusion	118 119 16
rt-PA	0.5 mg/ml 0.2 ml every 30 s for 20 min every 60 s thereafter 0.5 to 1 mg/cm occlusion length (microhole balloon catheter)	118 119
Intraoperative thrombolysis		
SK	50,000 to 150,000 IU slow bolus or infusion over 30 min	66, 120–122
UK	250,000 to 500,000 IU bolus in distal outflow vessel 1,000 to 2,000 IU/min into distal thrombus 250,000 IU over 30 min (with inflow occluded) 375,000 IU over 30 min (with inflow occluded)	69 123 124 125
rt-PA	3 × 5 mg bolus over 30 min	45

rial Surgery (TOPAS) trial compared the safety and efficacy of 3 dosage schemes of recombinant UK (Abbott, Abbott Park, Illinois) in comparison with operative intervention in 213 pa-

tients with acute lower extremity ischemia and concluded that 240,000 IU/hour for 4 hours and then 120,000 IU/hour to a maximum of 48 hours was the most appropriate regimen, maxi-

mizing lytic efficacy (71%) against bleeding risk (2%) (31). With rt-PA, the dosage schemes applied varied from 0.05 to 0.1 mg/kg/hour and from 0.25 to 10 mg/hour. In general, studies

comparing doses of rt-PA found no obvious benefit using higher doses (40–43). Currently, the most commonly applied infusion rates are either 1 mg/hour or 0.05 mg/kg/hour. With delivery systems that pursue “accelerated lysis,” initial bolus injections may be used.

Prospective randomized studies that compare different agents directly are few. One open trial compared intra-arterial SK to intra-arterial and intravenous rt-PA in 60 patients with recent onset or deterioration of limb ischemia (7); initial angiographic success was significantly greater with intra-arterial rt-PA (100%) than with intra-arterial SK (80%; $p < 0.04$) or intravenous rt-PA (45%; $p < 0.01$), the 30-day limb salvage rate being 80%, 60%, and 45%, respectively. In another open randomized trial (44) on 32 patients, rt-PA initially produced significantly faster lysis than UK, but the 24-hour and 30-day success rate did not achieve statistical significance. In the Surgery Versus Thrombolysis for Ischemia of the Lower Extremity (STILE) study, which was designed to evaluate surgery versus thrombolysis for lower extremity ischemia, there was no difference in efficacy or bleeding complications in patients receiving rt-PA compared with UK in a randomized but open fashion (3).

Table 2 summarizes doses that have been used in clinical practice. Absolute recommendations on drugs and doses to be preferred are not possible on the basis of available data. However, current clinical practice has moved away from using SK and favors the use of UK and rt-PA (45,46).

INDICATIONS FOR THROMBOLYSIS

The realistic potential benefits of intervention with thrombolysis as opposed to alternative treatment modalities must always be balanced against the potential risk of thrombolytic intervention.

Limb Threatening Ischemia: ACUTE OCCLUSION: Acute arterial occlusion presents a threat to the limbs of young patients and to the life and limb of older patients (47,48). Catheter-directed thrombolysis can be used as part of a treatment strategy designed to eliminate the acute thrombotic or embolic material and restore

perfusion. Gradual, low-pressure reperfusion is believed to be advantageous in preference to sudden, high-pressure reperfusion (49). Furthermore, in vessels suffering acute thrombosis, an underlying lesion is usually identified and should be corrected following successful thrombolysis (24,26).

Acute arterial occlusion can be associated with a spectrum of signs and symptoms. A patient without underlying arterial occlusive disease, who suffers an acute embolic occlusion at the femoral bifurcation, may present with a profoundly ischemic lower extremity, necessitating urgent intervention (see Emboli in normal limb arteries). An acute embolic or thrombotic occlusion of a chronically diseased, but only partially patent superficial femoral artery, may be associated with only mild progression of chronic symptoms and modest deterioration in hemodynamics.

The problems presented by the acutely ischemic limb are compounded by the problems following revascularization due to reperfusion injury. Therefore, the acutely ischemic limb can be an extreme clinical challenge to the clinician. Despite progress in many areas of vascular reconstruction, acute limb ischemia continues to be associated with substantial limb loss and appreciable mortality.

Therapeutic preintervention anticoagulation reduces morbidity and mortality (compared with not using anticoagulants) and is part of the overall treatment strategy for these patients (50,51).

Four prospective, randomized trials have been published upon which suggestions can be made regarding the treatment of patients with acute limb ischemia (2,3,31,52,53).

Recommendation 5: Intravenous heparin at full anticoagulant dosage should be administered as soon as possible (unless there is a specific contraindication to such therapy) and continued until other interventions, such as thrombolysis, are initiated. This is intended to reduce recurrent emboli and to prevent propagation of thrombus.

Recommendation 6: Intravenous administration of high doses of currently available thrombolytic agents should no longer be used for the treatment of leg arterial occlusion.

Recommendation 7: Full imaging by angiography or duplex scanning should be obtained.

Recommendation 8: The usual clinical procedure during arteriography for acute occlusion is to pass a guide-wire through the occluded artery. If the guide-wire passes, then intrathrombus lysis should be initiated. If the catheter fails to pass, a trial of regional lysis can be attempted for a limited period of time (e.g., 4 to 6 hours). If the guidewire can then be passed into the thrombus, thrombolysis can be continued. If the subsequent intrathrombus localization of the catheter cannot be achieved, then thrombolysis should be discontinued and alternative treatment modalities offered.

Recommendation 9: Prospective randomized studies suggest that a management strategy incorporating thrombolysis followed by definitive correction of an underlying lesion is an appropriate treatment for acute arterial occlusion (**Table 1**).

Primary amputation is preferred for patients with irreversible ischemia (**Table 1**) or if, in the judgment of the clinician, revascularization of the severely ischemic limb could jeopardize the patient's life. Immediate surgical revascularization may be indicated in the profoundly ischemic limb, especially if a delay is anticipated in initiating thrombolysis. However, in planning operative revascularization, it is recognized that the time from the decision to operate until reperfusion can be substantially longer than anticipated, due to factors outside of the surgeons control (e.g., operating theater availability, anesthesia preparation, technical details of the operation, etc.).

Recommendation 10: Primary amputation is recommended in patients with irreversible limb ischemia (**Table 1**).

Recommendation 11: If an unacceptable delay in effective reperfusion is anticipated with thrombolysis in view of the severity of the ischemia, immediate surgical revascularization is preferred. The converse is also true.

CHRONIC OCCLUSION: There is only 1 prospective, randomized trial that has evaluated patients with chronic arterial occlusion (3). Although all patients were prospectively randomized, results in patients with long-term isch-

emia (e.g., >14 days), obtained from a posthoc analysis, indicate that surgical revascularization was superior. The final results in patients who had native artery occlusions, 80% of whom had long-term ischemia, uphold this conclusion (53).

Recommendation 12: Surgical or endovascular therapy (excluding thrombolysis) is superior as the initial treatment strategy for chronic arterial occlusion leading to limb threatening ischemia. If these 2 approaches are not available or appropriate, thrombolysis should be considered.

OCCLUDED BYPASS GRAFTS: Open surgical procedures have been the traditional approach for bypass graft occlusion, directing procedures at the revision or replacement of the existing graft (54–56). Thrombolysis has been advocated as an alternate means of restoring arterial perfusion through the use of less invasive modalities, providing the opportunity to unmask stenotic lesions responsible for the occlusive event (11,57). The unmasked lesion is addressed with an endovascular or operative approach following successful thrombolysis, the nature of which is dependent on the anatomic characteristics of the lesion (neointimal or atherosclerotic, diffuse or focal).

The treatment strategy for bypass graft occlusion must be tailored to the clinical setting and the risks and benefits associated with therapeutic options. The parameters that are important in determining therapy include the severity of the patients' symptoms, the duration of the process, and the nature of occluded conduit (autogenous or prosthetic). For instance, in patients with occluded lower limb grafts who present with sudden onset claudication, the clinician will need to consider the original indication for the graft and possible future surgical options if no attempt is made to rescue the graft. Two trials indicate that thrombolysis is the preferred option to restore patency to grafts occluded <14 days (31,58).

Recommendation 13: Analogous to the indications for operative revascularization, thrombolysis in patients with bypass graft occlusion should be reserved for those individuals with threatened limb loss and for selected individuals with claudication.

A proportion of patients with by-

pass graft occlusion who are not acutely symptomatic at the time of closure may develop new ischemic symptoms, such as tissue loss with time. Potentially salvageable grafts by lysis might be permanently lost if not treated promptly. This might be particularly relevant in patients with insufficient vein for a new distal bypass or in patients who had previous episodes of graft loss with subsequent but delayed onset of ischemic symptoms.

Recommendation 14: Early postoperative graft failure. Patients with autogenous or prosthetic grafts occluding within 14 days of the primary operation should not be treated with thrombolysis.

Recommendation 15: Failure of established grafts. Patients with graft occlusions of <14 days duration should be offered thrombolytic therapy as a primary treatment modality.

EMBOLI IN NORMAL LIMB ARTERIES: The majority of patients should have high quality vascular imaging before any intervention.

However, in some cases, the clinical diagnosis of arterial embolism in the leg may be suggested on the basis of the following criteria: (1) sudden onset of clinical symptoms, (2) presence of embolic source, (3) absence of preceding claudication, and (4) presence of normal pulses and Doppler systolic blood pressures in the unaffected limb. Patients fulfilling these criteria and presenting with an acutely ischemic (white) leg due to a proximal embolus require emergency thromboembolectomy. This is usually through surgical intervention, but thrombolysis and, if necessary, surgical reconstruction could also be employed. If embolectomy is performed without imaging, incomplete clot removal may occur in up to 30% of cases (59). On-table angiography should be performed. Distal emboli may be treated by percutaneous clot aspiration or thrombolysis.

Prelysis echocardiography is not considered essential as the risk of subsequent procedural embolization from the heart is not increased (60).

Recommendation 16: Intravenous heparin at full anticoagulant dosage should be given as soon as possible unless there are specific contraindications to such therapy.

Recommendation 17: Preintervention imaging should be performed, if pos-

sible, to confirm the diagnosis of embolus and to illustrate the distribution and localization of the occlusion(s), but this must not delay the subsequent therapeutic intervention. An angiogram should also be performed after thrombectomy and/or embolectomy during the surgical and/or intervention procedure.

Recommendation 18: Suprainguinal emboli should be preferentially removed surgically.

Recommendation 19: In situations where there is a focal discrete infrainguinal embolus producing ischemia without propagated thrombus, surgical thromboembolectomy, percutaneous clot aspiration, or lysis are all appropriate management strategies.

Recommendation 20: Where the presenting embolus is fragmented and occludes many vascular branches or where it is complicated by propagated thrombus, thrombolysis may be a useful first choice of treatment.

Intraoperative Thrombolysis: In general, a recent operation is believed to be a contraindication to thrombolytic therapy. However, intraoperative thrombolysis has emerged as a widely employed and frequently successful adjuvant to open surgical thromboembolectomy. Clinical studies have documented a high frequency of residual intraluminal thrombus following balloon catheter thrombectomy (61–63). The infusion of thrombolytic agents following thrombectomy has been successful in dissolving residual thrombi, without an increase in perioperative bleeding complications (64–67). However, others have reported an increase in bleeding complications (68). In severely ischemic extremities, isolated limb perfusion with a high-dose thrombolytic agent has been useful in restoring arterial continuity (66).

In a prospective, randomized, blinded and placebo-controlled trial in patients undergoing elective infrainguinal reconstruction, the regional and systemic effects of 3 doses of UK (125,000, 250,000, and 500,000 IU) were investigated. Bolus infusions of these doses were safe and associated with a break-down of complexed fibrin (elevated D-dimer) but not with depletion of fibrinogen. Patients receiving UK had a significantly lower mortality compared with placebo controls (69).

Intraoperative thrombolysis has been used successfully for retained

thromboembolic material following mechanical thromboembolism (65,67), or for thrombotic occlusion of small arteries in patients already undergoing an open surgical procedure, (e.g., the tibial arteries or the plantar and metatarsal arteries of the foot, which are poorly accessible to mechanical thrombectomy) (63,66).

Recommendation 21: Intraoperative intra-arterial thrombolysis is a suitable procedure to dissolve residual thrombi following an incomplete thrombectomy or to dissolve thrombi in the small distal vessels in patients who undergo an open surgical procedure and in whom the distal runoff vessels appear to be occluded (see e.g., occluded runoff vessels from thrombosed popliteal aneurysm).

Technique and dose: Thrombolytic therapy should be given as a bolus or slow infusion as close as possible to the thrombus or intrathrombus. Acceptable doses are given in Table 2. The technique of continuing a postoperative infusion is associated with a high frequency of complications and is currently considered to be an experimental technique.

Thrombolysis in the Management of Acute Endovascular Complications: There is a well-defined role for the use of intra-arterial thrombolysis in the management of complications of endovascular procedures. These complications usually occur while the catheter is still in place, the vascular anatomy has been defined by arteriography, and the patient is in the interventional vascular suite.

Acute occlusion at the angioplasty site complicates 2% to 3% of percutaneous balloon angioplasties (70). It has a number of causes, the most common being an intimal flap, and may be managed by a low-pressure balloon catheter (71), atherectomy (72), or intra-arterial stent deployment. Acute thrombosis may complicate these mechanical interventions, and thrombolysis has an adjunctive role in this subgroup.

Distal embolization of atherothrombotic material into the crural circulation can be managed by aspiration thromboembolism (19). Catheter-directed thrombolysis may be used to treat associated thrombus formation, distal occlusion, or aspiration resistant embolism.

Iatrogenic acute thrombotic occlu-

sion responds well to rapid instillation of thrombolytic agents.

Recommendation 22: Thrombolysis may be usefully employed to dissolve emboli that have passed distally from the interventional site. Thrombolytic therapy may be given in isolation or combined with thrombus aspiration.

Recommendation 23: Access site occlusion after angioplasty is optimally managed by surgical correction.

Other Indications: INTERMITTENT CLAUDICATION: The management of patients with intermittent claudication should be tailored to individual patient lifestyle. Other medical conditions clearly need addressing as relief of claudication may not actually increase walking distance, which may be limited by dyspnea or even atherosclerotic disease in the contralateral leg. For those patients with mild or moderate claudication, with no significant impairment of lifestyle, intervention with thrombolysis is not justified.

For those patients with disabling claudication severely limiting their lifestyle, thrombolysis can be considered. However, the true risks of thrombolysis (see Complications) must be discussed with the patient and considered along with nonlysis interventional and surgical techniques. The risk of amputation also applies to thrombolysis as it does to interventional and surgical techniques. Thus, there is no justification for the use of thrombolysis in the management of patients with mild and/or moderate stable claudication at the present time.

Recommendation 24: In the light of the potential complications, thrombolysis has a limited role in the management of severe claudication.

THROMBOSIS OF POPLITEAL ANEURYSMS: The presentation of acute ischemia with an easily palpable contralateral popliteal pulse or a history of a popliteal or aortic aneurysm should raise the suspicion of a thrombosed popliteal aneurysm.

Recommendation 25: Suitable imaging techniques should confirm the diagnosis of the thrombosed popliteal aneurysm and establish patency of the distal run-off vessels.

The aim of thrombolysis in thrombosed popliteal aneurysm is only to restore patency to the thrombosed run-off vessel(s). A thrombosed popli-

Table 3
Contraindications

Absolute

1. Established cerebrovascular event (including TIAs within last 2 months)
2. Active bleeding diathesis
3. Recent gastrointestinal bleeding (<10 d)
4. Neurosurgery (intracranial, spinal) within last 3 months
5. Intracranial trauma within last 3 months

Relative major

1. Cardiopulmonary resuscitation within last 10 d
2. Major nonvascular surgery or trauma within last 10 d
3. Uncontrolled hypertension: >180 mm Hg systolic or >110 mm Hg diastolic
4. Puncture of noncompressible vessel
5. Intracranial tumor
6. Recent eye surgery

Minor

1. Hepatic failure, particularly those with coagulopathy
2. Bacterial endocarditis
3. Pregnancy
4. Diabetic hemorrhagic retinopathy

Modified from NIH Consensus Development Conference (73), with permission from the BMJ Publishing Group.

teal aneurysm with patent run-off vessels should not be thrombolysed.

Recommendation 26: For percutaneous thrombolysis, the infusion catheter should be positioned in the occluded run-off vessel(s).

TRASH FOOT (DISTAL MICROEMBOLIZATION): Although anecdotal evidence suggests that thrombolysis may be worthwhile, there are no controlled scientific studies of this condition.

CONTRAINDICATIONS

In general, thrombolytic therapy is contraindicated in any patient with a hemorrhagic disorder or an anatomic lesion that may bleed. Absolute and relative contraindications are listed in Table 3.

ADJUNCTIVE TREATMENT

Adjunctive Procedures: *Recommendation 27:* In patients in whom it

is important to accelerate thrombolysis, or in whom there is residual thrombus that is resistant to lysis, aspiration thrombectomy should be considered.

Recommendation 28: On completion of thrombolysis, every attempt should be made to identify and correct underlying lesions.

Anticoagulation: Anticoagulation should not hinder the start of thrombolysis. There are no scientific data that specifically address the potential advantages or disadvantages of heparinization during thrombolysis. Contemporary practice suggests that concomitant heparin administration may restrict pericatheter thrombosis and can be delivered either systemically or around the catheter through a proximal sheath. Following thrombolysis, practitioners may choose to continue anticoagulation orally. Potential benefits of long-term anticoagulation have not been investigated.

Recommendation 29: Postprocedural anticoagulation is appropriate and should be continued until the underlying cause of occlusion has been corrected. Long-term anticoagulation should be considered when no underlying cause has been identified or corrected.

Aspirin: Patients with peripheral arterial disease have a two- to three-fold increase in death rate due to cardiac disease. The collaborative overview of randomized trials of antiplatelet treatment, a meta-analysis of 125 studies on various categories of patients at high risk of vascular disease, calculated that antiplatelet agents—usually aspirin—reduce the odds of suffering fatal or nonfatal vascular events by roughly 25% (74). It would seem reasonable then to continue aspirin for patients undergoing thrombolysis. Aspirin has also been shown to possibly retard the progression of atherosclerosis and the occurrence of thrombotic complications in legs of patients with arterial disease (references in reference 75). The British Thrombolysis Study Group (76) has demonstrated improved outcome for those patients who were taking aspirin during thrombolysis.

Recommendation 30: Aspirin should be continued or initiated as soon as convenient, unless contraindicated.

MONITORING AND COMPLICATIONS

Monitoring: Patients undergoing thrombolytic therapy need expert clinical and nursing care in appropriate facilities where the staff are familiar with the thrombolytic procedure and its inherent risks. Every institution should establish guidelines for clinical and hemodynamic monitoring and surveillance of patients during and immediately after thrombolysis.

The clinical use of laboratory tests during thrombolysis is controversial. Some have advocated tests to detect and monitor the presence of a fibrinolytic state and to predict clinical outcome and the occurrence of complications, but common clinical practice suggests that this is not necessary. In individual patients, there is, however, no clear association between the result of any single coagulation or fibrinolytic test and reperfusion, reocclusion, or bleeding. For instance, a low fibrinogen level marks an increased bleeding risk but does not accurately predict hemorrhage, and patients bleed in the presence of a normal fibrinogen level. Daily estimation of hemoglobin or hematocrit may help to detect occult minor hemorrhage, and daily monitoring of renal function and urinary output is considered prudent.

Complications: Severe systemic or intracranial bleeding is the most significant clinical risk associated with any thrombolytic therapy. This feared complication of all thrombolytic agents may be due to lysis of a preexisting hemostatic plug, the induced fibrinolytic or anticoagulated state, or loss of vascular integrity via an already established vessel puncture.

The majority of the data on bleeding complications with thrombolytic therapy are derived from large-scale studies in myocardial infarction, but a direct comparison of bleeding risk between trials in this indication remains difficult because patient selection, dosage of thrombolytic drugs, concomitant medication, and definition of major and minor bleeding differ. Fewer data are available on bleeding rates with peripheral use of thrombolytic agents. Berridge et al (77) reviewed 19 prospective series of patients undergoing thrombolysis for leg arterial obstruction published between 1974 and 1988 to define the incidence of hemor-

rhagic stroke, major hemorrhage (causing hypotension or requiring transfusion or other specific treatment), and minor hemorrhage. The overall risk of hemorrhagic stroke was 1% (14 of 1,401 patients). Major and minor hemorrhage occurred in 5.1% and 14.8% of patients, respectively. There were no placebo control groups in these series. More recently, Dawson et al (78) reporting on a collected series of patients of the British Thrombolysis Study Group, found an incidence of (hemorrhagic and ischemic) stroke of 2.3% (27 of 1,157), half of which occurred during the thrombolytic procedure. Two recent prospective randomized trials comparing surgery with thrombolysis have recorded intracranial bleeding rates of 1.2% and 2.1%, respectively (3,31).

Prospective randomized trials comparing the local intra-arterial administration of 2 thrombolytic drugs are scarce and performed in a limited number of patients. Although there is a lower incidence of hemorrhagic complications with alteplase compared with SK (7), no difference was found in bleeding complications between alteplase and UK (3).

Most bleeding during catheter thrombolysis occurs at sites of venous or arterial puncture. Pericatheter bleeding is particularly common, typically delayed in onset and probably multifactorial in origin. Fortunately, local bleeding is usually minor and controlled with prolonged local pressure. If bleeding from the access site is a problem, increasing the catheter size or placing a vascular sheath around the catheter may be helpful. If this maneuver fails to achieve hemostasis, a surgical stitch into the vessel or graft may be useful, particularly in case of synthetic graft puncture. Bleeding into the retroperitoneal space from inadvertent posterior wall puncture may go undetected until hypotension develops.

Retroperitoneal or intra-abdominal bleeding may also occur spontaneously. Unexpected abdominal symptoms or back pain, or the sudden development of anemia without obvious blood loss, should prompt a search for an intra-abdominal or retroperitoneal hematoma.

Renal tract bleeding in the form of macroscopic hematuria is rare and may be the first sign of a bladder or

kidney tumor. Gastrointestinal bleeding is equally rare and may be overt or occult. Early overt bleeding is frequently the result of giving thrombolytic therapy to a patient with an undiagnosed peptic ulcer.

Irrespective of the site of severe bleeding, management follows a standard pattern: discontinue the thrombolytic agent and anticoagulants, replenish coagulation factors (e.g., fresh frozen plasma, cryoprecipitate), and blood, and intervene surgically only to evacuate hematoma causing pressure phenomena on adjacent tissues or to repair a vascular injury that continues to bleed. In the face of a life-threatening hemorrhage, rapid reversal of the fibrinolytic state (e.g., with tranexamic acid or epsilon-aminocaproic acid) has been used but remains controversial. When a neurologic deficit occurs, thrombolytic treatment should be discontinued and a computed tomography scan obtained to determine whether the stroke is thrombotic or hemorrhagic.

Recommendation 31: In case of major hemorrhage, thrombolytic treatment should be stopped and any coagulation defect corrected.

Recommendation 32: Bleeding from a puncture site should be controlled with local compression, an increase in catheter size, and placement of a sheath or a surgical stitch on the vessel or graft.

The use of thrombolytic agents may cause cleavage of thrombus and distal embolization of partially lysed fragments. Small emboli may be clinically silent or cause transient pain only. Larger fragments that occlude distal tibial or foot arteries are potentially more harmful and may lead to a clear clinical deterioration of the limb, particularly if secondary retrograde thrombosis follows. Acute deterioration of the limb due to increasing ischemia is common during thrombolysis.

Recommendation 33: Thrombolysis should be continued if distal embolization occurs. Additional measures to be considered are: repositioning of the catheter more distally, a new bolus dose, or an increased dose. Thrombus aspiration or surgery may be required if thrombolysis does not improve the clinical condition.

Further thrombolytic therapy is required in the event of pericatheter thrombosis, perhaps through a proxi-

mal sheath. If a pericatheter thrombus embolizes upon removal of the catheter system, surgical intervention may be needed.

Anaphylaxis is rare with any of the thrombolytic agents, but allergies are a complication with SK, characterized by early flushing, vasodilatation, rashes, and hypotension. It is unclear whether these are true allergic reactions: they usually respond to discontinuation of the infusion and administration of hydrocortisone and an antihistamine. Late "reactions" to SK include a serum-like illness presenting with joint pains, fever, and microscopic hematuria, 10 to 21 days after treatment. The outcome is usually benign, although permanent renal impairment has been reported.

APPENDIX A

Standardization of Thrombolytic Agents:

The original approach to the standardization of commercial SK involved the determination of the smallest dose that caused lysis of a standard fibrin clot at 35°C in 10 minutes (79). The World Health Organization Expert Committee in Biological Standardization used this clot lysis assay to establish an international standard with a stable but impure preparation provided by Lederle Laboratories (80). Since then, the so-called clot lysis assay was developed. This type of assay or some modification thereof is recommended for the assay of the various thrombolytic agents whose mechanism depends on plasminogen activation in the presence of fibrin clots. The international unit of SK is defined as the activity contained in 0.002090 mg of the international standard and corresponds to Christensen's postulated unit. The SK preparations for clinical use have a specific activity of about 100,000 IU/mg (81). Anistreplase is an equimolar complex of SK and human Lys-plasminogen in which the active site in the plasminogen moiety is reversibly blocked by acylation. One unit of anistreplase contains approximately 36,000 IU of SK (82).

At the time the first international UK standard was established (83). It was not realized that it contained a mixture of high (54 kD) and low (31 kD) molecular weight forms (84). The high molecular weight form is found primarily in the urinary commercial

preparations, whereas the low molecular weight form is mainly found in long-term cultures of neonatal kidney cells. A high molecular weight standard is now available (85). Recombinant single-chain UK-type plasminogen activator (scu-PA) can be obtained using prokaryotic (*E. coli*) (86), eukaryotic cells (Chinese hamster and Syrian hamster ovary cells) (87), and mouse hybridoma cells. The current standard for high molecular weight UK is being used in the calibration of scu-PA, which is activated by plasmin to a 2-chain plasminogen activator before calibration. Similar results are obtained using glycosylated scu-PA, irrespective whether a clot lysis or a chromogenic substrate assay is used: results with unglycosylated scu-PA are different in the 2 assay systems, thus further complicating the issue (88). Saruplase (Grunenthal, Aachen, Germany) contains 130,500 IU/mg (89), the preparation of Farmalicia Carlo Erba contains 160,000 IU/mg (90), and Prollyse (Abbott, Abbott Park, Illinois) contains 165,000 IU/mg.

The specific activity of alteplase is 500,000 to 580,000 IU/mg (91) and is usually >70% of the single-chain form. Duteplase is the generic name for a recombinant 2-chain form of human 1-PA. It differs from alteplase due to substitution of methionine for valine in position 245 in the amino acid sequence. The specific activity of this variant of the naturally occurring t-PA is approximately 300,000 IU/mg protein (91). Reteplase is a nonglycosylated mutant of human t-PA lacking the finger-, epidermal growth factor- and kringle-1 regions. It should be pointed out that while a claimed specific activity of about 550,000 IU/mg has been cited in the literature (92), other data (88) have shown that reteplase is a distinct molecule from the international standard of rt-PA and thus cannot be expressed in terms of this standard. A distinct standard has been established for reteplase. Definition of the dose during the preclinical and clinical development of reteplase was as kilounits per kilogram (kilo units; 1 kU = 1,000 u) or as megaunits per kilogram (mega units: 1 MU = 1,000 kU). However, the definition of units was changed as follows:

The specific activity of staphylokinase is 110,000 Home U/mg (by comparison with a home standard as-

	Old	New
Assay Standard Units	Amidolytic t-PA 1 MU 1 kU 1U	Clot lysis Retepase = 1 U = 1 mU = 1 μ U

signed a specific activity of 100,000 Home U/mg) (93).

In animal models with thrombosis, the thrombolytic potency (clot lysis vs dose) and specific thrombolytic activity (clot lysis vs plasma antigen level) of the agents to be compared can be determined (94). In patients, head-to-head comparisons are virtually impossible due to the multifactorial causes leading to thrombosis (vs a selective induced thrombosis model in healthy animals), the difficulty in quantifying the clot lysis obtained in patients, and the need to test multiple doses.

To prove the superiority of a given thrombolytic agent to another on the basis of gravimetric amounts is meaningless unless translated in specific activities. Even then one has to assume that the fibrinolytic activity of each thrombolytic drug was assessed with comparable in vitro methods (activity measured on fibrin plates, clot lysis assay, chromogenic assay).

APPENDIX B

Organizing Committee: Marc Verstraete, MD, (Chairman), Raymond Verhaeghe, MD, Leuven, Belgium; Jill J. Belch, MD, Dundee, John A. Dormandy, MD, London, United Kingdom.

Participants: Peter R.F. Bell, MD, Leicester, United Kingdom; David C. Berridge, DM, Leeds, United Kingdom; T.M. Buckenham, MD, London, United Kingdom; Jay D. Coffman, MD, Boston, MA; Anthony J. Comerota, MD, Philadelphia, PA; Jonathan J. Earnshaw, DM, Gloucester, United Kingdom; Peter A. Gaines, MD, Sheffield, United Kingdom; Claude Juhan, MD, Marscille, France; Krishna Kandarpa, MD, Boston, MA; Lars Norgren, MD, Lund, Sweden; Kenneth Ouriel, MD, Rochester, NY; Robert Rutherford, MD, Denver, Colorado; E. Schneider, MD, Zurich, Switzerland.

Collaborators: Anna-Maria Belli,

MD, John Reidy, MD, London, United Kingdom, for the Cardiovascular and Interventional Radiological Society of Europe, Zurich, Switzerland; David Bergqvist, MD, Uppsala, Sweden, José Fernandes e Fernandes, MD, Lisbon, Portugal, for the European Society of Vascular Surgery, Milan, Italy; Charles W. Francis, MD, Rochester, NY, Victor Gurewich, MD, Boston, MA, for the International Society of Thrombosis and Hemostasis, Chapel Hill, NC; Denis L. Clement, MD, Gent, Belgium, Andrew Nicolaides, MD, London, United Kingdom, for the International Union of Angiology, Toulouse, France.

References

- Working Party on Thrombolysis in the Management of Limb Ischaemia. Thrombolysis in the management of limb arterial occlusion. Towards a consensus interim report. *J Int Med* 1996; 240:343-355.
- Ouriel K, Shortell CK, De Weese JA, Green RM, Francis CW, Azodo MVU, Gutierrez DII, Manzione JV, Co C, Marder JV. A comparison of thrombolytic therapy with operative vascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg* 1994; 19:1021-1070.
- The STILE Investigators. Results of a prospective randomised trial evaluating surgery versus thrombolysis for ischaemia of the lower extremity. The STILE trial. *Ann Surg* 1994; 220:251-268.
- Rutherford RB, Flanigan DP, Gupta SK, Johnston KW, Karmody A, Whittemore AD, Baker JD, Ernst CB, Jamieson C, Mehta S. Suggested standards for reports dealing with lower extremity ischaemia. *J Vasc Surg* 1986; 4:80-94.
- Braithwaite BD, Petrik PV, Ritchie AWS, Earnshaw JJ. Computerised angiographic analysis of the outcome of peripheral thrombolysis. *Am J Surg* 1995; 170:131-175.
- Boyles PW, Meyer WH, Graff J. Comparative effectiveness of IV and IA fibrinolytic therapy. *Am J Cardiol* 1960; 6:439-445.
- Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg* 1991; 78:988-995.
- Dotter CT, Rosch J, Seaman AJ. Selective clot lysis with low-dose streptokinase. *Radiology* 1974; 111:31-37.
- Katzen BT, van Breda A. Low-dose streptokinase in the treatment of arterial occlusions. *Am J Roentgenol* 1981; 136:1171-1178.
- McNamara TO, Fischer JR. Thrombolysis of peripheral arterial and graft occlusions: improved results using high-dose urokinase. *Am J Roentgenol* 1985; 144:769-775.
- Ouriel K, Shortell CK, Azodo MW, Guttererz OH, Marder VJ. Acute peripheral arterial occlusion: predictors of success in catheter-directed thrombolytic therapy. *Radiology* 1994; 93:561-566.
- Sullivan KL, Gardiner GA, Shapiro MJ, Bonn J, Levin DC. Acceleration of thrombolysis with a high-dose transthorbus bolus technique. *Radiology* 1989; 173:805-808.
- Braithwaite BD, Buckenham TM, Galland RB, Heather BP, Earnshaw JJ. A prospective randomised trial of high dose versus low dose tissue plasminogen activator infusion in the management of acute limb ischaemia. *Br J Surg* 1997; 84:646-650.
- Hess H, Ingrisch H, Mietasch A, Rath H. Local low-dose thrombolytic therapy of peripheral arterial occlusions. *N Engl J Med* 1982; 307:1627-1630.
- Traugher PD, Cook PS, Micklos TJ, Miller FJ. Intra-arterial fibrinolytic therapy for popliteal and tibial artery obstruction: comparison of streptokinase to urokinase. *Am J Roentgenol* 1987; 149:443-456.
- Kandarpa K, Chopra PS, Arung JE, Meyerovitz MF, Goldhaber SZ. Intraarterial thrombolysis of lower extremity occlusion: prospective randomized comparison of forced periodic infusion and conventional slow continuous infusion. *Radiology* 1993; 188:861-867.
- Kandarpa K, Goldhaber SZ, Meyerovitz MF. Pulse-spray thrombolysis: the careful analysis. *Radiology* 1994; 193:320-324.
- Hye RJ, Turner C, Valji K, Wolf YG, Roberts AC, Bookstein JJ, Plecha EJ. Is thrombolysis of occluded popliteal and tibial bypass grafts worthwhile? *J Vasc Surg* 1994; 20:588-597.
- Cleveland TJ, Cumberland DC, Gaines PA. Percutaneous aspiration thromboembolectomy to manage the embolic complications of angioplasty and as adjunct to thrombolysis. *Clin Radiol* 1994; 49:549-552.
- Starck EE, McDermott JC, Crummy AB, Turnipseed WD, Archer CW, Burgess JH. Percutaneous aspiration thromboembolectomy. *Radiology* 1985; 156:61-66.
- Reekers JA, Kromhout JH, van der Waal K. Catheter for percutaneous

- thrombectomy: first clinical experience. *Radiology* 1993; 188:871–874.
22. Self SB, Coe DA, Normann S, Seeger JM. Rotational atherectomy for treatment of occluded prosthetic grafts. *J Surg Res* 1994; 56:134–140.
 23. Klatte BC, Becker GJ, Holden RF, Yune HY. Fibrinolytic therapy. *Radiology* 1986; 159:619–624.
 24. McNamara TO, Bomberger RA. Factors affecting initial and six month patency rates after intra-arterial thrombolysis with high dose urokinase. *Am J Surg* 1986; 152:709–712.
 25. Graor RA, Risius B, Young JR, Lucas FV, Beven EG, Hertzner NR, Krajewski LP, O'Hara PJ, Olin J, Ruschhaupt WF. Thrombolysis of peripheral arterial bypass grafts: surgical thrombectomy compared with thrombolysis. *J Vasc Surg* 1988; 7:347–355.
 26. Gardiner GA, Harrington DP, Koltun W, Whittemore A, Mannick JA, Levin DC. Salvage of occluded bypass grafts by means of thrombolysis. *J Vasc Surg* 1989; 9:426–431.
 27. McNamara TO. Thrombolysis as an alternative initial therapy for the acutely ischemic limb. *Semin Vasc Surg* 1991; 5:89–98.
 28. Sullivan KL, Gardiner GA, Kandarpa K, Bonn J, Shapiro MJ, Curabasi RA, Smullens S, Levin DC. Efficacy of thrombolysis in infrainguinal bypass grafts. *Circulation* 1991; 83(suppl 1): 99–105.
 29. Durham JD, Rutherford RB. Assessment of long-term efficacy of fibrinolytic therapy in the ischemic extremity. *Semin Intervent Radiol* 1992; 9:166–173.
 30. Verstraete M, Lijnen HR, Collen D. Thrombolytic agents in development. *Drugs* 1995; 50:29–42.
 31. Ouriel K, Veith FJ, Sasahara AA for the TOPAS Investigators. Thrombolysis or peripheral arterial surgery (TOPAS): phase I results. *J Vasc Surg* 1996; 23: 64–75.
 32. Hartmann JR, Enger EL, Villiard EM, Sasahara AA. Dose ranging trial of intraarterial r-prourokinase (A-74187) for thrombolysis of total peripheral arterial occlusions (abstr). *J Am Coll Cardiol* 1994; 23(Suppl):95A.
 33. Vanderschueren S, Stockx L, Wilms G, Lacroix H, Verhaeghe R, Verinylen J, Collen D. Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; 92:2050–2057.
 34. Collen D, Moreau H, Stockx L, Vanderschueren S. Recombinant staphylokinase variants with altered reactivity. II. Thrombolytic properties and antibody induction. *Circulation* 1996; 84:1216–1234.
 35. Collen D, Stockx L, Lacroix H, Suy R, Vanderschueren S. Recombinant staphylokinase variants with altered reactivity. IV. Identification of variants with reduced antibody induction but intact potency. *Circulation* 1997; 95:463–472.
 36. Hamano K. Thrombolysis enhanced by transcatheter ultrasound irradiation. *Tokyo Jikeikai Med J* 1991; 106: 533–542.
 37. Kashyap A, Blinc A, Marder VJ, Penney DP, Francis CW. Acceleration of fibrinolysis by ultrasound in a rabbit ear model of small vessel injury. *Thromb Res* 1994; 76:475–485.
 38. Luo H, Nishioka T, Fishbein MC, Cercek B, Forrester JS, Kim CJ, Berglund H, Siegel RJ. Transcutaneous ultrasound augments lysis of arterial thrombi in vivo. *Circulation* 1996; 94: 775–778.
 39. Tony WG, Gilula LA, McLennan BL, Ahmed P, Sherman L. Low-dose intravascular fibrinolytic therapy. *Radiology* 1982; 143:59–69.
 40. Graor R, Risius B, Lucas FV, Young JR, Ruschhaupt WF, Beven EG, Grossbard EB. Thrombolysis with recombinant human tissue-type plasminogen activator in patients with peripheral arterial disease. *Circulation* 1986; 74(Suppl 1):1–15.
 41. Verstraete M, Hess H, Mahler F, Mielaschek A, Roth FJ, Schneider E, Baert AL, Verhaeghe R. Femoro-popliteal artery thrombolysis with intra-arterial infusion of recombinant tissue-type plasminogen activator—Report of a pilot trial. *Eur J Vasc Surg* 1988; 2:155–159.
 42. Earnshaw JJ, Westhy JC, Gregson RHS, Makin GS, Hopkinson BR. Local thrombolytic therapy of peripheral arterial ischaemia with tissue plasminogen activator: a dose ranging study. *Br J Surg* 1988; 75:1196–1200.
 43. Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Intra-arterial thrombolysis using recombinant tissue plasminogen activator (rt-PA): the optimal agent. at the optimal dose? *Eur J Vasc Surg* 1989; 3:327–332.
 44. Meyerovitz MF, Goldhaber SZ, Reagan K, Polak JF, Kandarpa K, Grassi CJ, Donovan BC, Bettmann MA, Harrington DP. Recombinant tissue-type plasminogen activator versus urokinase in peripheral arterial and graft occlusions: a randomized trial. *Radiology* 1990; 175:75–78.
 45. Earnshaw JJ, Birch P. Peripheral thrombolysis: state of the art. *Cardiovasc Surg* 1995; 3:357–367.
 46. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE, Taylor LM. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996; 94:3026–3049.
 47. Abbott WM, McCabe C, Maloney RD, Wirthlin RS. Embolism of the popliteal artery. *Surg Gynecol Obstet* 1984; 159:533–536.
 48. Cambria RP, Abbott WM. Acute arterial thrombosis of the lower extremity. *Arch Surg* 1984; 119:784–787.
 49. Beyersdorf F, Matheis G, Kruger S, Hanselmann A, Freisteben HG, Zimmer G, Satter P. Avoiding reperfusion injury after limb revascularization: experimental observations and recommendations for clinical application. *J Vasc Surg* 1989; 9:757–766.
 50. Blaisdell FW, Steele M, Allen RE. Management of acute lower extremity ischemia due to embolism and thrombosis. *Surgery* 1978; 84:822–834.
 51. Jivegard L, Holm J, Schersten T. The outcome of arterial embolism. *Acta Chir Scand* 1986; 152:251–256.
 52. Nilsson L, Albrechtsson U, Jonung T, Ribbe E, Thorvinger B, Thome J, Astedt B, Norgren L. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomized controlled study. *Eur J Vasc Surg* 1992; 6:189–193.
 53. Weaver FA, Comerota AJ, Youngblood M, Froehlich J, Hosking JD, Papanicolaou G, and the STILE Investigators. Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. *J Vasc Surg* 1996; 24: 513–523.
 54. Ouriel K, Fiore WM, Geary JE. Limb-threatening ischemia in the medically compromised patient: amputation or revascularization? *Surgery* 1988; 104:667–672.
 55. Green RM, McNamara J, Ouriel K, DeWeese JA. Comparison of infrainguinal graft surveillance techniques. *J Vasc Surg* 1990; 11:207–214.
 56. DeWeese JA, Leather R, Porter J. Practice guidelines: lower extremity revascularization. *J Vasc Surg* 1993; 18:280–294.
 57. Berridge DC. Advances in thrombolytic therapy. *Br J Surg* 1994; 81:1249–1250.
 58. Comerota AJ, Weaver FA, Hosking JD, Froehlich J, Folander H, Sussman B, Rosenfield K. Results of prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. *Am J Surg* 1996; 172:105–112.
 59. Bosma HW, Jörning PJG. Intra-operative arteriography in arterial embolectomy. *Eur J Vasc Surg* 1990; 4:469–472.
 60. Lonsdale RJ, Berridge DC, Makin ES, Hopkinson BR. Role of echocardiog-

- raphy prior to peripheral arterial thrombolysis. *Br J Surg* 1990; 77:1429–1430.
61. Plecha FR, Pories WJ. Intraoperative angiography in the immediate assessment of arterial reconstruction. *Arch Surg* 1972; 105:902–907.
 62. Quinones-Baldrich WJ, Zierler RE, Hiatt JC. Intra-operative fibrinolytic therapy: an adjunct to catheter thromboembolism. *J Vasc Surg* 1985; 2:319–326.
 63. Parent FN, Bernhard VW, Pabst TS, McIntyre KE, Hunter GC, Malone JM. Fibrinolytic treatment of residual thrombus after catheter embolectomy for severe lower limb ischemia. *J Vasc Surg* 1989; 9:153–160.
 64. Quinones-Baldrich WJ, Ziomek S, Henderson TC, Moore WS. Intra-operative fibrinolytic therapy: experimental evaluation. *J Vasc Surg* 1986; 4:229–236.
 65. Norem RF, Short DH, Kerstein MD. Role of intra-operative fibrinolytic therapy in acute arterial occlusion. *Surg Gynecol Obstet* 1988; 167:87–91.
 66. Comerota AJ, White JV, Grosh JD. Intra-operative, intra-arterial thrombolytic therapy for salvage of limbs in patients with distal arterial thrombosis. *Surg Gynecol Obstet* 1989; 169:283–289.
 67. Garcia R, Saroyan RM, Sendowski J, Smith F, Kerstein M. Intra-operative, intra-arterial urokinase infusion as an adjunct to Fogarty catheter embolectomy in acute arterial occlusion. *Surg Gynecol Obstet* 1990; 171:201–205.
 68. Cahen LJ, Kaplan M, Bernhard VW. Intra-operative fibrinolytic therapy: an adjunct to catheter thromboembolism. *J Vasc Surg* 1985; 2:319–326.
 69. Comerota AJ, Rao KA, Thom RC, Skibinski CJ, Beck GJ, Ghosh S, Sun L, Curl GR, Ricotta JJ, Graor RA, Flinn WC, Roedersbeimer RL, Alexander JB. A prospective, randomized, blinded, and placebo controlled trial of intra-operative intra-arterial urokinase infusion during lower extremity revascularization: regional and systemic effects. *Ann Surg* 1993; 218:534–543.
 70. Gardiner GA, Meyerovitz MF, Stokes KR, Clouse ME, Harrington DP, Bettmann MA. Complications of transluminal angioplasty. *Radiology* 1986; 159:201–208.
 71. Belli AM. *Interventional Radiology of the Peripheral Vascular System*. London: Edward Arnold 1994:22.
 72. Maynar M, Reyes M, Cabrera V, Roman M, Pulido JM, Castaneda F, Letourneau JG, Castaneda-Zuniga WR. Percutaneous atherectomy as an alternative treatment for postangioplasty obstructive intimal flaps. *Radiology* 1989; 170:1029–1031.
 73. NIH Consensus Development Conference. Thrombolytic therapy in thrombosis. *Br Med J* 1980; 280:1585–1587.
 74. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet treatment. Part I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* 1994; 308:81–106.
 75. Verhaeghe R. Prophylactic antiplatelet therapy in peripheral arterial disease. *Drugs* 1991; 42(suppl 5):51–57.
 76. Braithwaite BD, Jones L, Yusuf SW, Dawson K, Berridge DC, Davies E, Bowyer R, Earnshaw JJ. Aspirin improves the outcome of intra-arterial thrombolysis with tissue plasminogen activator. *Br J Surg* 1995; 82:1357–1358.
 77. Berridge DC, Niakin GS, Hopkinson BR. Local low-dose intra-arterial thrombolytic therapy, the risk of major stroke and haemorrhage. *Br J Surg* 1989; 76:1230–1232.
 78. Dawson K, Armon A, Braithwaite B, Galland R, Kendrick R, Downes M, Buckenham T, Al-Kutoubi A, Berridge D, Earnshaw JJ, Hamilton G. Stroke during intra-arterial thrombolysis: a survey of experience in the UK (abstr). *Br J Surg* 1996; 83:568.
 79. Christensen LR. Methods for measuring activity of components of streptococcal fibrinolytic system, and streptococcal desoxyribonuclease. *J Clin Invest* 1949; 28:143–149.
 80. Taylor FB, Comp PC. Biochemistry of streptokinase. In: *Fibrinolytics and Antifibrinolytics*. F Markwardt, ed., Berlin: Springer Verlag, 1968:138–149.
 81. Heath AB, Gaffney PJ. A collaborative study to establish the second international standard for streptokinase. *Thromb Haemost* 1990; 64:267–269.
 82. Monk JP, Heel RC. Anisoylated plasminogen streptokinase activator complex (APSAC). A review of its mechanism of action, clinical pharmacology and therapeutic use in acute myocardial infarction. *Drugs* 1987; 14:25–49.
 83. World Health Organization. Twenty First Meeting. Expert Committee on Biological Standardisation. WHO Tech Rep Ser No 413. 1968.
 84. Philo RD, Gaffney PJ. Relative potencies of different molecular weight forms of urokinase. In: JF Davidson, I-M Nilsson, MM Samama, PC Desnoyers, eds. *Progress in Fibrinolysis and Thrombolysis*. Edinburgh: Churchill Livingstone, 1981; 5:220–222.
 85. Gaffney PJ, Heuth AB. A collaborative study to establish a standard for high molecular weight urinary-type plasminogen activator (HMW/u-PA). *Thromb Haemost* 1990; 64:398–401.
 86. Hanbucken FW, Schneider J, Gunzler W. Selective fibrinolytic activity of recombinant non-glycosylated human prourokinase (single chain urokinase-type plasminogen activator) from bacteria. *Drugs Res* 1987; 37:993–997.
 87. Noll ML, Sarubbi E, Robbiati F, Solfineri A, Blasi F, Parenti F, Cassani G. Production and characterisation of human recombinant single chain urokinase-type plasminogen activator from mouse cells. *Fibrinolysis* 1989; 3:101–106.
 88. Gaffney P. Standards in fibrinolysis—current status and future challenges. *Thromb Haemost* 1995; 74:1389–1397.
 89. de Boer A, Kluff C, Gerloff J, Dooijewaard G, Gunzler WA, Berer H, Van der Meer EJM, Coben AF. Pharmacokinetics of saruplase, a recombinant unglycosylated human single-chain urokinase-type plasminogen activator and its effects on fibrinolytic and haemostatic parameters in healthy male subjects. *Thromb Haemost* 1993; 70:320–325.
 90. Maia M, Mannucci PM, Pini M, Prandoni P, Gurewich V. A pilot study of pro-urokinase in the treatment of deep vein thrombosis. *Thromb Haemost* 1994; 72:430–433.
 91. Collen D. Designing thrombolytic agents: focus on safety and efficacy. *Am J Cardiol* 1992; 69:71A–81A.
 92. Martin U, Fischer S, Kobner U, Lill H, Rudolph R, Sponer G, Stern A, Strein K. Properties of a novel plasminogen activator BM 06,022, produced in *Escherichia Coli*. *Z Kardiol* 1990; 79(suppl 3):167–170.
 93. Collen D, Silence K, Demarsin E, De Mol M, Lijnen HR. Isolation and characterization of natural and recombinant staphylokinase. *Fibrinolysis* 1992; 6:203–213.
 94. Collen D, Lu HR, Lijnen HR, Nelles L, Stassen JM. Thrombolytic and pharmacokinetic properties of chimeric tissue-type and urokinase-type plasminogen activators. *Circulation* 1991; 84:1216–1234.
 95. Lammer J, Pilger E, Justich E, Neumayer K, Schreyer H. Fibrinolysis in chronic arteriosclerotic occlusions: intrathrombotic injections of streptokinase. *Radiology* 1985; 157:45–50.
 96. Lammer J, Pilger E, Neumayer K, Schreyer H. Intraarterial thrombolysis: long-term results. *Radiology* 1986; 161:159–163.

97. Pilger E, Lammer J, Beruch H, Steiner H. Intra-arterial fibrinolysis: in vitro and prospective clinical evaluation of three fibrinolytic agents. *Radiology* 1986; 161:597-599.
98. Hess H, Mietaschk A, Brückl R. Peripheral arterial occlusions: a 6-year experience with local low-dose thrombolytic therapy. *Radiology* 1987; 163:753-758.
99. Browse DJ, Barr H, Torrie EPH, Galland RB. Limitations to the widespread usage of low-dose intra-arterial thrombolysis. *Eur J Vasc Surg* 1991; 5:445-449.
100. Browse DJ, Torrie EPH, Galland RB. Low-dose intra-arterial thrombolysis in the treatment of occluded vascular grafts. *Br J Surg* 1992; 79:86-88.
101. Earnshaw JJ, Scott DJA, Horrocks M, Baird RN. Choice of agent for peripheral thrombolysis. *Br J Surg* 1993; 80:25-27.
102. Giddings AEB, Quaraishy MS, Walker WJ. Long-term results of a single protocol for thrombolysis in acute lower limb ischaemia. *Br J Surg* 1993; 80: 1262-1265.
103. Barr H, Lancashire MJR, Torrie EPH, Galland RB. Intra-arterial thrombolytic therapy in the management of acute and chronic limb ischaemia. *Br J Surg* 1991; 78:284-287.
104. Fiessinger JN, Aiach M, Capron L, Devanlay M, Vaissayrat M, Juillet Y. Effect of local urokinase on arterial occlusion of lower limbs. *Thromb Haemost* 1981; 45:230-232.
105. Fiessinger JN, Vitoux JF, Pernes JM, Roncato M, Aiach M, Gaux JC. Complications of intraarterial urokinase-lys-plasminogen infusion therapy in arterial ischemia of lower limbs. *Am J Roentengenol* 1986; 146: 157-159.
106. Pernes JM, de Almeida Augusto M, Vitoux JF, Raynaud A, Fiessinger JN, Brenot P, Fabiani JN, Murday A, Gaux JC. Local thrombolysis in peripheral arteries and bypass grafts. *J Vasc Surg* 1987; 6:372-378.
107. Enon B, Reigner B, Lescalie F, I'Hoste P, Peret M, Chevnlir JM. In situ thrombolysis for late occlusion of superficial femoral prosthetic grafts. *Ann Vasc Surg* 1993; 7:270-274.
108. Law MM, Gelabert HA, Quinones-Baldrich WJ, Ahn SS, Moore WS. Continuous postoperative intra-arterial urokinase infusion in the treatment of no reflow following revascularization of the acutely ischemic limb. *Ann Vasc Surg* 1994; 8:66-73.
109. Lonsdale RJ, Berridge DC, Earnshaw JJ, Harrison JD, Gregson RHS, Wenham PW, Hopkinson BR, Makin GS. Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis. *Br J Surg* 1992; 79:272-275.
110. Lacroix H, Suy R, Nevelsteen A, Verheyen L, Stockx L, Wilms G, Verhaeghe R. Local thrombolysis for occluded arterial grafts: is the yield worth the effort? *J Cardiovasc Surg* 1994; 35:187-191.
111. Krupski WC, Feldman RK, Rapp JH. Recombinant human tissue-type plasminogen activator is an effective agent for thrombolysis of peripheral arteries and bypass grafts: preliminary report. *J Vasc Surg* 1989; 10:491-500.
112. Risius B, Graor RA, Geisinger MA, Zelch MG, Lucas FV, Young JR. Thrombolytic therapy with recombinant human tissue type plasminogen activator: a comparison of two doses. *Radiology* 1987; 164:465-468.
113. DeMaiores CA, Mills JL, Fujitani RM, Taylor SM, Joseph AE. A re-evaluation of intraarterial thrombolytic therapy for acute lower extremity ischemia. *J Vasc Surg* 1993; 17:888-895.
114. Parent FN, Piotrowski JJ, Bernhard VM, Pond GD, Pabsi TS, Bull DA, Hunter GC, McIntyre KE. Outcome of intra-arterial urokinase for acute arterial occlusion. *J Cardiovasc Surg* 1991; 32:680-690.
115. Juhan C, Hauptert S, Miltgen G, Girard N, Dulac P. A new intra-arterial rt-PA dosage regimen in peripheral arterial occlusion: bolus followed by continuous infusion. *Thromb Haemost* 1991; 65:635.
116. Buckenharn TM, George CD, Chester JF, Taylor RS, Dormandy JA. Accelerated thrombolysis using pulsed intra-thrombus recombinant tissue type plasminogen activator. *Eur J Vasc Surg* 1992; 6:237-240.
117. Yusuf SW, Whitaker SC, Gregson RHS, Wenham PW, Hopkinson BR, Makin GS. Experience with pulse-spray technique in peripheral thrombolysis. *Eur J Vasc Surg* 1994; 8:270-275.
118. Valji K, Bookstein JJ, Roberts AC, Sanchez RB. Occluded peripheral arteries and bypass grafts: lytic stagnation as an endpoint for pulse-spray pharmacomechanical thrombolysis. *Radiology* 1993; 188:389-394.
119. Schneider E. Die perkutane transluminale Angioplastie, lokale Thrombolysse und perkutane Thrombenextraction in der Behandlung von Extremitäten Arteri-enverschlüssen. *Internist* 1989; 30:440-446.
120. Quinones-Baldrich WJ, Zierler RE, Hiatt JC. Intra-operative fibrinolytic therapy in acute arterial occlusion. *Surg Gynecol Obstet* 1988; 167:87-91.
121. Beard JD, Nyameke J, Earnshaw JJ, Scott DJA, Thompson JF. Intra-operative streptokinase: a useful adjunct to balloon catheter embolectomy. *Br J Surg* 1993; 80:21-24.
122. Earnshaw JJ, Beard JD. Intraoperative use of thrombolytic agents. *Br Med J* 1993; 307:638-639.
123. Riggs P, Ouriel K. Thrombolysis in the treatment of lower extremity occlusive disease. *Surg Clin N Am* 1995; 75:633-645.
124. Gonzales-Fajardo JA, Perez-Burkhardt JL, Mateo AM. Intraoperative fibrinolytic therapy for salvage of limbs with acute arterial surgery: an adjunct to thromboembolectomy. *Ann Vasc Surg* 1995; 9:179-186.
125. Knaus J, Ris HB, Stirnemann P. Intraoperative catheter thrombolysis as an adjunct to surgical revascularisation for infrainguinal limb-threatening ischaemia. *Eur J Vasc Surg* 1993; 7:507-512.