

SIR Reporting Standards for the Treatment of Acute Limb Ischemia with Use of Transluminal Removal of Arterial Thrombus

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J Vasc Interv Radiol 2003; 14:S453-S465

Abbreviations: PAD = peripheral arterial disease, PAT = percutaneous aspiration thrombectomy, PMT = percutaneous mechanical thrombectomy, SVS/ISCVS = Society of Vascular Surgery/International Society of Cardiovascular Surgery, TRT = transluminal removal of thrombus

ACUTE limb ischemia is any sudden decrease or worsening in limb perfusion that causes a potential threat to limb viability (1). Acute peripheral arterial occlusion may be caused by in situ thrombosis or embolus. In this article, the term "thrombus" will be used to describe arterial occlusion caused by in situ thrombosis or embolus. Percutaneous or "open" surgical techniques can be used to remove the thrombus. Current percutaneous methods for transluminal removal of thrombus (TRT) include thrombolytic therapy (ie, catheter-directed, pharmacomechanic), percutaneous aspiration thrombectomy (PAT), and percutaneous mechanical thrombectomy (PMT). These methods may be used in combination. Surgical techniques entail an

"open" procedure that necessitates an arteriotomy for the removal of thrombus.

Of the various TRT methods used to treat acute limb ischemia, catheter-directed thrombolytic therapy with urokinase has been the most widely studied. Catheter-directed thrombolytic therapy has at least three theoretical and practical advantages over surgical thromboembolectomy: less endothelial trauma, angiographic visualization of the underlying lesion(s) and runoff vessels, and, in many cases, ready access for definitive transluminal therapies that address the underlying lesion (1,2). In addition, it has been suggested that gradual, low-pressure reperfusion may offer certain advantages over sudden, high-pressure reperfusion associated with surgical revascularization (1,3,4). Recently, the Food and Drug Administration recalled urokinase (Abbokinase; Abbott Laboratories, Abbott Park, IL). As a result, a critical evaluation of alternate methods to treat acute limb ischemia with use of other thrombolytic drug strategies, PAT and/or PMT, will be needed.

Reporting standards for the treatment of peripheral arterial disease (PAD) and practice guidelines for thrombolytic therapy for acute limb ischemia have been published (1,2,5-7). However, there is insufficient evidence in the literature to determine the

best therapy in a given case of acute limb ischemia. This is because the literature is replete with individual or institutional reports of surgical and thrombolytic therapy that are either biased or lack concurrent controls and standardized reporting practices (1). The purpose of this document is to establish reporting standards for subsequent studies pertaining to TRT in the treatment of acute limb ischemia. Consistent data reporting is needed to help precisely define the safety, efficacy, and long-term outcome of TRT procedures (1,8,9). Only then can the appropriate treatment be determined for patients presenting with acute limb ischemia.

PATIENT SELECTION

Demographic data are important to assess any differences between study groups, and they also allow a clinician to determine whether the study is relevant to his or her patient population. Useful demographic data includes age, sex, and race.

Thrombus can cause occlusion of native arterial segment(s) or surgical bypass graft(s). For a given occlusion, a clear determination of embolic versus in situ thrombotic etiology may not be possible. Nevertheless, an attempt should be made to distinguish between these two etiologies with use of the criteria in the Pretreatment Eval-

This article first appeared in J Vasc Interv Radiol 2001; 12:559-570.

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DOI: 10.1097/01.RVI.0000094619.61428.11

uation section. The atheromatous narrowing of PAD or the neointimal proliferation seen within surgical bypass grafts may lead to in situ thrombosis. An embolus characteristically lodges in a vascular bed where there has been no previous stimulus for collateral development (1).

Although multiple case series include data on the efficacy and safety of thrombolytic therapy, most series are small and cannot offer definitive conclusions (3,10–20). Several prospective randomized trials have been valuable in determining the patient population most likely to benefit from thrombolytic therapy (21–27). These studies also suggest that a management strategy must incorporate definitive correction of any underlying lesion disclosed after thrombolytic therapy. Patient selection has benefited from an improved understanding of the factors influencing the technical and clinical success of thrombolytic therapy (28–31).

Recently, in an attempt to expedite restoration of blood flow to an acutely ischemic limb and to reduce the risk of bleeding complications associated with thrombolytic therapy, multiple mechanical devices have been employed (32–38). These devices work by several different methods, including aspiration, pulverization, destruction, and recirculation of the thrombus. Mechanical devices may allow percutaneous treatment of more profound ischemia than is currently possible with thrombolytic therapy alone.

Patients presenting with “blue toe syndrome” (atherothrombotic microembolization) usually have transient fixed ischemia, occasionally with minor tissue loss, but without diffuse forefoot ischemia. These patients should not be included in reporting experiences of acute limb ischemia and are better reported separately.

Recommendations for Reporting Standards

Demographic data, which includes age, sex, and race, must be reported. For categorical variables (ie, sex, race), the proportions of the subjects in each of the categories must be reported. For continuous variables (ie, age), the mean or median (for nonparametric variables), SD or SEM, and range must be reported. The target population of

the study must be relevant to the hypotheses being tested. The target population must be defined and the method of assigning treatments to subjects must be described. The number and description of patients considered for but not treated by TRT should be tabulated as a screening log. This screening log should include the reason for exclusion in each case. It is important to explicitly state the selection (inclusion) criteria for choosing the study patients and control subjects from the patient population. In addition, the exclusion criteria must be reported. Possible exclusions include contraindications to thrombolytic therapy or profound, progressive acute limb ischemia that cannot afford the time needed to undergo thrombolytic therapy.

Treatment of acute limb ischemia caused by in situ thrombus versus embolus must be studied and reported separately (39). When possible, selection should be stratified according to native arterial versus graft occlusion, duration of symptoms, and disease severity. These are detailed in the Pretreatment Evaluation section of this article.

PRETREATMENT EVALUATION

Clinical Evaluation

Clinical evaluation of revascularization procedures, particularly those that compare different treatment methods, may be difficult to interpret unless differences in factors that can affect outcome are identified and characterized. The history and physical examination will help define risk factors, comorbidities, previous interventions and operations, and the severity and duration of ischemia. Tobacco use, hypertension, diabetes, hyperlipidemia, and hypercoagulable states (protein C, protein S, and antithrombin III deficiency, anticardiolipin syndrome, etc.) may affect patency (1,7). Cardiac, pulmonary, renal, and carotid artery disease and malignancy may influence morbidity and mortality (1,7). To our knowledge, there are no published studies evaluating the influence of a history of PAD or earlier revascularization (surgical graft composition, age, and earlier graft interventions) on clinical success and outcome of TRT

and it would therefore be helpful to collect data on these factors.

A history of claudication, recent diagnostic catheterization, or lower extremity intervention (ie, percutaneous transluminal angioplasty [PTA], stent placement, bypass graft, endarterectomy) suggests in situ thrombosis. The following features may suggest the clinical diagnosis of arterial embolism to the limb: (a) sudden onset of symptoms, (b) known embolic source, (c) no antecedent claudication, (d) normal pulse and Doppler systolic blood pressures in the unaffected extremity (1).

Preintervention anticoagulation with therapeutic levels of heparin has been shown to reduce morbidity and mortality and is part of the overall treatment strategy for patients with acute limb ischemia (40,41). Therefore, preprocedural medications affecting the coagulation pathway or platelet activity may affect the outcome of interventional procedures for thrombus removal. To our knowledge, there are no published studies evaluating the role of vasoactive drugs in acute limb ischemia (1).

There is a need for objective measures of the severity of acute limb ischemia to predict outcome more accurately. Classification systems for the severity of acute limb ischemia must (a) be clinically relevant to the diagnosis and treatment and (b) meaningfully stratify patients for outcome assessment (1). The Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS) clinical category of acute limb ischemia is a useful classification scheme (Table 1). Immediate revascularization is indicated in the profoundly ischemic limb (7). The sudden onset of hypoperfusion of the lower extremity leads rapidly to systemic acid-base and electrolyte disorders that impair cardiopulmonary function. Elevated myoglobin level is associated with irreversible renal failure. Successful revascularization may induce a severe reperfusion injury, causing further neuromuscular damage to the extremity (1).

The duration of ischemia may affect the duration of infusion and overall dose of thrombolytic drug needed (1,42). Also, clinical and temporal criteria may help define the role of mechanical thrombectomy devices in the treatment of profound limb ischemia.

Table 1
SVS/ISCVS Clinical Categories of Acute Limb Ischemia

Category	Description	Findings		Doppler Signal	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. marginal	Salvageable if promptly treated	Minimal (toe) or none	None	Often inaudible	Audible
b. immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Usually inaudible	Audible
III. Irreversible*	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

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* When presenting early, the differentiation between category IIb and III may be difficult.

Hemodynamic Evaluation

This includes subjective and objective evaluation of the acutely ischemic limb. Pulse examination is a subjective method. Noninvasive tests such as segmental pressures, ankle-brachial index (ABI), toe systolic blood pressures, transcutaneous oxygen measurements, pulse volume recording, and treadmill/postexercise pressures are objective methods of determining the hemodynamic significance of a peripheral occlusion. However, standards for the use of these tests were designed for chronic ischemia only (1).

Anatomic Evaluation

Duplex scanning may be of value in the detection and localization of an obstruction in a native artery or a surgical bypass graft, but it has not been properly evaluated in the setting of acute limb ischemia. Arteriography is the preferred method of evaluating the acutely ischemic limb because it provides clear details on the location and length of occlusion, extent of any underlying PAD (inflow and outflow), and the status of the collateral bed. In combination with clinical findings, arteriography also often allows distinction between in situ thrombosis and embolus. Arteriographic findings of embolus are (a) sharp cutoff, reverse meniscus, or thrombus silhouetted by contrast material (tram track sign, filling defect), (b) multiple sites of occlusion, (c) poorly developed collaterals in an otherwise normal vessel, and (d)

poor distal flow or occlusion (1). The information provided by arteriography serves as the basis for therapy and is an essential first step in TRT.

The status of the arterial inflow and outflow and the location and length of the occlusion may help predict the technical success and outcome of thrombolytic therapy (28–31). The location and length of the occlusion determines the potential for collateral development. For example, longer occlusions obstruct more potential collateral pathways (30). Thrombosis generally tends to extend to the next large collateral inflow; however, the low-flow state below the occlusive thrombus may lead to further distal propagation. The SVS weighing scheme for runoff arteries (Tables 2,3) enables grading of the extent of occlusion and the relative contribution to outflow of each runoff vessel (7).

Recommendations for Reporting Standards

Studies evaluating patency, morbidity, and mortality must provide standardized information on appropriate risk factors with a clearly defined grading system (7). The use of the SVS/ISCVS grading system for common risk factors (Table 4) is recommended. The use of any pretreatment medication affecting the coagulation pathway or platelet activity must be reported and its protocol of use (method of administration, dose, method for titration) must be described in detail.

The severity of ischemia must be reported with the SVS/ISCVS clinical categories of acute limb ischemia (Table 1). No standard scheme for categorizing the duration of ischemia exists. We propose the following scheme: (a) hyperacute (<24 h), (b) acute A (1–7 d), (c) acute B (8–14 d), (d) subacute (14 d to 3 mo), and (e) chronic (>3 mo).

Although evaluation of the pulses of the acutely ischemic limb is subjective, the following classification is recommended: (a) normal, (b) weakly palpable, (c) “Dopplorable” only, and (d) “non-Dopplorable.” The status of the distal pulses (ie, dorsalis pedis and posterior tibial artery) should be reported.

Complete preinterventional arteriography evaluating the inflow and outflow of the ischemic limb must be performed. The status of the arterial inflow must be reported (7,43). The location and length of the occlusion must be reported. For description of arterial inflow and arterial occlusions, the arterial segments should be divided into aortic, iliac, femoropopliteal, and infrapopliteal. Surgical bypass grafts should be divided into suprainguinal (includes femoral-femoral), femoral-popliteal (above-knee vs below-knee), femoral-tibial, and popliteal-distal. The composition of a surgical graft (in situ vein, synthetic, modified biograft, autologous vein, cryopreserved vein or artery, or composite) and its manufacturer must be reported. The age of the surgical graft, number of earlier revisions, and the

Table 2
SVS/ISCVS Weighing of Runoff Arteries According to Site

Site of Distal Anastomoses (artery)	Number of Units Assigned		
	3	2	1
Common iliac	Common femoral	External iliac	Internal iliac
External iliac		SFA	DFA
Common femoral		SFA	DFA
Popliteal above-knee	Distal popliteal		Anterior tibial
Popliteal below-knee			Posterior tibial
Anterior tibial		Distal tibial	Peroneal
Posterior tibial		Distal tibial	Pedal arch
Peroneal		Pedal runoff	Pedal arch
Pedal/inframalleolar			Collaterals to anterior and posterior tibial arteries

Note.—Reprinted with permission from Reference 7.

SFA = superficial femoral artery; DFA = deep femoral artery (profunda femoris).

Table 3
SVS/ISCVS Weighing of Runoff Arteries According to Occlusion

Degree of Occlusion	Number of Points Assigned per Unit				
	3	2.5	2	1	0
Major runoff vessels	Occluded throughout length	Occluded less than half of length Visible collaterals	50%–99% greatest stenosis	20%–49% greatest stenosis	Less than 20% greatest stenosis
Pedal runoff	No primary pedal artery patent	Partially patent or fully patent beyond critical in line occlusive lesion	In line continuity with patent outflow vessel but incomplete arch	One or more substantial stenoses distally but no in line	Fully patent pedal runoff (<20% stenosis)

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SFA = superficial femoral artery; DFA = deep femoral artery (profunda femoris).

time from last revision to thrombosis should be tabulated. Any earlier endovascular or surgical interventions performed on the acutely ischemic limb should be tabulated. The patency of the distal arterial bed must be assessed with use of the SVS weighing scheme for runoff arteries (Tables 2,3).

TREATMENT DESCRIPTION

Transluminal Removal of Thrombus

Currently, there are three TRT methods used to treat acute limb ischemia: thrombolytic therapy, PAT, and PMT. Thrombolytic therapy refers to the use of a thrombolytic drug to dissolve thrombus in the vascular system. The infusion of a thrombolytic drug (streptokinase, urokinase, tissue plasminogen activator) upregulates the

conversion of endogenous plasminogen to plasmin. As a result, plasmin-mediated biochemical cleavage of fibrinogen is promoted. Thrombolytic therapy may be accomplished by systemic infusion or catheter-directed infusion or by pharmacomechanical techniques. Systemic infusion refers to the intravenous administration of the thrombolytic drug (17). Catheter-directed infusion is subdivided into end hole, stepwise, and intrathrombotic infusion as outlined in Table 5. Intra-thrombus bolus administration (lacing of the clot), with a small concentrated volume of the thrombolytic drug administered before the initiation of infusion, has been shown to significantly decrease the duration of infusion of the thrombolytic drug needed to dissolve the thrombus (12). Pharmacome-

chanical thrombolysis refers to the fragmentation and dissolution of the thrombus by forced periodic injection of the thrombolytic drug through a catheter embedded in the thrombus (pulse-spray mechanical thrombolysis) or the use of a device (ie, microporous balloons, ultrasonic equipment) in conjunction with the intrathrombotic delivery of the thrombolytic agent (13). PAT refers to the use of a catheter or Fogarty balloon and suction with a syringe to remove the thrombus. PAT has been used with thrombolytic therapy or as a stand-alone procedure but may lead to increased blood loss during aspiration and clot removal (12,33,44). PMT refers to fragmentation, maceration, and/or mobilization of thrombus with use of balloons, catheter aspiration

Table 4
SVS/ISCVS Grading System for Common Risk Factors

Risk Factor	Grade	Complication
Diabetes	0	None
	1	Adult onset, diet controlled
	2	Adult onset, insulin controlled
	3	Juvenile onset
Tobacco use*	0	Never or none for last 10 years
	1	None current, but smoked in last 10 years
	2	Less than 1 pack/day†
Hypertension	3	Greater than 1 pack/day
	0	None‡
	1	Easily controlled with single drug
Hyperlipidemia	2	Controlled with two drugs
	3	Requires more than 2 drugs or uncontrolled
	0	Cholesterol/triglycerides within normal limits for age
Cardiac Status	1	Mild elevation, controlled by diet
	2	Types II, III, IV requiring strict diet control
	3	Requiring diet and drug control
Carotid Disease	0	Asymptomatic, normal ECG
	1	Asymptomatic, h/o MI >6 mo or occult MI by ECG
	2	Stable angina, controlled ectopy or asymptomatic arrhythmia, drug compensated CHF
	3	Unstable angina, symptomatic or poorly controlled ectopy/arrhythmia, poorly compensated CHF, MI within 6 months
Renal Status	0	No symptoms, bruit or evidence of disease§
	1	Asymptomatic but evidence of disease
	2	Transient or temporary stroke
Pulmonary Status	3	Completed stroke with permanent neurologic deficit
	0	No known renal disease, serum creatinine <1.5 mg/dL, creatinine clearance >50 mL/min
	1	Serum creatinine 1.5–3.0 mg/dL, creatinine clearance 30–50 mL/min
Pulmonary Status	2	Serum creatinine 3.0–6.0 mg/dL, creatinine clearance 15–30 mL/min
	3	Serum creatinine >6.0 mg/dL, creatinine clearance <15 mL/min, or on dialysis or with transplant
	0	Asymptomatic, normal CXR, PFT 20% of predicted
	1	Asymptomatic or mild dyspnea on exertion, mild CXR parenchymal changes, PFT 65%–80% of predicted
Pulmonary Status	2	Between 1 and 3
	3	PFT: VC <1.85, FEV ₁ <1.2 L or <35% of predicted, Max. Vol. ventilation <28 L/min or <50% of predicted, PCO ₂ >45 mm Hg, supplementary oxygen needed, pulmonary hypertension

Note.—ECG = electrocardiography; MI = myocardial infarction; CHF = congestive heart failure; CXR = chest radiograph (x-ray); PFT = pulmonary function test; VC = vital capacity; FEV₁ = forced expiratory volume in 1 second; PCO₂ = partial pressure of carbon dioxide. Reprinted with permission from Reference 7.

* 0 = absent, none, negligible; 1 = mild; 2 = moderate; 3 = severe.

† Includes abstinence less than 1 year.

‡ Cutoff point, diastolic pressure regularly above or below 90 mm Hg.

§ Determined by noninvasive test or arteriography.

Table 5
Thrombolytic Therapy: Methods for Administering the Fibrinolytic Agent

- Systemic intravenous infusion
- Catheter-directed intraarterial infusion
 - a. End hole: defined as catheter tip positioned immediately adjacent to the thrombus
 - b. Stepwise: defined as embedding the catheter into the proximal portion of the thrombus and infusing the lytic drug over a short period of time. As the thrombus dissolves, the catheter is advanced and the process repeated until the entire thrombus burden has dissolved.
 - c. Intrathrombotic: defined as a multiple side hole infusion catheter and/or wire embedded in the entire thrombus burden. Infusion may be preceded by intrathrombus bolusing (lacing) with a concentrated amount of lytic drug.
 - I. Graded: defined as the periodic tapering of the amount of the lytic drug with the highest dose given initially.
 - II. Continuous: defined as infusion of a fixed amount of the lytic drug.

Adjunctive Procedure(s)

When the thrombus has been removed and blood flow restored, complete arteriography is generally performed to define the vascular anatomy, areas of PAD that may require treatment, and the status of the outflow bed. An underlying cause of thrombosis should be identified if present. Failure to detect and rectify an underlying lesion is associated with poor long-term patency (3,12,15,16,25). To achieve long-term patency, the underlying lesion should be treated with use of the most appropriate percutaneous or open surgical technique (48,49).

It should be noted that methods of TRT cannot be compared if they are linked with different methods of treating the underlying lesion(s); for example, endovascular techniques (ie, PTA, stent placement) should not be compared to surgical techniques (ie, endarterectomy, patch angioplasty, bypass graft). All clinical trials to date have judged, for the most part, throm-

systems, or mechanical devices. PMT has been used less frequently because of the potentially higher risk of embolization and vascular injury (45–47). Some PMT devices may also produce hemolysis (45–47). The efficacy of PMT depends mainly on the age of the

thrombus; fresh thrombus responds better than older material (16,32,33). The preliminary available experience suggests that some patients treated with PMT will still require infusion of a thrombolytic drug, but at a reduced dose over a shorter interval (38)

bolytic therapy linked with PTA, surgical thrombectomy, endarterectomy, patch angioplasty, and/or bypass. The only way TRT methods can be compared is if the treatment of the underlying lesions is standardized in the protocol.

Recommendations

The method(s) of TRT must be described. If a thrombolytic drug is used, then the following must be reported: (a) thrombolytic drug (type, manufacturer, city, state) and its concentration, (b) method of administration as defined in **Table 5**, (c) the total dose of drug used, and (d) the total duration of the drug infusion. For pharmacomechanical thrombolysis, the protocol for the use of the thrombolytic drug and catheter or device (type, manufacturer, city, state) must also be described. For PAT and PMT, the device or catheter system (type, manufacturer, city, state) and protocol of its use (ie, thrombus aspiration, maceration, mobilization performed in conjunction with a mechanical device or catheter system, application of an external cuff to prevent distal emboli) must be described in detail. If adjunctive anticoagulant or antiplatelet medications are used with TRT, their protocol of use (method of administration, dose, method of titration) must be described in detail. The method of patient monitoring, both clinical and laboratory, must be described in detail. For studies of techniques designed to shorten revascularization time (PAT and PMT), total procedure time and fluoroscopy time should be reported. Blood loss and amount of hemolysis should be reported for PAT and PMT.

Adjunctive treatment given to patients should be tabulated. The location, length, and morphology of any underlying lesion(s) should be described. The selection criteria for treatment of any underlying lesion by endovascular versus surgical methods should be outlined and standardized. The method used (**Table 6**) to treat the underlying lesion must be reported. The patency of the distal arterial bed, again according to the SVS scheme for weighing of runoff arteries, must be assessed before and after adjunctive treatment. After intervention, the protocol for use of any adjunctive medical therapy (antiplatelet, anticoagulation,

Table 6
Types of Adjunctive Procedures

- Percutaneous transluminal angioplasty
- Stent
- Atherectomy
- Surgical
 - Thrombectomy/embolectomy
 - Endarterectomy ± patch angioplasty
 - Insertion of a new graft
 - Insertion of a jump graft
 - Graft revision
 - Patch angioplasty
 - Excision of diseased segment and reanastomosis with or without an interposition graft
 - Ligation of arteriovenous fistula

etc.), short- or long-term, must be described in detail.

POSTTREATMENT EVALUATION

There are multiple single-center reports of the short- and long-term results on the revascularization of the acutely ischemic limb. Unfortunately, these studies are difficult to compare and apply directly to patient management. This problem is attributable to differences in study populations, differences in reporting methods, and lack of relevant outcome data. The evaluation of therapeutic effectiveness requires patient outcome measures rather than hemodynamic measures alone (1).

Immediate success is determined by technical success, hemodynamic success, and clinical success. Potential outcomes such as a decrease in requirement of surgical intervention and replacement of major surgery by a minor surgery or endovascular intervention are also relevant in the assessment of immediate success. The short- and long-term outcome measures depend on the hypothesis of the study. Outcome endpoints can be gauged by a number of parameters such as patency (primary, primary-assisted, secondary), 1-year major amputation-free survival, partial limb salvage, recurrent ischemia, complications, and death, or with use of a composite outcome incorporating some or all of these elements ("event-free survival"). Standardized definitions are provided herein.

Technical Success of TRT

Technical success of TRT is defined as restoration of antegrade flow and complete or near complete (95% by volume) removal of the thrombus (50). This definition allows evaluation of TRT separately from the adjunctive procedure(s), if needed. Initial failure of TRT should be analyzed as to find a cause of failure: (a) inability to catheterize, embed an infusion system, or advance a mechanical device into the thrombosed segment; (b) treatment aborted as a result of complications; or (c) treatment performed but not technically successful. If the purpose of the study is to evaluate the effectiveness of the use of a thrombolytic drug alone for TRT, removal of any residual thrombus by other methods is regarded as a technical failure. Similarly, if the intended TRT method involves only the use of a device, removal of any residual thrombus by other methods is regarded as a technical failure.

Hemodynamic Success

The ideal definition of hemodynamic success is the return of the patient to at least his/her preocclusive baseline ABI. There are several problems with the use of this definition. Pretreatment ABI is frequently not recorded in the setting of acute limb ischemia because its significance, as noted earlier, is unclear. The posttreatment ABI usually includes the TRT and the adjunctive procedure if there is an underlying lesion, and the final ABI will be largely determined by the adjunctive procedure and may be higher than baseline level. A more qualitative assessment that may be reported is the return of pulses distal to the treated segment, although this depends on the presence and treatment of the underlying lesions. For these reasons, reporting of hemodynamic success is of limited value. Nonetheless, it is important to report the final ABI because it will be used to evaluate recurrent ischemia during follow-up.

Clinical Success of TRT

Clinical success of TRT is defined as relief of the acute ischemic symptoms or reduction of the level of the subsequent surgical intervention or amputation needed (**Table 7**). To comment

Table 7
Recommended Scale for Gauging Changes in Clinical Status in Acute Limb Ischemia after Thrombolysis

-1	Ischemia is worse (by at least one major or minor category from SVS/ISCVS Clinical Categories of Acute Limb Ischemia)
0	No change (failure)
+1	Ischemia improved
	a. Revascularization with thrombolytic methods alone
	I. amputation necessary but at a lesser level‡
	b. Adjunctive surgical revascularization necessary but at a lesser level†
	I. amputation necessary but at a lesser level‡
	c. Adjunctive endovascular revascularization necessary (angioplasty, stent, atherectomy, etc.)
	I. amputation necessary but at a lesser level‡

Note.—Categories a, b, and c do not imply greater or lesser degrees of success.

† Levels of surgical revascularization: 1, Major: insertion of new bypass graft, replacement of an existing bypass graft, or excision or repair of an aneurysm. 2, Moderate: graft revision, patch angioplasty, endarterectomy, or profundaplasty. 3, Minor: thrombectomy/embolectomy or fasciotomy

‡ Levels of amputation: 1, above the knee; 2, below the knee; 3, transmetatarsal; and 4, toe.

on how TRT changed the surgical treatment option, it is necessary to record which surgical treatment would have been performed had TRT not been attempted.

Overall Clinical Success

Overall clinical success, or clinical success for the TRT procedure plus adjunctive therapy of underlying lesions, is defined by relief of the acute ischemic symptoms and return of the patient to at least his/her preocclusive clinical baseline level after the TRT and adjunctive procedures.

Patency

Patency applies only to the treated segment, refers to continued flow through the treated segment, and must be documented. Duplex Doppler ultrasonography, conventional angiography, or magnetic resonance angiography can be used to assess patency. Stenosis developing within the treated segment without reocclusion is not considered a loss of patency but will contribute to recurrent ischemia (6).

Primary patency is defined as the time from the revascularization procedure to either revision or the first occurrence of thrombosis of the treated segment. Any treatment to deal with disease progression in the adjacent na-

tive vessel is not considered a loss of primary patency.

Primary assisted patency is defined as the time from the revascularization procedure to thrombosis, irrespective of any interval therapy to restore or maintain flow within the treated segment. Patency may be maintained by percutaneous or surgical procedures other than bypass (ie, focal endarterectomy, PTA, stent placement, patch angioplasty) performed to treat one or more stenoses in the treated segment.

Secondary patency is defined as the time from the procedure to the permanent loss of flow in the treated segment, irrespective of any interval therapies. Patency may be restored and maintained by percutaneous (ie, thrombolysis, PTA, stent placement, atherectomy) or surgical (thrombectomy, endarterectomy, patch angioplasty) interventions. Secondary patency is lost if the treated segment is surgically bypassed.

One-year Major Amputation-free Survival

One-year major amputation-free survival means a patient has had no amputation or a minor amputation leaving sufficient functional foot remnant to allow walking without a prosthesis for at least 1 year after treatment. Minor amputation allows the patient to ambulate without the use of a prosthesis and is represented for the

most part by toe or metatarsal amputations. Syme amputation and most high forefoot amputations (ie, Chopart) are included as major amputations. This definition applies only to the evaluation of therapeutic outcome of procedures that are intended to avoid major amputation. In a patient with established tissue loss, a revascularization procedure that allows a minor amputation to heal qualifies as a success. An unexpected minor amputation as a result of the TRT method is regarded as a major complication.

Partial Limb Salvage

Applies only to the therapeutic outcome of surgical or endovascular intervention(s) that are intended to change the level of an inevitable major amputation. For example, a revascularization procedure qualifies as a success if it allows healing of a below-knee amputation when an above-knee amputation was otherwise predicted.

Recurrent Ischemia

Recurrent ischemia is defined as recurrence of ischemic symptoms or a decrease in ABI of >0.15 from the posttreatment (TRT and adjunctive) baseline level (6). Acute limb ischemia caused by recurrent embolization may be experienced by as many as 43% of patients in the absence of anticoagulation therapy (51). Each episode reduces the likelihood of complete restoration of blood flow to the limb. Ischemia from in situ thrombosis also has a high incidence of recurrence (52,53). If the underlying lesion disclosed by thrombolytic therapy is not treated, the recurrence rate may be as high as 53% (1). Recurrent ischemia may also be a result of loss of primary patency of the adjunctive procedure used to treat the underlying lesion.

Health-related Quality of Life

Health-related quality of life is used to identify the general well being of a patient through evaluation of overall functional status, perceived health, psychologic well-being, and role function. The use of a validated quality-of-life questionnaire is recommended to measure the general health status after treatment in patients with acute limb ischemia (1). The SF-36 is a standard-

ized and validated method for this assessment (1).

Functional Status

For patients with chronic limb ischemia, the Walking Impairment Questionnaire is useful in evaluating the impact of mild to moderate limb ischemia on leg function (1). Currently, there is no method for evaluating patients with acute limb ischemia.

Recommendations

The overall success and clinical outcome of the study group(s) must be reported. The study patients must be stratified into native arteries versus grafts and vein grafts versus prosthetic/composite grafts, and analyses of the groups must be performed separately and together. The success and outcome data must take into account differences in risk factors between groups. Therefore, the patients must also be sub-stratified by severity of acute limb ischemia with use of the SVS/ISCVS clinical categories, duration of ischemia, etiology of occlusion (in situ thrombosis vs embolus), and risk factors/comorbidities according to the outline in the Pretreatment Clinical Evaluation section of this article.

As stated previously in other SIR documents, follow-up periods are defined as immediate (1–30 d after the procedure), short-term (30 d to 12 mo after the procedure), and long-term (>12 mo after the procedure) (5,6). Immediate success must be evaluated by intent to treat and by the intended primary method for thrombus removal (“per-protocol analysis”). The immediate technical and clinical success must be reported. Hemodynamic success may be reported, depending on study design. The incidence and causes of primary treatment failure (before treatment with another modality) must be described.

The primary endpoints that must be reported include patency, 1-year amputation free survival, partial limb salvage, and mortality. The secondary endpoints reported will depend on the purpose of the study. Previous reports of thrombolytic therapy trials have included composite outcomes in their statistical analysis (22). We recommend that composite outcomes should not be used because specific outcomes

of interest tend to be hidden when grouped together. The number and nature of procedures to maintain primary assisted or secondary patency must be reported. The secondary endpoints that must be reported include primary treatment failure, major morbidity, and recurrent ischemia. Thirty-day or even 6-month outcomes may be insufficient, particularly if one treatment has a shorter durability of success than the other. Follow-up should be at least 6 months for meaningful comparisons of therapy (1).

COMPLICATIONS

Complications may be hemorrhagic or nonhemorrhagic. The bleeding can be local or remote and should be divided into major and minor. Major bleeding is defined as an intracranial bleed, bleeding resulting in death, or bleeding requiring transfusion, surgery, or cessation of TRT. Minor bleeding is defined as less severe bleeding managed by local compression, increases in vascular sheath size, or decreases in dose of the lytic, anticoagulant, or antiplatelet drug. Non-bleeding complications include puncture-related injury, local arterial injury (perforation, dissection, occlusion), embolization requiring intervention, rethrombosis, pericatheter thrombosis requiring unexpected additional intervention, reperfusion injury, compartment syndrome, renal failure, acute myocardial infarction, etc. The SIR complications list is provided in **Table 8**.

Reperfusion injury is one of the most common complications leading to prolonged morbidity. The sudden return of oxygenated blood to the acutely ischemic muscle causes the generation and release of oxygen free radicals and subsequent cellular damage. Failure to anticipate or recognize this complication can lead to the rapid development of compartment syndrome and myonecrosis. Treatment consists of fasciotomy (1).

An unexpected amputation (ie, caused by distal emboli) or an increase in the level of amputation as a direct result of the revascularization procedure is regarded as a major complication. Any adverse effect occurring during the time period beginning with the diagnostic arteriogram to 24 hours after revascularization is defined as a

procedure-related complication. Other adverse events that are detected more than 24 hours after revascularization may also be procedure-related (acute renal failure, delayed embolization, or hematoma from the intervention or access site, etc.).

Recommendations for Reporting Standards

All complications must be tabulated and reported. Also, the complications must be classified by outcome as major or minor (**Table 9**), with the most severe complication incurred by the patient to be reported for use in the classification (6). Procedure-related and overall complication rates must be reported. The 30-day morbidity and mortality rates must be reported. Also, the overall (beyond 30 d) morbidity and mortality rates must be reported to gauge the long-term effects of the treatment.

COSTS

Thrombolytic therapy has been criticized because of high costs associated with the thrombolytic drug. The cost of thrombolytic therapy has been evaluated in only a few studies (54,55). Van Breda et al (56) examined the cost of two thrombolytic drugs, urokinase and streptokinase, in the treatment of peripheral arterial occlusive disease. Despite the greater cost of urokinase, the total cost of care was greater with streptokinase because urokinase therapy had greater success with fewer complications. Janosik et al (57) examined the length of hospital stay in patients treated with surgery or thrombolytic therapy for peripheral arterial occlusive disease. The length of hospital stay was identical between the group treated by surgical revascularization and the group treated by thrombolytic therapy with streptokinase, averaging 21 hospital days. However, thrombolytic therapy with urokinase was associated with a reduction in hospital stay, which averaged 11.5 hospital days. In the Rochester trial, costs were calculated for patients randomized to undergo thrombolytic therapy with urokinase versus those undergoing primary surgical intervention (25,58). The cost of hospitalization (technical component) in the thrombolytic therapy arm was

Table 8
SIR Complications Master List

Complication Class	Complication
Vascular	Hematoma/bleeding at needle, device path: nonvascular procedure
	Hematoma/bleeding, puncture site: vascular procedure
	Hematoma/bleeding, remote from puncture site
	Arterial occlusion/thrombosis, puncture site
	Arterial occlusion/thrombosis, remote from puncture site
	Venous occlusion/thrombosis, puncture site
	Venous occlusion/thrombosis, remote from puncture site
	Vasospasm, severe
	Intimal injury/dissection
	Pseudoaneurysm
	Arteriovenous fistula
	Vascular perforation or rupture
	Arterial embolization
	Ischemia/infarction of tissue or organ
	Pulmonary embolism
	Other
Device-related	Migration
	Malposition
	Device malfunction with adverse effect
Contrast-related	Other
	Allergic/anaphylactoid reaction
	Renal failure
	Other dose-dependent complication
Medication-related	Tissue extravasation
	Other
	Incorrect drug
	Incorrect dosage
	Incorrect site of administration
Neurologic	Idiosyncratic reaction
	Other
	Transient ischemic attack
	Stroke
	Seizure
	Other CNS complication
Cardiac	Other neurologic
	Peripheral nervous system complication
	Hypotension, profound
	Vagal reaction
	Arrhythmia, significant
	Angina/coronary ischemia
	Myocardial infarction
Congestive heart failure	
Respiratory/pulmonary	Other
	Hypoxia, profound
	Pulmonary edema
	Pulmonary embolism
	Respiratory arrest
	Other respiratory/pulmonary
	Contamination of pleural cavity (urine, bile, empyema, malignancy, etc.)
	Pneumothorax
	Other pleural complication
	Local infection
Infectious/inflammatory	Septicemia/bacteremia
	Septic Shock
	Pancreatitis
	Peritonitis
	Other infectious/inflammatory
	Abscess
	Fluid/electrolyte imbalance
General nonvascular	Noninfected fluid leak
	Unintended perforation of hollow viscus
	Other general nonvascular
Death	Death related to procedure (<30-day mortality)
	Death unrelated to procedure

Note.—CNS = central nervous system.

Table 9
Classification of Complications by Outcome

Minor complications:
No therapy, no sequela
Minor therapy or minor sequela, includes unplanned overnight hospital admission for observation only (<24 hours)
Major complications:
Requires major therapy or unplanned hospitalization (24–48 hours)
Requires major therapy, unplanned increase in the level of care, prolonged hospitalization (>48 hours)
Permanent adverse sequela
Death

slightly higher than that in the surgical arm, but lower professional fees with thrombolytic therapy balanced this. Overall, the conclusion of this trial was that the cost of treating a patient was not significantly increased when thrombolytic therapy was employed, even after consideration of the relatively substantial cost of urokinase. The use of other thrombolytic drugs or TRT techniques may also allow reduced drug costs compared to urokinase (59–61).

With the growing concern for cost containment and efficient use of hospital resources, scientific studies are needed to establish the exact role of TRT in the treatment of patients with acute limb ischemia. The cost of the thrombolytic drug, catheters, and device(s) is only one parameter that determines the impact of TRT on cost. Professional fees, technical resources, and hospital costs must all be entered into the equation. In this regard, it is more appropriate to use cost data rather than charge data, because charges bear a poor relationship to the actual economic impact of therapy (62,63).

Recommendation for Reporting Standards

The cost effectiveness of TRT and its risk-benefit ratio must be examined in depth (64). Costs should be analyzed over a long follow-up period to address potential differences in the

durability of procedures. Ideally, costs should be compared with an assessment of quality of life so that costs per quality-adjusted life year can be determined (65–67). Cost analysis might be done best as a separate study.

COMPARISON BETWEEN TREATMENT GROUPS

There are two general types of studies that can be used in clinical trials to evaluate TRT (5,68). The first is a randomized clinical trial, which involves the random assignment of treatment to each subject (69). The double-blind randomized clinical trial is the “gold standard” of clinical research. However, it is often not feasible to conduct such studies because of cost, patient recruitment issues, and/or ethical considerations. If a clinical trial is either not possible or not feasible, much can be learned from an observational study (ie, case-control study, cross-sectional study, and cohort study) in which treatment is not assigned randomly. These studies often can be performed more easily than randomized clinical trials and can be very informative. A randomized, prospective study is the methodology of choice for determining the safety and efficacy of a given TRT method and for comparing various TRT methods to one another or to surgical revascularization. Reports must indicate whether the study is single-center, multi-center, sponsored (if so, by whom), and, if sponsored, whether it was performed under the aegis of the United States Food and Drug Administration or other regulatory body. The institutional review board status must be provided. For multi-center trials, the number of cases enrolled by each center and the individual institutional experience must be reported.

The hypothesis must be clearly stated. The primary and secondary endpoints of the study must be clearly stated. The study design, estimated SD, significance level, sample size, statistical power, and statistical analyses must be reported. Depending on the purpose of the study, there should be a sufficient number of patients treated so that the descriptive statistics and outcomes can be reported for each stratum, each sub-stratum, and the study population as a whole. Consultation with a statistician in the meth-

Table 10
Recommendations for Reporting Standards

Data	Highly		
	Required	Recommended	Recommended
Patient Selection			
Define target population	X		
Justification of study design	X		
Inclusion criteria	X		
Description of methods of assigning treatment	X		
Exclusion criteria	X		
Stratification of study group	X		
Pretreatment			
Risk factors/comorbidities	X		
Pre-procedure medications		X	
Disease severity	X		
For surgical bypass graft occlusions: type of graft	X		
Recent interventions (endovascular or surgical) to the ischemic limb	X		
Treatment description			
Level of operator experience			X
Details of thrombolytic method used	X		
Lytic drug: type used, total amount used, duration of use	X		
Device: type used, protocol of use	X		
Method of patient monitoring			X
Method of treatment assessment (eg, imaging)	X		
Regimen of concomitant anticoagulation (dose, titration)	X		
Description of underlying lesion (morphology, location, length)	X		
Adjunctive treatment (type, location)	X		
Assessment of distal arterial bed			
preadjunctive treatment	X		
postadjunctive treatment	X		
Posttreatment pharmacologic management (eg, ASA, ticlid, etc.)		X	
Posttreatment evaluation			
Immediate success	X		
Reporting causes for failures	X		
Long-term results			
Patency	X		
1-year amputation free survival	X		
Mortality	X		
Partial limb salvage		X	
Recurrent ischemia		X	
Statistics			
Demographics	X		
Survival curves	X		
Complications			
48 hours post-TRT			
Major	X		
Minor			X
30-day and overall			
Major	X		
Minor			X
Bleeding			
Major	X		
Minor			X
Costs			X
Quality of life assessment			X

Note.—ASA = aspirin.

odology of the study design and statistical analysis is recommended before commencement of the study.

Primary statistical analyses should be reported based on intent-to-treat and per-protocol analyses. With an intent-to-treat approach, subjects are analyzed with the group to which they were randomized, even if they dropped out of the study or the treatment was not performed. The justification for this is that the study will then measure the benefit or harm of making a change in the practice of medicine. A per-protocol analysis considers only those patients receiving the intended treatment.

There are several statistical methods that could be used for the analysis of data that is generated by a revascularization study. Because much of the data are time-to-event data, survival analysis should be performed with use of either life-table or Kaplan-Meier techniques (70,71). Survival analysis can easily deal with missing data because it merely treats the missing data as if it were censored. Most other statistical methods do not handle missing information nearly as neatly. If a substantial portion of the data are missing, an adjustment for it should be made in the analysis (72). Survival curves should be compared with use of either the log-rank test or the Wilcoxon test. If the outcome variables are not time-to-event data, there are other statistical methods that would be appropriate. If the response is binary (ie, a patient does or does not have a particular adverse event at a specific time), the different arms of the study can be compared with either χ^2 test or logistic regression. If there are demographic or stratification variables that should affect the results of the analysis, logistic regression will allow for the estimated treatment effects to be adjusted for the effects of the other covariates. It is important to report test results, even if they are not significant, to reduce the inherent publication bias in the literature.

CONCLUSION

Published studies on thrombolytic therapy for the treatment of acute limb ischemia have been limited by inconsistencies in study design, and published studies on mechanical thrombectomy are currently lacking. It is the

purpose of these reporting standards to bring greater uniformity to research on TRT for the treatment of acute limb ischemia. A summary of the recommendations and requirements for reporting are provided in **Table 10**.

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