Cardiovasc Intervent Radiol (2011) 34:1123–1136
DOI 10.1007/s00270-011-0258-z

CIRSE STANDARDS OF PRACTICE GUIDELINES

Quality Improvement Guidelines for Percutaneous Catheter-Directed Intra-Arterial Thrombolysis and Mechanical Thrombectomy for Acute Lower-Limb Ischemia

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Received: 3 December 2010 / Accepted: 27 July 2011 / Published online: 1 September 2011

Introduction

Thrombolytic therapy has been an established and effective treatment for acute limb ischemia for years [1–3]. The treatment options for this life-threatening condition are "open" surgery, percutaneous endovascular treatment, and intravenous (i.v.) systemic thrombolysis. Current percutaneous treatment includes catheter-mediated infusion of fibrinolytic agents (pharmacological thrombolysis), pharmacomechanical thrombolysis, catheter-mediated thrombus aspiration, mechanical thrombectomy, and a combination of the above [4–10]. This study was designed to quality assurance guidelines concerning the treatment of acute and subacute arterial limb ischemia, with the use of percutaneous catheter-directed pharmacological thrombolysis and mechanical thrombectomy or a combination of both.

Thrombolytic Agents

Thrombolytic agents, also named fibrinolytic because fibrin is the basic constituent of thrombus, are exogenous substances that enhance the natural endogenous thrombolytic system and have been extensively used for the therapy of ischemia. Their mechanism of action involves the activation of plasminogen [11–18]. More specifically, the physiologic pathway of thrombolysis that leads to clot degradation includes the conversion of plasminogen into plasmin, through the hydrolysis of the arginine-lysine bond, and the consequence production of plasmin degrades fibrin into soluble fibrin degradation products. The catalyst of the intravascular conversion of inactive single-chain plasminogen into active two chain plasmin is tissue-type plasminogen activator [19–24]. The available thrombolytic agents are analytically presented in Table 1.

Percutaneous Catheter-Directed Thrombolytic Therapy and Mechanical Thrombectomy for Acute Limb Ischemia

Acute limb ischemia (ALI) is any sudden decrease or worsening in limb perfusion causing a potential threat to extremity viability (TASC II, Recommendation 45). Acute limb-threatening ischemic event is considered an episode occurring less than 14 days from presentation (hyper acute: 24 h, acute A <7 days, acute B <14 days), subacute between 15 days and 3 months and chronic after 3 months [25]. It may occur as a result of a rapid disease progression in an already symptomatic patient suffering from peripheral arterial disease or as an acute onset in a previously asymptomatic patient [26]. The etiology of the disease is mainly attributed to native thrombosis and embolism; other causes, such as trauma, acute arterial dissection, reconstruction/graft thrombosis, and peripheral aneurysm provoking thrombosis or emboli, present less frequently [9, 27].

Arterial thrombosis accounts for 85% of arterial occlusions. Embolic event are responsible for 15% of ALI

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Table 1 Available thrombolytic agents [12–20]

Name	Mechanism of action	Half-life
Urokinase	Cleavage of the Arginine–Valine bond in plasminogen leading in active plasmin	7–20 min
Natural streptokinase	Irreversible binding and activation of SK to plasminogen. Indirect activation. Vaguely fibrin-specific	12–18 min
Anistreplase	Similar to streptokinase	70–120 min
Tissue plasminogen activator	Fibrin-selective. Binds and activates fibrin by cleavage of an arginine–isoleucine bond after which it activates plasminogen by cleaving Arg560–Val561	2–6 min
Alteplase	Tissue plasminogen activator produced by recombinant DNA technology. Fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin.	3–6 min
Reteplase	Similar to Alteplase. Lower fibrin binding and superior penetration ability	14–18 min
Tenecteplase	Similar to Alteplase. Greater binding affinity for fibrin	20–24 min

Table 2 Clinical categories of acute limb ischemia [25, 36]

Doppler signal		Clinical symptoms			
Categories	Description	Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened	Salvageable if promptly treated	Minimal (toe) or none	None	Often audible	Audible
a. Marginal					
b. Immediate	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Usually audible	Audible
III. Irreversible[a]	Major tissue loss or permanent nerve damage inevitable	Profound anesthetic	Profound paralysis (rigor)	Inaudible	Inaudible

[a] In early presentation, the differentiation between IIb and III may be difficult

incidents, whereas 90% of the emboli are of a cardiac origin [28]. It is reported that asymptomatic popliteal artery aneurysms cause a 5-year complication rate of 60–70% if not treated and 17–46% of complications of ALI are due to thrombosis or/and distal embolization [29–31].

Despite the enormous advancement of diagnostic and therapeutic tools available today, ALI continues to be associated with elevated major amputation and mortality rates (10–20%), usually because of comorbidities, such as cardiopathy [26, 32–35].

This document does not include the treatment of atherothrombotic microembolization disease, also known as "blue toe syndrome."

Indications

With regard to the patient's risk-benefit balance, only salvageable limbs with audible venous Doppler signal and incomplete motor and sensory loss are eligible for percutaneous catheter-directed thrombolysis (categories I and IIa–IIb in Table 2). Life-style limiting intermittent claudication is not an indication for thrombolysis. Patients presenting with profound limb muscle paralysis (muscle rigor) and sensory loss, inaudible venous Doppler signal, and absent capillary return (category III in Table 2) should be considered for an attempt at surgical revascularization or if ischemia is too severe, primary amputation, especially in the clinical setting of a life-threatening condition; it has been reported that severe systemic electrolyte disorders, provoked by acute limb ischemia, may lead to cardiopulmonary impairment [19, 25, 36]. A thorough clinical evaluation, including detailed medical history, is of the utmost importance to identify the cause, severity, and exact time of the ischemic event, as well as various comorbidities, because this will affect both treatment selection and outcome. A history of vascular surgery should orientate the diagnosis toward a thrombosed bypass graft. Risk factors, such as atrial arrhythmia, could help to identify a possible embolic source. Previous history of PAD, intermittent claudication, as well as atherosclerotic risk factors should

be evaluated. It is of a great importance to distinguish whether acute limb ischemia occurred in a healthy, arterial bed or if the acute event took place in a chronic atherosclerotic background. The severity of an acute event on a limb that has not yet formed collateral blood vessels is even greater and requires immediate therapeutic intervention, whereas acute critical limb ischemia in the setting of chronic atherosclerotic arteries could rouse only mediocre deterioration of the limb symptomatology and therefore therapy could wait [9]. Clinical evaluation should provide information about the severity of the disease as classified by The Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS) clinical category of acute limb ischemia (Table 2) [37]. Patients suffering from acute limb ischemia usually present with a cold and painful limb, with concomitant pulselessness, pallor, paresthesia, and paralysis. Thrombolysis should be performed in recent occlusive events (during the first 14 days), as prompt revascularization demonstrated superior success rates [38–40]. All patients with clinical suspicion of ALI should be examined by a vascular specialist and a Doppler examination should be performed. The differential diagnosis of patients with ALI clinical symptomatology includes pathologies, such as systemic shock, acute compressive neuropathy, and phlegmasia cerulean dolens.

Contraindications

Absolute contraindications for catheter-directed thrombolysis include, ongoing bleeding, intracranial hemorrhage, compartment syndrome, and severe limb ischemia that requires immediate surgical procedure. Relative contraindications include major nonvascular surgery or trauma within past 10 days, intracranial tumor, recent eye surgery or neurosurgery within past 3 months, intracranial trauma within 3 months, recent gastrointestinal bleeding (10 days), an established recent cerebrovascular event, and life expectancy $\leq$1 year. Absolute and relative contraindications are analytically reported in Table 3. However, these contraindications are supported by trials mainly regarding systemic thrombolysis. Catheter-directed pharmacological fibrinolysis has been proven to cause less bleeding events and therefore the treatment decision should always depend on the risk-benefit ratio of each different patient [7]. In a case of active bleeding, where open surgery is further compromised by the patient's general condition, a life-saving percutaneous thrombolysis procedure could follow after an attempt to control the site of hemorrhage with intra-arterial embolization [7, 40]. Contrast-media severe allergic reaction and high risk of acute renal injury could be confronted, if absolutely necessary, according to the ESUR guidelines with the proper pharmacological means and adequate hydration [41].

Table 3 Contraindications to percutaneous catheter-directed thrombolysis [7, 9, 40, 41]

Absolute
Ongoing bleeding after failed hemostasis or active bleeding not viable to treat
Intracranial hemorrhage
Presence or development of compartment syndrome
Severe limb ischemia, which in the judgment of the treating physician requires immediate operative intervention
Relative
Major nonvascular surgery or trauma within past 10 days
Uncontrolled hypertension: 180 mmHg systolic or 110 mmHg diastolic blood pressure
Puncture of noncompressible vessel
Intracranial tumor
Recent eye surgery
Neurosurgery within past 3 months
History of severe contrast allergy or hypersensitivity
Intracranial trauma within 3 months
Recent gastrointestinal bleeding (10 days)
Established cerebrovascular event (including transient ischemic attacks within past 2 months)
Recent internal or noncompressible hemorrhage
Hepatic failure, particularly in cases with coagulopathy
Bacterial endocarditis
Pregnancy/postpartum status
Diabetic hemorrhagic retinopathy
Life expectancy $\leq$1 year

Preprocedural Imaging

In patients with clinically diagnosed ALI, a preoperative duplex ultrasound represents a fast, radiation-free, cost-effective imaging modality and should be performed as a first-line diagnostic tool. Digital subtraction arteriography (DSA) also can provide numerous essential information for the design of a therapeutic scheme. If a percutaneous intra-arterial thrombolysis is indicated, the location and morphology of the occlusive event, as well as the estimation of the arterial hemodynamic status, collateral flow, inflow, outflow, distal runoff vessels, and the actual occluded length should be evaluated [26, 42–44].

Multidetector CT (MDCT) and magnetic resonance (MR) angiography could be employed as imaging modalities to establish an accurate diagnosis and to provide information concerning the anatomical location and extension of the disease, especially when surgery is planned [45, 46]. However, whenever the treatment of choice is percutaneous revascularization, DSA could be preferred to avoid any unnecessary delays and excessive iodine contrast media administration. In cases where a popliteal artery aneurysm is suspected, Duplex ultrasound or alternatively

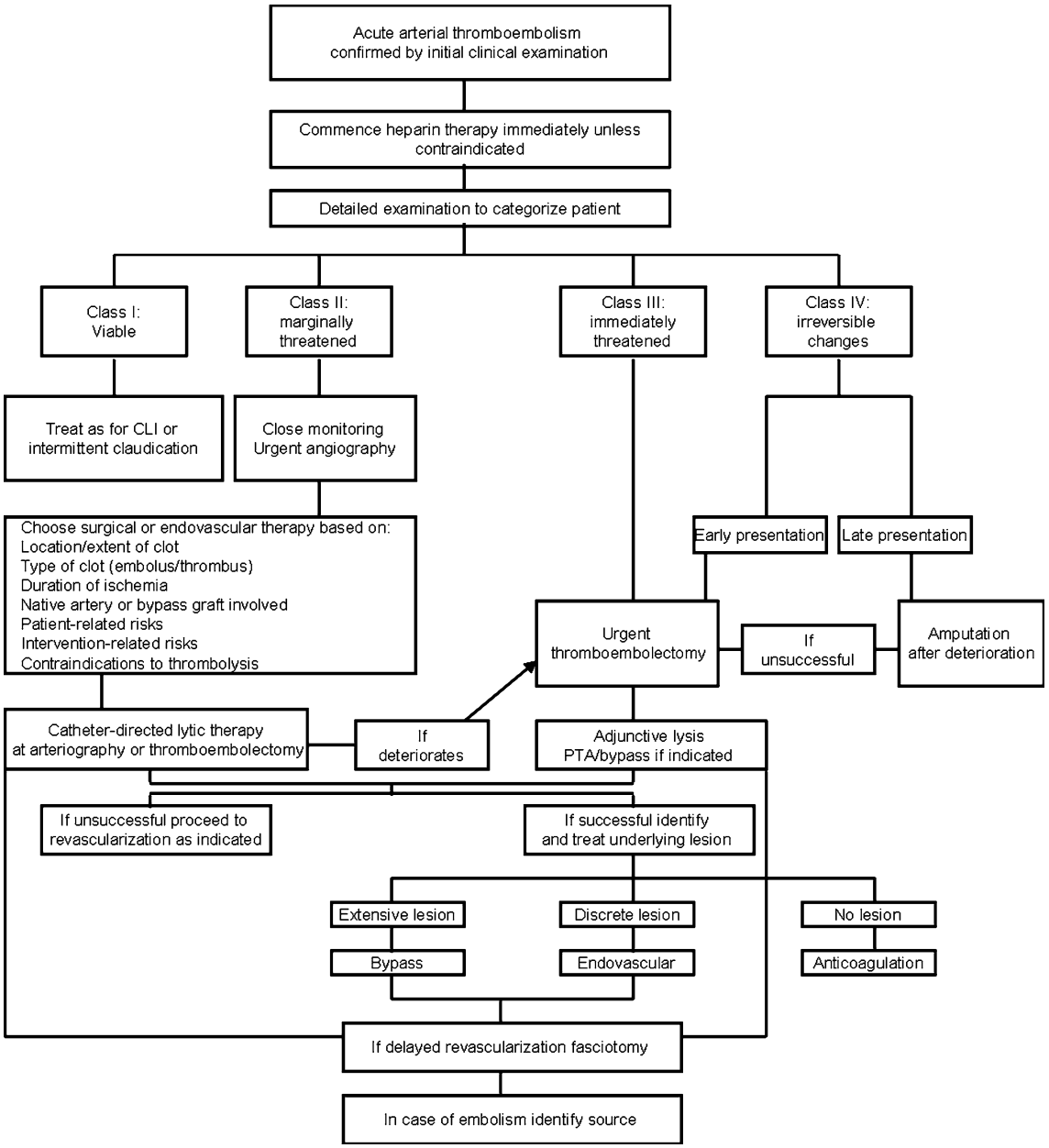

Fig. 1 Treatment algorithm regarding acute limb ischemia as proposed by the Inter-Society Consensus for the Management of Peripheral arterial Disease (TASC II) document [26]

MDCT and MR angiography, should be preferred, because they can demonstrate both the occlusion and the thrombosed aneurismal lumen. Consecutively they are advantageous over an unnecessary DSA, which could furthermore misdiagnose the specific pathology, especially if vessel-wall calcifications are not present [47].

Preprocedural Laboratory Investigations

Laboratory examinations should include baseline hematocrit and hemoglobin, platelets, clotting profile (prothrombin time, partial thromboplastin time, INR), renal function, and acid-base equilibrium markers. A cardiological assessment could detect any unknown and therefore untreated arrhythmias, as well as any recent occult myocardial infarction events. In patients suspected for hypercoagulate disorders, antibody to factor IV and anticardiolipin antibodies and protein S, C, and antithrombin III deficiency tests should be requested [48]. The treatment algorithm for acute limb ischemia, as proposed by TASC II working group, is presented in Fig. 1 [26]. Preprocedural i.v. administration of unfractionated heparin in therapeutic dosages has been

reported to prevent thrombus propagation and to improve the morbidity and mortality rates of patients treated for ALI [4, 49, 50].

In case of fever, aspirin or acetaminophen can be administrated. Puncture site should be periodically checked [51].

Serum fibrinogen monitoring during the procedure as a tool for predicting bleeding events has not been justified until today, by relative clinical trials. There is no evidence that "vasoactive" drugs or sympathectomy are of benefit for the treatment of acute limb ischemia. Preoperative and postoperative oxygen inhalation, as well as simple clinical actions to improve limb perfusion could be helpful [26, 52].

Percutaneous Catheter-Directed Thrombolytic Therapy

Definitions

Percutaneous catheter-directed thrombolytic therapy is defined as the process of percutaneous thrombus lysis with the use of special designed interventional equipment and can be achieved currently by simple pharmacological or combined pharmacomechanical thrombolysis.

Pharmacological thrombolysis is herein defined as the process of thrombus dissolution through the selective catheter-directed infusion of thrombolytic agents. Mechanical thrombolysis (thrombectomy) is herein defined as mechanical disruption of the thrombus. Pharmacomechanical thrombolysis is herein defined as the mechanical disruption of the thrombus combined with pharmacological thrombolysis.

Vascular Access

Vital signs' monitoring, including continuous electrocardiogram, heart and respiratory rate, oxygen saturation, brachial blood pressure, and strict nursing care, should be guaranteed during the procedure. In cases where noninvasive arterial evaluation has been performed previously, the appropriate vascular access will be chosen accordingly. If the primary diagnostic modality is DSA, the angiography should be performed via retrograde, contralateral common femoral artery access. If the patient presents a limb with weak or absent pulses, an ultrasound-guided puncture would be helpful [53]. An antegrade, retrograde, or crossover arterial approach should be consistent with the location of the lesion and the anatomical particularities of the patient (body mass index, vessel characteristics, and patency). A single-wall puncture is preferred even if lytic therapy was not anticipated to minimize the risk of puncture-related complications. After sheath placement, vascular access is secured and a high-quality diagnostic angiogram should be obtained to visualize the morphology and the extension of the lesion, the outflow of the occluded artery, and the run-off vessels. This diagnostic imaging is essential not only for the planning of the percutaneous procedure but also for an eventual bypass surgery after a failed revascularization attempt.

Guidewire Traversal Test

The next steps include the advancement and crossing of the guidewire, through the lesion. The latter is described as the "guidewire traversal test," and the main concept is that a more recent, fresh, thrombus should be crossed easier than an older and already organized one. Published data suggest that a positive guidewire traversal test is a positive predictor of procedural technical success [54]. It is crucial for the success of the procedure to cross the lesion carefully without causing an intimal flap. If the guidewire cannot be passed all of the way through the thrombus, the catheter tip should be placed in the proximal end of the thrombus.

Technique of Thrombolysis

When the guidewire has crossed the lesion, a catheter is placed and the operator can initiate the lytic therapy. Usually a $\leq$5-F caliber catheter is used. There are many different catheters available in the market dedicated for thrombolytic therapy, but until today there has been a lack of evidence concerning the superiority of any of these drug delivery catheters over another. Any catheter that can reach the occlusion and be positioned properly can be used for thrombolytic agent delivery [25].

Thrombolytic Agent Infusion: Techniques and Results

The established local drug delivery techniques of pharmacological thrombolysis are:

1. *Regional intra-arterial infusion* is divided in nonselective infusion where the catheter is positioned proximal to the occlusion without entering the lesion and selective infusion where the catheter tip is inside the proximal portion of the occlusion.
2. *Intrathrombus infusion* is described as the method where the fibrinolytic agent is delivered inside the occlusion as the catheter tip is embedded inside the thrombus. This is the most commonly used technique, and it has been reported that in the majority of the cases a complete thrombolysis is achieved and superior profit was observed once delivery is performed into the thrombus [8, 55].
3. *Intrathrombus bolusing or lacing* is the initial delivery of concentrated thrombolytic agent inside the thrombus, designed to saturate the occluded vessel area from the drug. This method is performed with the use of an

end-hole or a multiple side-holes catheter, or an infusion wire, which is primarily positioned at the distal end of the lesion; as thrombolysis proceeds, the catheter is gradually redrawn, delivering the lytic agent along the thrombosed area [56–60].

4. *Stepwise infusion* is the delivery of the fibrinolytic agent initially in the proximal part of the thrombus. As the thrombus begins to dissolve, the operator advances "step by step" the catheter toward the distal part of the lesion [61].
5. *Continuous infusion* is the standard technique of intrathrombus delivery. The catheter is connected to a pump and a constant drug delivery is obtained.
6. *Graded infusion* refers to a time-dependant dose of agent delivery, where a high dose of drug is administrated within the first hours of the procedure to achieve a shorter procedural time [62].
7. *Forced periodic infusion (pulse-spray technique)* is vigorous intrathrombus drug infusion aimed at thrombus laceration and creating a wider surface of drug delivery. With this method, superior fibrinolytic agent penetration–enzymatic action and concentration inside the occluded lesion should be achieved, leading to shorter procedural time [63–66]. Initially the catheter tip is placed just above the end distal part of the occlusion, leaving a small occluded part untreated, preventing in this way any possible distal microembolic events. The forceful injection of lytic agent is provided manually through a syringe, every 20–30 s.

Intrathrombus high-dose bolusing or lacing, followed by low-dose continuous infusion, should be considered the least effort-demanding and at the same time highly effective infusion technique [8, 67].

Once the catheter is secured, the patient can be transferred to an intermediate or intensive care unit. During the infusion, lysis should be monitored with periodic angiograms preferably every 10–12 h, if this is possible and can be performed with safety, to adjust the infusion rate according to the lytic process and to correct any accidental catheter misplacement. The patient should be kept under continuous surveillance to detect any eventual signs of hemorrhage, and frequent hematocrit/hemoglobin counts should be compared to baseline values.

Finally, after a negative angiographic control, demonstrating no signs of significant intraluminal, residual disease and providing that this remains invariable after numerous angiography runs, the treatment of the underlying lesion can be performed with relative safety. The reported 24-month vessel patency rates after thrombolysis was 79% after the underlying lesion was identified and treated versus 9.8% when not [68]. Primary stenting, if possible without any pre- and postdilatation, should be considered. An inverse relationship between amputation after thrombolysis and number of patent vessels, providing blood to the limb has been annotated [69]. The reported rates of distal embolization ranges from 3.8 to nearly 24%.

After sheath removal, consider the use of a vascular closure device. However, no reports from randomized, controlled studies have investigated the safety and effective use of arterial closure devices compared with classic manual compression, following such high bleeding risk procedures [70].

Whenever the percutaneous endovascular procedures available do not ensure immediate technical success with sufficient blood supply to the extremities together with an acceptable long-term patency rate, bypass surgery for the treatment of the primary lesion should be preferred. The reported dosage regimens of the various thrombolytic agents used for the management of ALI are analytically reported in Table 4 [48, 54, 71–86, 130].

Streptokinase should not be preferred in everyday clinical practice, because it is proved less effective and more antigenic. Recently published data demonstrate that there are no sufficient evidence to support any significant difference regarding the safety and effectiveness of rt-PA compared with UK, regarding patients suffering from an acute peripheral arterial occlusion, although some evidence propose that initial lysis may be more rapid with rt-PA [87].

Anticoagulant and Antiplatelet Agents

Parenteral anticoagulant therapy with heparin should be immediately administrated provided that heparin is not contraindicated and that spinal/epidural anesthesia is not planned [26, 88].

The STILE trial subgroup analysis indicated a 1-year sustained benefit in heparin use during thrombolysis with Alteplase, with regard to the composite clinical endpoint (death, amputation, major morbidity, recurrent ischemia). No significant difference in bleeding complications between the UK and rt-PA arms, with or without heparin administration, was detected [37]. Moreover, catheter thrombosis is likely to occur when heparin is not administrated during the procedure (54). To consider seriously the risk of bleeding, a through-the-sheath, low-dose heparin (400–600 IU/h) protocol can be followed to avoid pericatheter thrombus formation. Heparin should be adjusted to maintain aPTT at desirable levels, whereas ACT during the procedure should be kept at 300 s. Some authors propose a lower dose of 100 IU/h [16, 89, 90].

The mixture of heparin and Alteplase in the same syringe or catheter should be avoided, because it has been reported to result in precipitation. This does not preclude the concomitant administration of these two substances if Alteplase is administrated through the catheter placed into

Table 4 Infusion protocols, technical success, clinical success, and complication rates concerning various thrombolytic agents

Agent	Infusion protocol	Technical/clinical success	Complications
Urokinase	250,000 IU/h in the first 2 h, followed by the infusion of 120,000 IU/h for 2 h and 60,000 IU/h for the remaining procedure [14, 75, 76, 130]	70% complete clot dissolution	Major bleeding: 11%
	240,000 IU/h in the first 4 h followed by 120,000 IU/h for up 48 h (with or without 250,000 IU bolus) [14, 37, 77–79]	69–81% vessel patency	Major bleeding: 5.6–12.5%
	Low-dose regimen: 50,000 IU/h [80]	Same with high-dose regimen of 250,000 U/h for 4 h and then 125,000 U/h (65–85%)	Significantly less minor complications compared with the high-dose regimen
Alteplase (rt-PA, t-PA)	Weight-based scheme: 0.001-0.02 mg/Kg/h Nonweight-based scheme: 0.12–2.0 mg/h. Maximum dose: 40 mg [40, 57]	88.6–91.8% successful thrombolysis	Major bleeding: 6.1–6.8%
Reteplase (r-PA)	Suggested: from 0.25 to 1.0 mg/h. Maximum: 20 IU in 24 h [19]	Thrombolytic success: 83.8–86.7%	Major bleeding: 13.3% in 0.5 mg/h regimen, 5.4% in 0.25 mg/h regimen (statistically significant)
	Low-dose regimen: 0.125 mg/h [85]	Thrombolytic success: 85.3%	Major bleeding: 2.9% (statistically significant)
Tenecteplase (t-NK)	Bolus infusion of 1–5 mg, followed by infusions ranging from 0.125–0.5 mg/h [54, 86–90]	Technical success: 91%	Major bleeding: 6.3%

or close to the lesion and heparin by the sheath placed proximally in the same artery [91].

Results

The definitions and threshold values that follow are mainly adopted from the SIR Reporting Standards for the Treatment of Acute Limb Ischemia, the TASC II Inter- Society Consensus for Peripheral arterial disease, and the recent SIR Standard of Practice Committee Quality Improvement Guidelines [25, 40, 48].

Technical success is defined as the restoration of antegrade blood flow with complete or near complete (95% by volume) lysis of the thrombus or embolus (70% threshold).

Thrombolysis failure is defined as the lack of clinical success [92].

Clinical success is defined as relief of the acute ischemic symptoms or reduction of the level of the subsequent surgical intervention or amputation.

Overall clinical success is defined as the relief from ischemic symptoms and return of the patient to at least one of his preocclusive clinical baseline levels after the removal of thrombus and performance of adjunctive procedures.

Major complications are defined as any undesired event that:

(a) Requires therapy, minor hospitalization (<48 h)
(b) Requires major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h)
(c) Has permanent adverse sequelae, or
(d) Results in death

Minor complications are defined as any undesired event that:

(a) Resolves without therapy and has no consequence, or
(b) Requires nominal therapy, has no consequence, and may include overnight admission for observation only.

Major hemorrhage is defined as blood loss that leads to extended or unexpected hospitalization, surgery, or blood transfusion.

Intracranial hemorrhage of any size is considered major.

The most important prospective, randomized trials that investigated percutaneous, endovascular, catheter-directed pharmacologic thrombolysis resulted in similar limb salvage rates and inferior mortality rates at 6 and 12 months compared with surgical repair [14, 37, 71, 73, 93, 94]. However, subgroup analysis of the STILE trial demonstrated that patients with less than 14 days ischemic symptomatology, randomized in the percutaneous thrombolysis group, suffered significantly lower amputation rates compared with those randomized to undergo surgical repair, after 6 months follow-up (30 vs. 11%, respectively). These outcomes were attributed to the significantly lower 12-month amputation rates achieved subsequent to thrombolysis versus open surgery, in the acute graft occlusion group (20 vs. 48%, respectively).

On the other hand, the trial was prematurely interrupted, because the bleeding complications and technical failure indicated by ongoing ischemia rates in the thrombolysis group were unacceptably higher than those in the surgery group. The inferiority of the thrombolytic therapy in the treatment of subacute or chronic ischemic events is a possible justification of these outcomes [37, 95]. Of note, amputation rates in the thrombolysis group, regarding native arteries occlusions, was 10 versus 0% in the surgery group.

The post-hoc analysis of the TOPAS trial, comparing open surgery and recombinant, demonstrated superior 12-month limb salvage rates in the thrombolysis group when long occlusions (>30 cm) were treated, whereas surgery was proven to be more effective in shorter occlusions [14, 100]. The Rochester was the only trial to report significantly lower mortality rate (62%) regarding the comparison of these two treatment modalities.

Until today, it has not been clear which therapeutic modality provides the best immediate and long-term results. Evidence-based results provided from randomized, clinical trials suggest that thrombolytic therapy is superior to surgery to treat acute (less than 14 days) events regarding bypass graft occlusions and long occlusions without adequate run-off vessel suitable for surgical bypass. On the other hand, open surgery should be preferred for subacute or chronic occlusions and in native arteries occlusions, providing that these patients are fit for surgery. Suprainguinal lesions usually provide better long-term outcomes compared with infrainguinal occlusions [42, 96]. The mortality rate of the disease ranges from 15 to 20% [10, 97]. The reported major amputation rates reach up to 25%. The above-knee to below-knee ratio in ALI is 4:1, whereas for chronic critical limb ischemia this ratio is 1:1. Major hemorrhage rates range from 10 to 15%. Reperfusion syndrome following successful revascularization and requiring fasciotomy ranges from 5 to 25% and rhabdomyolysis resulting in acute renal insufficiency is observed in up to 20% [26, 98, 131].

Table 5 Complications of percutaneous intra-arterial catheter-directed thrombolysis and mechanical thrombectomy as well as their respective reported rates

Major peripheral hemorrhage	1–25%
Cerebral hemorrhage	0–2.5%
Compartment syndrome	1–10%
Distal embolization after thrombolysis	1–5%
Distal embolization after mechanical thrombectomy	0–14%
Perforation after mechanical thrombectomy	0–4%
Dissection after mechanical thrombectomy	0–6%

The results obtained from the use of different fibrinolytic agents suggest that "urokinase may be associated with a lower incidence of complications than rtPA," because the reported overall major hemorrhage and intracerebral hemorrhage rates were significantly lower among patients treated with UK (6.2 vs. 8.4%; and 0.4 vs. 1.1%, respectively). Mortality rates were significantly lower for UK (3.0 vs. 5.6% for rtPA), as well as the need for transfusions (11.1% UK vs. 16.1% rtPA) (99). However, the 2010 Cochrane systematic review, which included five RCTs, stated that "incidences of hemorrhagic complications were not statistically significantly greater with rt-PA than with other regimes" [87]. Complication rates are analytically reported in Table 5.

Percutaneous Aspiration Thrombectomy

Another method of percutaneous, catheter-guided thrombus removal alternative to open surgery is percutaneous aspiration thrombectomy (PAT). It is an easy, low-cost, rapid technique, which is applicable with the use of a large-lumen catheter (6–8-F), or even smaller (5-F) for the crural arteries. The catheter is connected to a 60-ml syringe, and the thrombus is forcefully aspirated out of the vessel [100, 101].

The use of combined mechanical and thrombolytic therapy (pharmacomechanical thrombolysis) is used to increase the lytic effect and reduce procedural time, especially in advanced ischemia, when time is crucial for limb salvage. The results of the combined PAT/thrombolysis therapy are very promising. PAT alone has been reported to result in only 31% procedural success rates, but combined with thrombolysis and PTA the primary success rate reached up to 90%, with a limb salvage rate of 86% and primary patency rates of 58%, in up to 4 years follow-up [102–106].

PAT also can be proven highly effective when it comes to the immediate treatment of iatrogenic acute distal atherothrombotic embolization, occurring during percutaneous endovascular therapeutic procedures [107].

Percutaneous Mechanical Thrombectomy

General Considerations

Percutaneous mechanical thrombectomy is defined as the endovascular thrombus maceration and removal with the use of Fogarty balloons or dedicated percutaneous thrombectomy devices (PTDs). The use of Fogarty balloons are the cheapest, simplest, and fastest method of thrombectomy compared with the more sophisticated PTDs. These balloons are very effective in declotting infrainguinal lesions, through common femoral or popliteal artery puncture, but they are difficult to utilize in chronic stenosis of diseased arteries and well-organized thrombus.

PTDs can be categorized in four types, according to their mechanism of action: mechanical clot dissolution catheters, hydrodynamic/rheolytic catheters, mixed type, and ultrasonic catheters [108–118]. All available PTD are analytically reported in Table 6. Although most PTDs have received CE approval for dialysis grafts and native fistulas declotting, special attention should be given when treating ALI. The main difference is that although microembolization does not produce any clinically significant pulmonary events, the same does not apply for the distal vasculature of an ischemic limb, where microembolic events could result in limb loss. It is a requisite that any PTD used for the revascularization of an ischemic limb should not only provide sufficient, immediate, technical success rate but also secure a safe, embolic-free procedure. For this reason, devices with additional fragment aspiration are preferred for the treatment of ALI. The devices that should be preferred for peripheral applications are the Hydrolyzer, the BSIC Oasis system, the AngioJet, the ThrombCat thrombectomy catheter system, the Bacchus Trellis, the OmniSonics Resolution Wire, and the Ekos Lysus system. Their mechanism of action is briefly described in Table 6.

Results

Only a few of the abovementioned devices have been studied in the periphery. The safety and efficacy of the Rotarex device in peripheral arterial use has been reported. Technical success rates were 95%, whereas distal calf embolization rate reached 9% [118]. The Hydrolyser catheter has been reported to generate significantly less neointimal hyperplasia than the conventional Fogarty thrombectomy, using an in vivo goat model [119]. Compared with the Angiojet device, the Hydrolyzer was found to produce significantly lower embolization rates [120]. The reported success rate is 88 and 73% for grafts and native vessels, respectively, whereas the reported amputation rate is 11%, with 42% of patients necessitating additional thrombolysis [121]. The technical success rates of the Angiojet Rheolytic device range from 56 to 95% and primary patency rates from 68 to 58% at 1 and 3 years, respectively. Distal embolization has been observed in up to 9.8% and amputation-free survival rates of 75% at 2 years. Additional thrombolysis has been used in 29% of the cases. The Angiojet also has been used as a stand-alone method due to contraindicated thrombolysis, with limb salvage rates of 95% at 1 month [122–126, 132]. Rheolytic devices can incite hemolysis and renal failure secondary to free hemoglobin release and therefore a considerable amount of fluids has to be administrated. The manufacture company indicates less than a 10-min application in a flowing blood field to prevent excessive hemolysis.

Due to the lack of well-organized, multicenter, randomized, controlled studies that investigate the performance of PTDs, there are no clear indications regarding their application in ALI treatment. However, the abovementioned clinical trials underline the safety and efficacy of these devices, and their use becomes necessary especially in cases of absolute contraindication in lytic agent administration, or whenever an unsuccessful catheter-guided thrombolysis points out the absolute need for an immediate time-saving procedure. Amongst the great advantages of mechanical thrombectomy is the inferior procedural time, as well as the fact that can it be used as monotherapy when thrombolysis is contraindicated or in combination with a minimal amount of thrombolytic agents in cases of high bleeding diathesis. The latter also could imply lower hemorrhagic complications rates. The advantages of pharmacological over mechanical thrombectomy are the less traumatic effect on the already thrombogenic endothelial environment and the infiltration of the lytic agent in collateral and runoff vessels too small for any type of mechanical thrombectomy catheter. Percutaneous mechanical thrombectomy is recommended in cases of stage Rutherford IIb ischemia and high surgical risk, because thrombolysis is time-consuming and could result in clinical deterioration or/and compartment syndrome. Mechanical thrombectomy should be performed in cases where thrombolysis is contraindicated, although it can provide adjunctive effect in partially successful lytic therapy. The Angiojet and ThrombCat are the only devices CE-marked for peripheral use. The authors recommend the use of the mechanical thrombectomy in the setting of acute or subacute ALI, using the Angiojet or the Rotarex device because both can perform clot suction and have been successfully utilized in clinical practice, as well as the Rheolytic ThrombCat device, which has been recently marked for peripheral applications. Ultrasound-based devices, such as the OmniSonics OmniWave Endovascular System and the Ekos Lysus system, seem promising. Finally, PTDs are not recommended for the treatment of

Table 6 Commercially available percutaneous thrombectomy devices

Name	Company	Type	Mechanism of action
Arrow-Trerotola PTD	International Inc, Reading, PA, USA	Mechanical clot dissolution catheters	Mechanically remove thrombus, without adjunctive aspiration of the fragmented material[a]
Castaneda Brush	Micro Therapeutics, Aliso Viego, CA, USA		
Cragg Brush	Micro Therapeutics Aliso Viego, CA,USA		
Helix	Microvena, White Bear Lake, MN, USA		
Roratex/Aspirex catheters	Straub Medical AG, Wang, Switzerland		Directly fragmentize the thrombus via rotation and simultaneously remove it via suction
Gelbfish-Endovac	NeoVascular Technologies, NY, USA		
Hydrolyzer	Cordis, Miami, FL, USA	Hydrodynamic (rheolytic) catheters	Powerful hydrodynamic recirculation system to dissolve the thrombus, while its simultaneous removal is based on the Bernoulli principle and the Venturi effect
BSIC Oasis system	Boston Scientific, Watertown, MA, USA		
AngioJet	Possis Medical, Minneapolis, MN, USA		
ThrombCat thrombectomy catheter system	Kensay Nash Corporation, Exton, PA, USA		
Bacchus Trellis	Bacchus Vascular, Inc, Santa Clara, CA, USA	Pharmacomechanical thrombectomy catheter	Balloon contained local drug delivery plus dispersion wire and thrombus aspiration
OmniSonics Resolution Wire	OmniSonics Medical Technologies, Inc, Wilmington, MA, USA	Ultrasound energy devices	Applies low power acoustic energy 360° around the active Wire to resolve blood clots
Ekos Lysus system	Ekos Corporation, Bothwell, WA, USA		Pulsed-wave ultrasound energy combined with local drug infusion through pores

[a] Not recommended for peripheral arterial use

ALI involving the iliac, the common femoral, and the profunda femoral artery.

Acute Complications of Endovascular Procedures

Endovascular revascularization techniques, such as angioplasty used for the treatment of peripheral arterial disease, can be the origin of ALI due to arterial thrombosis and/or distal embolization complications in approximately 2–3% [127].

It is reasonable that in the setting of an already accessed artery due to ongoing endovascular procedure, complicated with ALI, the treatment of choice is PAT. This method frequently fails to establish blood flow, because the emboli are in the vessels are two small to be reached with a catheter or because the thrombus simply cannot be detached from the vessel wall and retrieved. In that case, thrombolysis, percutaneous thrombectomy devices, and pharmacomechanical thrombolysis with the use of both PMDs and lytic agents should be considered.

Postprocedural Patient Medication and Follow-Up

Clinical success in the setting of ALI is usually synonymous to limb salvage. To achieve long-term amputation-free survival, a rigorous postprocedural medication therapy and clinical follow-up must be ensured. Final postprocedural ABI should be obtained to serve as a baseline value to compare easily in clinical follow-up visits. Heparin should

be prescribed immediately after the procedure followed by warfarin for at least 3–6 months to avoid recurrence of the disease [26]. The post-thrombolysis medication protocol should include antiplatelet therapy if embolization was the cause of the disease, when the underlying lesion has not yet been treated, and when angioplasty and/or stenting of the underlying lesion has been performed. Low molecular weight heparin also should be considered as an additional aid to double antiplatelet treatment regimen. The duration of the antiplatelet therapy is still a subject of investigation.

However, whether heparin is administrated before, during the procedure, or through the follow-up period, physicians should always consider the risk of severe immune-mediated heparin-induced thrombocytopenia thrombosis (HIT/T) syndrome. This particular syndrome usually occurs 4–14 days after heparin administration and could be fatal. Therapy is consisted of immediate stopping of heparin and the adjustment of therapin with the use of direct thrombin inhibitors, such as daparanoid, bivalirudin, and fondaparinux [128, 129].

Summary

Percutaneous catheter-directed intra-arterial thrombolysis is a safe and effective method of treating acute and subacute lower limb ischemia, as long as accurate patient selection and procedural monitoring are ensured. Although larger, controlled trials are needed to establish the role of PTDs in ALI, mechanical thrombectomy could currently be applied combined with lytic infusion in selected cases where rapid recanalization is required or as a stand-alone therapy when the administration of thrombolytic agents is contraindicated.

Conflict of interest The authors declare that they have no conflict of interest.

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