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# Thrombolytic therapy using recombinant tissue plasminogen activator (r-tPA): the position of the Polish Society for Vascular Surgery

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## 1. Introduction

Thrombolytic therapy is currently used to treat coronary thrombosis, cerebral artery thrombosis, and massive hemodynamically unstable pulmonary embolism. For many years, thrombolytic therapy has also been used in patients with acute limb ischemia and deep vein thrombosis. While fibrinolytic medications can be administered intravenously in the first three indications, the latter two require them being targeted directly into thrombus or its vicinity by means of a catheter.

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For many years, alteplase — a recombinant tissue plasminogen activator (r-TPA) — has been the only fibrinolytic medication available in Poland. However, the treatment of limb ischemia is not a registered indication as per the summary of product characteristics.

## 2. Indications for fibrinolytic therapy in peripheral arterial and venous diseases

This work is aimed at presenting the off-label uses of recombinant tissue plasminogen activator (r-TPA). Registered indications and uses in line with these indications will not be discussed.

### 2.1. Acute limb ischemia (ALI)

Acute limb ischemia (ALI) and deep vein thrombosis (DVT) are sudden-onset disorders requiring urgent treatment due to their potential for causing serious complications directly threatening the limbs and even the lives of patients.

ALI is characterized by a sudden stop of blood flow to tissues and is associated with a risk of limb loss as well as a risk to patient life. Most commonly, ALI is caused by an embolism or a thrombus within the arteries. Thrombosis may occur within an atherosclerotically remodeled artery, a peripheral arterial aneurysm, previously implanted stent or vascular bypass or, less frequently, within a region of arterial delamination or injury. The disorder requires emergency diagnostics and treatment. ALI is diagnosed if symptoms have been observed for less than 2 weeks.

Clinical classification of acute limb ischemia as proposed by Rutherford (TASC II) [1] consists of four categories:

I — limb survival not directly at risk,

IIa — limb survival at borderline risk, limb salvation possible upon timely treatment, IIb — limb survival at immediate danger, immediate intervention required III — irreversible ischemia. The rate of amputations due to ALI is 10 to 15%, and the associated 30-day mortality rate ranges from 15 to 25% [2].

In the case of category IIa or IIb ischemia , revascularization must be undertaken immediately (within 6 hours) [3, 4] to reduce the risk of progression to category III. Thrombolysis may also be a preliminary procedure for arterial bridging operations, e.g. in the case of popliteal or crural aneurysm thrombosis.

### 2.2. Deep vein thrombosis (DVT)

Deep vein thrombosis within the iliofemoral segment poses an exceptional risk of both early and distant complications. The most serious early complication of DVT is pulmonary embolism which is a direct threat to patient's life. The prevalence of pulmonary embolism is estimated at 50–100/100,000, and fatal pulmonary embolism is detected in 50/100,000 autopsies each year. Almost 1/3 of pulmonary embolism cases have been shown to lead to death within the first few hours from the onset of symptoms. This is usually a period when proper treatment cannot be given. However, in cases where proper diagnosis had been made early and proper treatment was initiated, the mortality rate is only about 7% [5]. Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe distant complication of pulmonary embolism. It is a rare yet potentially fatal complication. It is observed in approximately 4% of patients with the history of PE. Another significant distant complication of deep venous thrombosis within the iliofemoral segment if the post-thrombotic syndrome observed in 20–30% of patients with the history of DVT. An increasing number of reports suggest that post-thrombotic syndrome is more common if the thrombosis affects the iliofemoral segment and the patient is treated with oral anticoagulants alone. Targeted thrombolysis should be considered as a means to reduce the risk of early and distant complications in these cases [5].

Indications for thrombolytic therapy of DTV include:

1. Phlegmasia cerulea dolens.
2. Acute, proximal, massive and symptomatic deep lower limb vein thrombosis in all patients.
3. Iliofemoral segment thrombosis in young patients at low risk of bleeding and high risk of distant complications resulting from vessel obstruction or post-thrombotic syndrome.
4. Acute symptomatic thrombosis of the axillary and/or subclavian vein associated with the thoracic outlet syndrome (TOS).

## 3. Contraindications for thrombolytic therapy

Thrombolysis is contraindicated in patients with increased risk of bleeding. Since cancer and old age have not been clearly identified as treatment exclusion criteria, they do not constitute a definite contraindication for thrombolysis, but an increased risk of bleeding should always be considered. Contraindications for thrombolysis were categorized into absolute, major, and minor contraindications (see Table 1) [5, 6].

## 4. Methods and techniques for fibrinolytic therapy of peripheral arterial and venous thrombosis

Treatment of patients with AIL may consist in surgical thromboembolectomy or catheter-directed thrombolysis (CDT) and/or thromboaspiration. The selected

**Table 1.** Contraindications for thrombolytic therapy of acute limb ischemia

| |
|---|
| **Absolute** |
| History of cerebrovascular incident [including TIA (transient ischaemic attack)] within the last two months |
| Active hemorrhagic diathesis |
| Recent history of gastrointestinal bleeding (< 10 days) |
| History of neurosurgical (intracranial, cortical) procedure within the last three months History of craniocerebral trauma within the last three months |
| Movable left heart thrombus |
| Irreversible limb ischemia (severe sensory disorders and muscle stiffness) |
| **Major** |
| History of CPR within the last 10 days History of major non-vascular surgery or trauma within the last 10 days |
| History of biopsy within the last 10 days |
| Uncontrolled hypertension: systolic pressure > 180 mm Hg or diastolic pressure > 110 mm Hg. |
| Puncture of a non-susceptible vessel Intracranial tumor |
| Recent history of eye surgery |
| **Minor** |
| Hepatic insufficiency, particularly with coagulopathy |
| Severe renal insufficiency |
| Bacterial endocarditis |
| Pregnancy |
| Diabetic hemorrhagic retinopathy |
| Thrombocyte count < 100,000/mm$^3$, prothrombin index < 50% |

technique should ensure the most rapid restoration of arterial flow at the lowest risk to the patient. Catheter-directed thrombolysis can ensure rapid restoration of blood supply to the affected limb, particularly in the case of fresh thrombotic lesions, bypass graft or stent thrombosis [7, 8]. A great advantage of thrombolysis consists in that in contrast surgical thrombectomy where thrombi can be removed only from large arteries, lysis can be achieved in both large and small arteries as well as within the arterial capillary bed.

### 4.1. Methods for thrombolytic therapy

1. Pharmacological thrombolysis consists in administration of thrombolytic drugs without the use of mechanical thrombectomy devices; it is divided into the following sub-categories:

a) systemic thrombolysis — thrombolytic medication being administered through an IV catheter away from the affected limb (currently abandoned and hence not discussed in this document);

b) flow-directed thrombolysis — thrombolytic medication being administered through an IV catheter placed within the peripheral part of the ischemic limb, with or without compression bands to deliver the medication to the deep venous system;

c) catheter-directed thrombolysis (CDT) — thrombolytic medication being administered through an infusion catheter placed inside the thrombus (arterial or venous). After the catheter is in place, medication is slowly infused into the thrombus (via a catheter, usually featuring multiple side holes, such as fountain catheter). Ultrasound-assisted CDT consists in the medication being administered through an infusion catheter which simultaneously emits ultrasound wave energy into the thrombus (e.g. EkoSonic catheter; EKOS, Bothell, WA, USA).

2. Percutaneous mechanical thrombectomy (PMT) consists in the use of endovascular mechanical devices which facilitate the removal of clots by means of their fragmentation, maceration and/or aspiration without the administration of thrombolytic medication (will not be discussed due to the nature of the document).
3. Pharmacomechanical CDT (PDCT) consists in the thrombus being dissolved and removed by simultaneous pharmacological CDT and PMT. PCDT

involves a combination of techniques, including the use of multiple side-hole infusion catheters, pulsed spraying technique for applying the liquid to the thrombus manually or using a dedicated device (e.g. AngioJet Rheolytic Thrombectomy System; Medrad, Warrendale, PA, USA) with or without segmental isolation by means of catheter-mounted balloons (e.g. Trellis Peripheral Infusion System; Covidien, Mansfield, MA, USA). The commonly used auxiliary intravascular techniques include aspiration thrombectomy (syringe being used to aspirate blood clots from a vein via the catheter, device, or sheath), balloon maceration (angioplasty balloon being used for thrombus maceration or fragmentation), balloon angioplasty, and stenting.

### 4.2. Thrombolytic medications — a pharmacologist's perspective

In the past, an indirect, non-fibrin-specific plasminogen activator streptokinase was used as the first fibrinolytic agent. Its use was discontinued due to low efficacy, increased risk of hemorrhagic complications, and highly allergenic nature.

Urokinase is the only non-specific plasminogen activator registered for the treatment of limb ischemia in Poland. However, the drug is currently unavailable in the country which could prevent a large group of patients from receiving thrombolytic treatment of limb ischemia or venous thrombosis.

Alteplase, a recombinant tissue plasminogen activator (r-tPA) is a widely available drug for the treatment of cerebral ischemia, cardiac ischemia, and pulmonary embolism yet not indicated in the treatment of peripheral thromboembolism. Alteplase is widely used worldwide and has been included in the guidelines of many scientific societies despite the lack of formal registration. An additional argument supporting the use of alteplase consists in urokinase being withdrawn from use e.g. in the US. Alteplase is currently the most widely used thrombolytic medication; notably, it is the only medication of this type available in Poland. Alteplase is a fibrin-specific agent which preferentially activates fibrin-bound (i.e. clot-bound) plasminogen. Its higher specificity to fibrin has the advantage consisting in reduced rates of systemic hemorrhagic complications.

Alteplase is a glycoprotein (serine protease) obtained by DNA recombination in Chinese hamster ovary (CHO) cells, its activity being identical to that of the endogenous tissue plasminogen activator (novel, third-generation thrombolytic drugs feature a modified t-PA structure to present with modified pharmacological properties such as longer duration of action) [9]. Alteplase is activated upon fibrin binding and directly activates plasminogen to form plasmin which digests the clot proteins, particularly fibrin. The thrombus is made up of fibrin monomers cross-linked via side lysine chains characterized by high affinity for plasminogen. Alteplase's affinity to fibrin-bound plasminogen determines its being activated mainly within the thrombus and results in a lower risk of hemorrhagic complications as compared to classical fibrinolytic medications with a non-fibrin-specific effect (streptokinase, urokinase). The relative affinity towards fibrin causes alteplase to moderately reduce the blood fibrinogen levels resulting in a minor generalized fibrinolytic effect. Plasminogen deficiency and elevated levels of plasminogen activator inhibitor (PAI) may reduce the activity of alteplase.

Alteplase is the first recombinant plasminogen activator registered for the treatment of fresh myocardial infarction (1987), acute massive pulmonary embolism (1990), acute ischemic stroke (1996), and restoration of patency in central venous or other vascular catheters (2001) [10]. Currently, the medication is registered in Poland in the first three of these indications; it is not registered for use in acute limb ischemia (it is worth noting that the summaries of product characteristics are different in different EU countries, with no unified binding document being available). Alteplase is used in intravenous or intraarterial injections. Pharmacokinetic data are mainly derived from studies in acute myocardial infarction which may be relevant in other patient populations, particularly in the elderly. The pharmacokinetic model is a two-compartmental one. The half-life of the drug is short, amounting to only 3–6 minutes in the alpha phase (corresponding mainly to distribution) and 26–40 minutes in the beta phase (corresponding mainly to elimination) in healthy volunteers [11–13]. This means that plasma alteplase levels following a bolus administration are virtually indeterminable after 40 minutes [14]. Therefore, continuous intravenous infusion is required to sustain the medication effect [15].

Due to its structure, alteplase is metabolized in in the liver with the formation of low molecular weight, water-soluble fractions subsequently excreted with urine. The metabolism largely depends on hepatic blood flow; however, no data are available regarding the consequences of this fact for alteplase dosing. Nitroglycerin bay reduce the efficacy of alteplase by significantly dilating veins and thus increasing hepatic blood flow [16].

Simultaneous anticoagulants, antiplatelet drugs or other agents increasing the risk of coagulation disorders may increase the risk of hemorrhagic complications of alteplase treatment. Contraindications for alteplase treatment are related to indications for use and associated with the severity of clinical condition/prognosis and the expected benefits of treatment in terms of possible adverse reactions and complications. Notably, the use of

this fibrinolytic medication may also have an impact on administration restrictions, i.e. Systemic administration is more dangerous than CDT.

Hemorrhagic complications are the main adverse effects of alteplase treatment; severe adverse effects, including symptomatic intracerebral hemorrhage, are rather rare (about 1%) and obviously dependent on the medication dose as well as numerous factors affecting hemostasis. Anaphylactic reactions are rare (small amounts of gentamycin are produced during the manufacturing process and may also be responsible for allergic reactions) and usually limited to oral edema, including angioedema (probably secondary to a plasmin-dependent kinin release mechanism), and hypotonia. As a rule, all these symptoms respond well to antihistamine and glucocorticosteroid treatments; however, angioedema may be a life threatening condition which requires intubation. No immunological data are available indicating the long-term production of antibodies against recombinant human tissue plasminogen activator molecules. This means that the medication can be used in a repeatable and anaphylaxis-safe manner even in short intervals.

According to the summary of product characteristics for Actylise®, the only product containing alteplase available in Poland, the solution (after mixing all the powder and solvent in provided in the packaging; 10 mg, 20 mg, and 50 mg preparations available) contains 1 mg of alteplase in 1 mL. Further dilution with sterile physiological saline (do not use injection water or carbohydrate solutions for infusions, e.g. glucose, due increased turbidity) is possible down to the minimum concentration of 0,2 mg of alteplase in 1 mL of solution. The medication should not be mixed with other agents (including heparin) vials in the same vial or catheter. Alteplase has a shelf life of 2 to 3 years and should be stored away from direct sunlight. After opening, alteplase can be stored at 2–8°C for up to 24 hours.

Protocols for transcatheter administration of alteplase in peripheral vascular embolism vary [17]. Different durations of infusions are used to sustain the medication's effect. Lower doses of medication are characterized by efficacy similar to the higher ones, additionally reducing the risk of hemorrhagic complications upon longer infusions.

### Alteplase dosing

The recommended quantity of r-tPA is 0.5–1.0 mg/h; alternatively, the maximum starting dose 0.01 mg/kg/h is administered via an infusion catheter over 12–24 hours. Upon the administration of r-tPA, subtherapeutic doses of non-fractionated heparin can be delivered simultaneously in 300–500 U/h IV infusion from a peripheral catheter or sheath without initial UFH bolus. Therapeutic aPTT levels should only be reached after CDT has been completed.

## 5. Fibrinolytic therapy monitoring and safety conditions

During CDT, the patient should remain in the high dependency unit so that vital signs and neurological parameters of the limb can be monitored. The level of fibrinogen should be monitored every 4–6 hours due to its documented direct relationship with hemorrhagic complications. If the fibrinogen level drops below 150 mg/dL, the r-TPA infusion rate should be cut by a half; infusion should be stopped if the fibrinogen level drops below 100 mg/dL. In addition, hemoglobin level as well as activated partial thromboplastin time (APTT, in cases of simultaneous heparin infusion) should be monitored every 4–6 hours. The objective is to reach the subtherapeutic APTT of < 50 seconds during the administration of r-TPA and heparin. Arteriographic/phlebographic follow-up should be performed 12–36 hours after the initiation of thrombolytic therapy to verify its efficacy. The following options are possible depending on the results:

1. Continued infusion of alteplase and another follow-up in 12–36 h.
2. Repositioning/replacement of the catheter (so that the "working part" is located within the remaining thrombus) and follow-up in 12–36 h.
3. Termination of thrombolytic therapy and initiation of causative treatment: angioplasty/stenting of the vessel of origin or a classical surgery to remove the origin (and removal of vascular access).
4. Termination of therapy and removal of vascular access.
5. The procedure rarely requires continuation beyond 48 hours, up to a maximum of 72 hours. After this time, infusion must be interrupted and the catheter must be removed. The total r-tPA dose should not exceed 100 mg [18]. After CDT is completed and vascular access is removed, manual compression or closure systems are used to obtain hemostasis and the patient remains immobilized in bed for 6–24 hours. Therapeutic-level anticoagulation treatment is resumed within 2 hours after hemostasis has been obtained. If UFH was administered during CDT, no bolus is given. In patients receiving LMWH, the previous treatment regimen is continued. Vitamin K or DOAC antagonists are administered as indicated on the day of sheath removal.

## 6. Complications of fibrinolytic therapy

The main potential complication following the administration of a thrombolytic agent consists in bleeding which may result in discontinuation of treatment. Bleeding occurs in 13–30% of cases, including the most severe intracranial bleeding in 0.4–2.3% [19]. In the case of severe bleeding complications, transfers of blood products, cryoprecipitate, freshly frozen plasma, and platelets are delivered along with antifibrinolytic medications (tranexamic acid).

## 7. Early and distant outcomes of fibrinolytic therapy of peripheral arterial and venous thrombosis

CDT has the advantage over surgical treatment in grade IIa AIL [20, 21]. Recently, intravascular treatment is also used for grade IIb AIL, including percutaneous mechanical thrombectomy (PMT) being added to local thrombolysis. This approach results in similar revascularization outcomes with lower 30-day mortality rates as compared to open surgery [22–24].

## 8. Summary

Alteplase is a modern, effective thrombolytic medication and should be used in local treatment of arterial and venous thrombosis. Due to the absence this indication in the summary of product characteristics, a separate patient's consent is necessary for the off-label use of the medication.

Legal aspects and opinions of medical law experts for off label application of Alteplase in Poland are included in the attachement 1 and 2 of Polish version of this Guidelines. Please note, that this legal opinions are only applicable in Poland.

## Conflict of interest

None.

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