Prescribing and Administration Guide for Intra-Arterial Tenecteplase for the Treatment of Acute Limb Ischemia

- **Background**

Acute limb ischemia (ALI), defined as any sudden decrease in, or worsening of limb perfusion causing a threat to extremity mobility and viability that has been present for less than 14 days.[1]
Patients with ALI are considered candidates for thrombolysis when they present with Rutherford category 1 or IIa ischemia.[2]

Table I. Clinical categories of acute limb ischemia

		Findings		*Doppler signals*	
Category	*Description/prognosis*	*Sensory loss*	*Muscle weakness*	*Arterial*	*Venous*
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitables	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Modified from Rutherford RB, Flanigan DP, Gupta SK, et al. Suggested standards for reports dealing with lower extremity ischaemia. J Vasc Surg 1986;4:80–94, with permission from The Society for Vascular Surgery.

- **Contraindications of thrombolytic therapy**[2]

In general, thrombolytic therapy is contraindicated in any patient with a haemorrhagic disorder or an anatomical lesion that may bleed. Absolute and relative contraindications are listed below:

- **Absolute contraindications**

1- Active clinically significant bleeding
2- Intracranial hemorrhage
3- Presence/development of compartment syndrome
4- Absolute contraindication to anticoagulation

- **Relative contraindications**

1- Bleeding diathesis
2- Disseminated intravascular coagulation
3- Established cerebrovascular event(including transient ischemic attacks)within past 2mo
4- Neurosurgery(intracranial,spinal),or intracranial trauma within past3 mo

5- Cardiopulmonaryresuscitation within past10d
6- Major surgery ,or major trauma within past10d
7- Recent eye surgery within past 3mo
8- Intracranial tumor, vascular rmalformation, aneurysm, or seizure disorder
9- Uncontrolled hypertension(> 180 mm Hg systolic or >110 mm Hg diastolic blood pressure)
10- Recent internal hemorrhage ,puncture of non -compressible vessel or organ biopsy
11- Recent major gastrointestinal bleeding within past10d
12- Serious allergic or other reaction to thrombolytic agent, anticoagulant,or contrast media(not controlled by steroid/antihistamine pretreatment)
13- Severe thrombocytopenia
14- Pregnancy and immediate postpartum status
15- Severe liver dysfunction, particularly incases with coagulopathy
16- Bacterial endocarditis
17- Diabetic hemorrhagic retinopathy
18- Life expectancy of o 1 y

- **Thrombolysis method**

Systemic administration of a thrombolytic agent to treat ALI carries a high morbidity and mortality risk with poor clinical outcomes, and is not recommended. Intra-arterial catheter-directed administration of thrombolytic agents can achieve thrombolysis of the thrombosed segments and unmask a causative lesion in most cases. [2]
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA. [3]

Following a diagnostic angiogram, a sheath will be inserted into the affected artery and a catheter inserted through the sheath with its tip positioned within the thrombus if possible. This achieves maximal concentration of the drug within the thrombus and directly delivers the agent to the vicinity of thrombus-bound plasminogen. A loading bolus of thrombolytic agent may be administered by the radiologist during catheter placement. Thrombolytic agent is then infused into the thrombus via the catheter, and heparin infused via the sheath side arm to reduce the risk of peri-catheter thrombosis. [4]

- **Procedure**

When the patient goes to radiology with the intention of starting thrombolysis, the ward nursing staff should send two syringe drivers, two line labels, the patient's drug chart and a thrombolysis monitoring sheet (see **appendix 1**) with the patient. Following assessment by a radiologist, the patient will have a sheath inserted intra-arterially. The catheter is inserted through the sheath with its tip positioned in close proximity to the thrombus. The sheath and catheter set-up is shown schematically below in figure 1, and the bedside arrangement with **Tenecteplase** and Heparin infusions in situ shown in figure 2.[4]

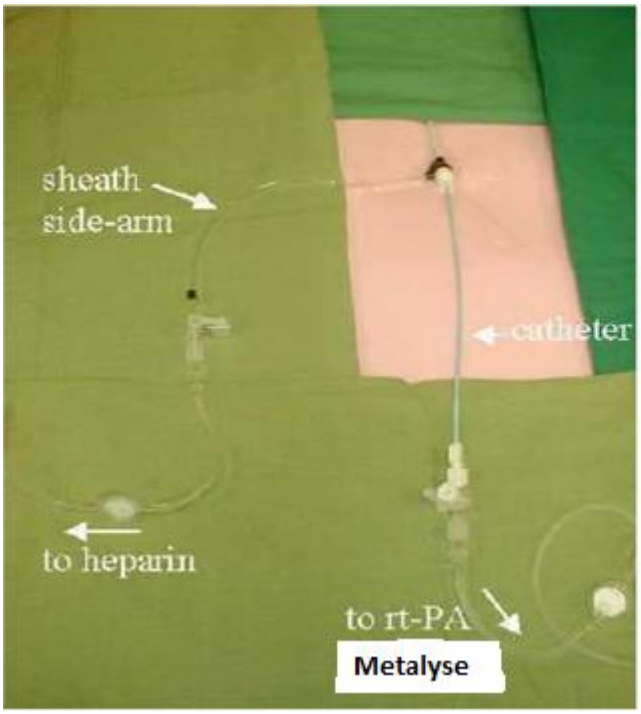


Fig. 1 Catheter and sheath side arm

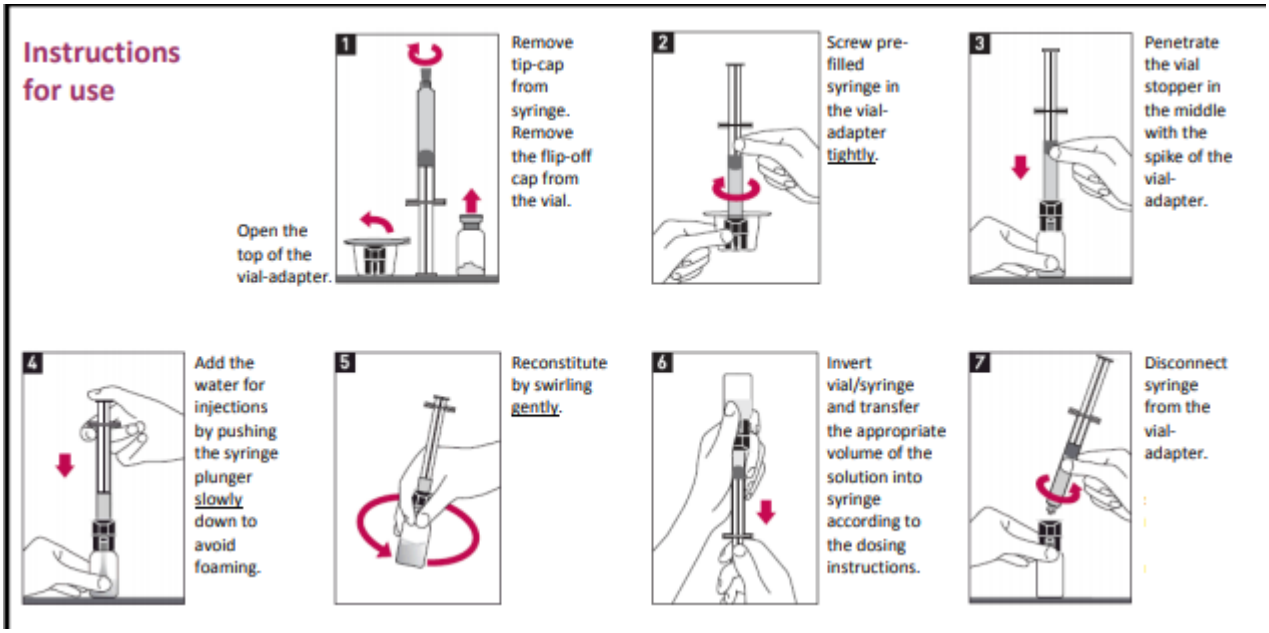
Fig. 2 Tenecteplase and Heparin infusions in situ

The radiologist will prescribe the thrombolysis on the drug chart and radiology staff will initiate the tenecteplase and heparin infusions and commence the thrombolysis monitoring sheet. Tenecteplase is administered via the catheter and heparin via the sheath side arm. The tenecteplase and heparin infusion prescription is described below.
If the syringe drivers, drug chart etc, are not sent down to radiology, the patient will return to the ward with the catheter and sheath in situ and sterile bungs on the hubs. The radiology staff will contact the ward medical staff for prescription and initiation of the infusions. One of the parameters of the thrombolysis monitoring sheet includes the length in cm from line to skin in order to detect if line displacement occurs.
It is imperative that no other medication or agents are administered via the thrombolysis catheter.

- ## Thrombolysis Infusion Regimen

1- (Tenecteplase / Metalyse®)
Once administered, **Tenecteplase** binds to the fibrin clot and induces the conversion of plasminogen to plasmin, which in turn induces fibrinolysis (breakdown) of the clot [3].
Tenecteplase is available in KAUH as Metalyse® (10,000 IU/50 mg) .
The carton contains one vial with a lyophilised powder with 50 mg tenecteplase, one ready for use pre-filled syringe with 10 ml solvent, one vial adapter and one needle[3]. It should be administered according to the following directions:

1. The contents of a 50 mg injection vial of **Metalyse®**should be reconstituted with 10ml water for injection under strict Aseptic non-touch technique (ANTT) conditions, to give a final concentration of 5mg / ml. This should be gently mixed, and any vigorous agitation or shaking should be avoided to prevent foam formation. Following reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and 8 hours at 30°C. From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C. [3]



2. The mixture should be drawn into the syringe according to the dosing instructions, which is then labelled and signed by 2 nurses. The expiry time must also be recorded on the syringe label.

3. The 5mg / 1ml **Metalyse**® solution is then infused via the intra-arterial catheter as follow:
Bolus infusion of 1–5 mg (0.2-1 ml), followed by infusions ranging from 0.125–0.5 mg/h at the discretion of the prescriber.[2,5]

4. The intra-arterial line should be labelled accordingly with a line label.

5. A dedicated thrombolysis monitoring sheet will be initiated in radiology and transferred back to the ward with the patient where it should be attached to the patient's bedside chart so that ward nursing staff can continue to record the infusion rate and volume.

2- Heparin

- Heparin acts to prevent immediate re-thrombosis of the treated vessel and to prevent peri-catheter thrombosis. Use of an equivalent heparin dose with tPA-derived thrombolytics increases bleeding complications but does not improve efficacy. It is now standard to use a ''subtherapeutic'' dose that produces only mild prolongation of the APTT. A bolus at the time of thrombolysis initiation is not recommended. An infusion rate to raise PTT to only 1.25 to 1.5 of control is recommended. [5]
- Precipitation of tenecteplase with heparin has not been reported. [5]
- Heparin is administered concurrently with tenecteplase and should be given via the **sheath side arm** (see fig 1 & 2) to reduce the risk of peri-catheter thrombosis. Heparin available in KAUH as Heparin Sodium injection 25,000 IU / 5 ml (5000 IU /ml), it should be administered according to the following directions:

1. 25,000 IU heparin should be diluted to a total volume of 250 mls using 0.9% sodium chloride or water for injection (giving a dilution of 100 IU heparin / ml) in a a syringe[6], which is then labelled and signed by 2 nurses.

2. This dilution of heparin should then be connected to the **sheath side arm** via a non-return valve connecting tube and a three way tap having excluded any air from the syringe, connecting tube and tap (see fig 1 & 2).
3. The sheath side arm should be labelled accordingly with a line label.

4. The 25,000IU / 250ml Heparin solution is infused initially at 4ml / hr (i.e. 400IU / hr), and again the infusion rate and volume should be recorded on the dedicated thrombolysis monitoring sheet and transferred back to the ward with the patient where it should be attached to the patient's bedside chart so that ward nursing staff can continue to record the infusion rate and volume.

The patient will return to radiology and undergo subsequent angiograms every 4 to 8 hours (usually 6 hours and at least one per day) in order to determine the effectiveness of thrombolysis[7]. The decision to discontinue thrombolysis will be made by the radiologist based on angiography results. Upon discontinuation of the tenecteplase infusion, heparin may be changed to the standard peripheral IV regimen with APTT monitoring as per Trust heparinisation guidelines.
Post-procedural anticoagulation is appropriate and should be continued until the underlying cause of occlusion has been corrected. Long-term anticoagulation should be considered when no underlying cause has been identified or corrected. [4]

- ## Nursing Observations and Patient Care

Due to the increased risk of haemorrhage and shock during thrombolysis treatment, the patient should be strictly confined to bed rest and kept lying as flat as possible. If not already catheterized, the patient should be offered bed pans / urinals.
Patient observations (BP, HR, Temp, RR) should be recorded every 30mins initially and then every 1 – 2 hours once stabilized on the thrombolysis monitoring sheet.
Persistently low blood pressure and / or tachycardia may indicate haemorrhage and necessitates pausing both infusions until this has been resolved.
Nursing staff need to be aware of the risk of intracranial hemorrhage which occurs in 1-2% of thrombolysis cases.
The catheter site should be monitored on an hourly basis, and observations recorded on the thrombolysis monitoring sheet. Special consideration should be given to any bruising or hard swelling around the site, which should be treated as a hematoma and medical advice sought.
Although the infusions may be prescribed and initiated in radiology, the continuing care of the patients on the ward is the responsibility of the vascular surgical team.
It is essential that they are aware that their patient is having thrombolysis. Once thrombolysis has been stopped, the arterial catheter should be removed. In some cases, the sheath may be removed at the same time and homeostasis achieved using a closure device such as Angioseal. In other cases, the patient will return to the ward with the sheath remaining in situ. Radiology will inform the ward nursing staff if an INR check is required prior to sheath removal. Sheath removal should be undertaken by an appropriately trained and experienced member of staff. Firm pressure must be applied to the puncture site until haemostasis has been achieved. This may take 30 minutes or more. A sterile transparent dressing should then be placed over the site to allow observation and monitoring for haemorrhage and haematoma. These observations should continue every half hour to hourly for at least 4 hours and then 2 hourly after that, and recorded on the thrombolysis monitoring sheet.
Blood should be drawn for a complete blood count (CBC), prothrombin time (PT), (APTT), platelet level, and fibrinogen blood level at baseline and 6 hours after thrombolysis began.
Angiography was repeated in 4 to 8 hours (usually 6) unless clinically indicated. [7]

- **References:**

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- **Glossary**

ALI	Acute limb ischemia
ANTT	Aseptic non-touch technique
APTT	Activated partial thromboplastin time
BP	Blood pressure
HR	Heart rate
INR	International normalised ratio
IU	International units
IV	Intravenous
mg	Milligram
ml	Millilitre
RR	Respiratory rate
rt-PA	Recombinant human tissue-type plasminogen activator
Temp	Temperature

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