MIL

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Guidelines for the prescribing and administration of alteplase for adults with haemodynamically unstable pulmonary embolism (PE) (including patients in cardiac arrest)

Alteplase (recombinant tissue plasminogen activator, rt-PA) is a thrombolytic agent that removes embolic material via the dissolution of fibrin clots. Alteplase is indicated in the management of:

- **Cardiac arrest caused by proven or strongly suspected acute pulmonary embolism (PE) (unlicensed)**
- **Haemodynamically unstable acute PE**

The dosage regimens for each indication are not interchangeable, with alteplase being given more quickly in the highly critical arrest situation. It is **not** routinely indicated in the management of haemodynamically stable PE, or cardiac arrest due to myocardial infraction.

1. MANAGEMENT OF CARDIAC ARREST

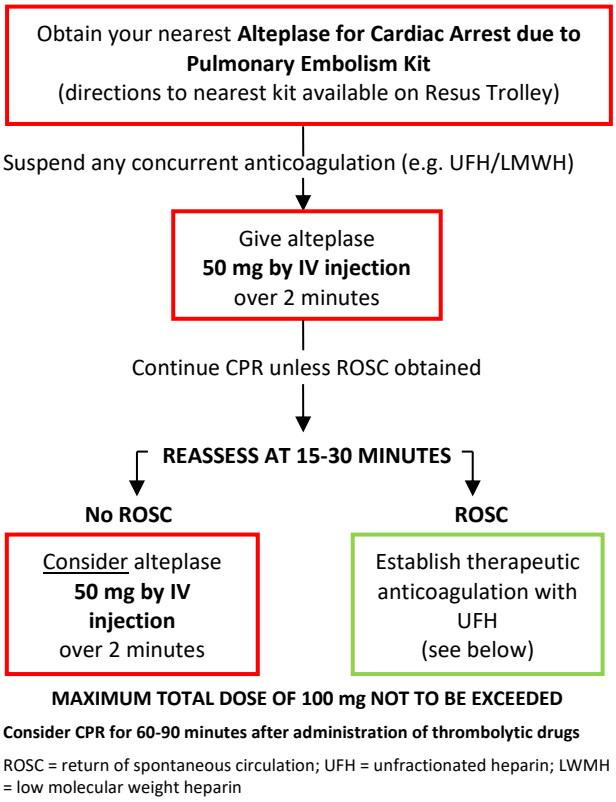
The Resuscitation Council (UK) Advanced Life Support (ALS) guidelines do not recommend the routine use of thrombolysis in cardiac arrest. However, they do advise considering thrombolytic therapy during cardiac arrest caused by **proven or strongly suspected acute PE**. Ongoing CPR is <u>not</u> a contraindication to thrombolysis.

Decision to thrombolyse

The decision to administer alteplase will be taken by the clinician **leading** the resuscitation effort. The decision-making process is time critical. If PE is strongly suspected the decision to thrombolyse may be taken without confirmatory diagnostic imaging. If decision-making support is required (e.g. where there are absolute contraindications to thrombolysis, see below) it would be appropriate to contact a senior doctor in Respiratory, Cardiology or Intensive Care Medicine stating the urgency of the situation. Note that Intensive Care should always be made aware of a patient receiving alteplase for PE. Thrombolytic drugs may take up to 90 minutes to be effective so should only be administered if it is appropriate to continue CPR for at least 60-90minutes.

Dose and administration

There is little evidence to support a particular dosing regimen when alteplase is used in cardiac arrest. The dosing regimen provided below is unlicensed, but has been guided by this limited evidence, advice from Resuscitation Council (UK), and practicality in an arrest situation. This regimen has been agreed by the Trust Resuscitation Committee.



MAXIMUM TOTAL DOSE OF 100 mg NOT TO BE EXCEEDED

Consider CPR for 60-90 minutes after administration of thrombolytic drugs

ROSC = return of spontaneous circulation; UFH = unfractionated heparin; LWMH = low molecular weight heparin

Specific alteplase kits for use in cardiac arrest due to PE have been developed and are located at specified locations across the Trust with a kit being available in each main hospital block. The location of the nearest kit is available on a poster near each Resus Trolley; and a full list of locations can be found on the Resuscitation Department's intranet site under emergency equipment. (Equipment/ Emergency Medicines. Each kit contains:

- Alteplase 50 mg x 2 vials with diluent.
- Alteplase injectable monograph (specific to cardiac arrest due to PE).

Once used the kit must be returned to Pharmacy promptly for replenishment.

2. MANAGEMENT OF UNSTABLE PE

Definition of haemodynamically unstable PE

The haemodynamically unstable patient subgroup can be defined by a systolic blood pressure less than 90mmHg or a pressure drop of greater than or equal to 40mmHg for more than 15 minutes if not caused by an arrhythmia, hypovolaemia or sepsis.

Dose and administration

Alteplase is given as a bolus dose followed by an infusion over 2 hours:

Weight	Bolus dose	Infusion over 2 hours
Less than 50kg	10mg	50mg
50-64kg	10mg	70mg
65kg and over	10mg	90mg

3. CONTINUING ANTICOAGULATION

Cardiac arrest

Unfractionated heparin (UFH) is the initial anticoagulant of choice following cardiac arrest caused by PE due to its shorter half-life and greater reversibility when compared to Low Molecular Weight Heparin (LMWH). Following alteplase administration APTT should be checked as soon as possible, and again at 4 hours. Heparin should be initiated (or resumed, *omitting the loading dose*) when the APTT value is less than 60 seconds (twice the upper limit of normal). The rate of infusion should be adjusted to maintain the APTT according to MIL Vol. 5, No. 6 *Guidelines on when to use and how to monitor unfractionated heparin in adults*.

Haemodynamically unstable PE

If the patient was given therapeutic dose LMWH prior to thrombolysis, this can be continued in place of UFH once clinically stable.

4. MONITORING, CONTRAINDICATIONS AND INTERACTIONS

Monitoring

Blood pressure monitoring during treatment and for 24 hours after is recommended. Alteplase is contraindicated in severe uncontrolled arterial hypertension. For PE, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk in patients with systolic blood pressure above 160 mm Hg.

Absolute contraindications to using alteplase

In cases of cardiac arrest contraindications may not be absolute

Decisions to thrombolyse should be made by the clinician **leading** the resuscitation effort, on a case-by-case basis balancing the bleeding risk against the potential benefit of alteplase.

- Significant bleeding disorders within the past 6 months
- Recent (less than 10 days) traumatic external heart massage; obstetric delivery; puncture of non-compressible blood vessel (e.g. subclavian or jugular)
- Recent (less than 3 months) Intracranial or intraspinal surgery or trauma
- Recent (less than 3 months) major surgery or trauma
- Intracranial neoplasm
- Arteriovenous malformation (AVM) or aneurysm
- Any known history of haemorrhagic stroke or stroke of unknown origin
- Known history of ischaemic stroke or TIA in the preceding 6 months (except current ischaemic stroke within 4.5 hours)

- Known haemorrhagic diatheses
- Severe uncontrolled hypertension
- Bacterial endocarditis, pericarditis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm
- Severe liver disease or active hepatitis

Relative contraindications to using alteplase

The following conditions may increase the risk of bleeding and must be weighed against anticipated benefits:

- Hypertension: systolic BP greater than 160mmHg or diastolic BP greater than 110mmHg
- Likelihood of left heart thrombus
- Pregnancy
- Haemostatic defects secondary to severe hepatic or renal disease
- Diabetic haemorrhagic retinopathy or other ophthalmic haemorrhage
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Small recent trauma such as biopsies, puncture of major vessels, intramuscular injections, cardiac massage for resuscitation

Significant interactions

The risk of haemorrhage is increased if a patient is administered any of the following medications before, during or within the first 24 hours after treatment with alteplase:

- Vitamin K antagonists
- Other oral anticoagulants (e.g. apixaban dabigatran, rivaroxaban or edoxaban)
- Platelet aggregation inhibitors

Concomitant use of GPIIA/IIB antagonists such as abciximab, eptifibatide or tirofiban increase the risk of bleeding. Concomitant treatment with ACE inhibitors may enhance the risk of the patient suffering an anaphylactic reaction

References

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