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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. Thrombolysis is **not** routinely indicated in the management of haemodynamically stable PE, or cardiac arrest due to myocardial infarction.

1. MANAGEMENT OF CARDIAC ARREST

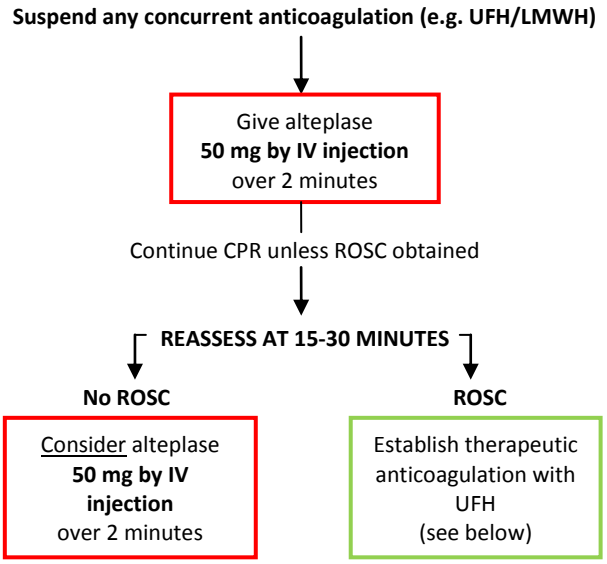
The Resuscitation Council (UK) Advanced Life Support (ALS) guidelines do not recommend the routine use of thrombolysis in cardiac arrest. However, they do advise considering thrombolytic therapy during cardiac arrest caused by **proven or strongly suspected acute PE**. Ongoing CPR is not a contraindication 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 60-90 minutes.

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

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

2. MANAGEMENT OF HAEMODYNAMICALLY UNSTABLE PE

Haemodynamically unstable PE may be suspected in patients:

- with a systolic blood pressure of less than 90 mmHg or a blood pressure drop of greater than or equal to 40 mmHg, that is sustained for more than 15 minutes, **and**
- with evidence of right heart strain either clinically or on imaging, **and**
- in the absence of an alternative diagnosis (e.g. cardiac arrhythmia, hypovolaemia, sepsis)

The diagnosis should, wherever possible, be confirmed by imaging modalities such echocardiography or computed tomography pulmonary angiogram.

Decision to thrombolyse

The decision to thrombolyse a patient with a haemodynamically unstable PE should only be made by a doctor with appropriate experience, and of specialist registrar level or above.

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

The alteplase (PE) injectables monograph, produced by pharmacy, gives more information on how to reconstitute and administer alteplase.

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 dalteparin. 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 dalteparin prior to thrombolysis, this can be continued in place of UFH.

4. MONITORING, CONTRAINDICATIONS AND INTERACTIONS

The absolute contraindications listed below may not always apply in cardiac arrest

Decisions to thrombolyse should be made by the clinician leading the resuscitation effort on a case-by-case basis. In patients where such conditions are present bleeding risk will be high. However, this must be balanced against the potential benefit of alteplase. Urgent senior decision-making support may be required in such cases.

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 mmHg.

Absolute contraindications to using alteplase

(except in cardiac arrest, assess on a case-by-case basis)

- 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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6. *Venous thromboembolic diseases: diagnosis, management and thrombophilia testing* NICE CG144, June 2012 (updated Nov 2015)
7. *Advanced Life Support (2016 7th Edition*), Resuscitation Council (UK) London p59 & p194
8. American Heart Association. *2015 Guidelines for CPR & ECC. Part 10.3: Special Circumstances – Cardiac arrest associated with pulmonary embolism – Updated ALS 435*. Available from: https://eccguidelines.heart.org/index.php/accessibility-version/?volid=7342#3 [Accessed 27/07/16].
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