

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

Ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

A pulmonary embolism (PE) is a blockage in an artery in the lungs, usually caused by a blood clot (embolus). This is usually treated with anticoagulant drugs. This stops further clotting but does not dissolve the embolus. For severe PE, thrombolysis is sometimes used: a catheter (tube) is inserted into a blood vessel (usually in the groin), moved into the artery in the lungs and used to deliver clot-busting drugs to dissolve the clot (thrombolysis). In this procedure ultrasound energy is also used, with the aim of making thrombolysis work better and faster.

The National Institute for Health and Care Excellence (NICE) is examining ultrasound-enhanced, catheter-directed, thrombolysis for pulmonary embolism and will publish guidance on its safety and efficacy to the NHS. NICE's Interventional Procedures Advisory Committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The Advisory Committee has made provisional recommendations about ultrasound enhanced, catheter-directed, thrombolysis for pulmonary embolism.

This document summarises the procedure and sets out the provisional recommendations made by the Advisory Committee. It has been prepared for public consultation. The Advisory Committee particularly welcomes:

- comments on the provisional recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.

- The Advisory Committee will meet again to consider the original evidence and its provisional recommendations in the light of the comments received during consultation.
- The Advisory Committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the [Interventional Procedures Programme process guide](#), which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 5th February 2015

Target date for publication of guidance: March 2015

1 Provisional recommendations

- 1.1 The evidence on ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism raises no major safety concerns over those of catheter-directed thrombolysis (CDT) alone. With regard to efficacy, evidence of any enhancement of thrombolysis over CDT alone is inadequate in quality and quantity. Therefore this procedure should only be used with special

arrangements for clinical governance, consent and audit or research.

- 1.2 Clinicians wishing to undertake ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) for pulmonary embolism (PE) should take the following actions.
- Inform the clinical governance leads in their NHS trust.
 - Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's [information for the public](#) *[[URL to be added at publication]]* is recommended.
 - [Audit](#) *[[URL to audit tool to be added at publication]]* and review clinical outcomes of all patients having UE-CDT for PE (see section 7.1).
- 1.3 NICE encourages further research into ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism. Ideally these should be comparative studies against catheter-directed thrombolysis alone. Patient selection should be explicitly documented. The dose of thrombolytic agent used and the duration of thrombolysis should be reported, together with all complications. Outcome measures should include the success of thrombolysis (complete, partial or failed) and long-term sequelae. NICE may update the guidance on publication of further evidence.

2 Indications and current treatments

- 2.1 Pulmonary embolism (PE) is a condition in which a thrombus, most commonly from a deep vein thrombosis (DVT) in the legs or pelvis, obstructs the pulmonary arterial system. Symptoms of PE depend

on the extent of obstruction to the pulmonary arteries: they include chest pain, dyspnoea and haemoptysis. In severe cases PE can result in reduction in cardiac output, cardiogenic shock and sudden death. Risk factors for PE include surgery, immobility, trauma, malignancy, acquired or inherited hypercoagulable states, use of oral contraceptives, hormone replacement therapy, pregnancy and dehydration.

- 2.2 A PE is normally treated with unfractionated or low molecular weight heparin, followed by oral anticoagulants (typically warfarin). The newer factor X inhibitors may be used without preliminary heparin. Massive and sub-massive PEs are sometimes treated with systemic thrombolysis or, occasionally, with endovascular interventions such as catheter-directed thrombolysis and percutaneous mechanical thrombectomy. Thrombolysis is associated with a risk of haemorrhagic complications including stroke. Surgical thrombectomy may occasionally be performed for patients with a life-threatening PE.

3 The procedure

- 3.1 Ultrasound-enhanced, catheter-directed thrombolysis is an endovascular technique that uses high-frequency, low-energy ultrasound waves in combination with infusion of a thrombolytic drug, with the aim of accelerating plasmin-mediated thrombolysis. It aims to reduce treatment time, the dose of thrombolytic drug delivered and thrombolysis-related complications, compared with catheter-directed thrombolysis alone.
- 3.2 The procedure is usually done using local anaesthesia, with imaging guidance by fluoroscopy. Therapeutic doses of heparin are

administered through a peripheral catheter before and during the procedure.

- 3.3 With the patient in the supine position, an angiographic catheter is inserted from the femoral vein into the main pulmonary artery. The position of the pulmonary embolic occlusion is identified using angiography. A guide wire is passed into the embolus and the angiographic catheter is removed. A multi-lumen infusion catheter is passed over the guide wire into the embolus and the guide wire is replaced with an ultrasound wire. This wire has multiple small ultrasound transducers that deliver ultrasound waves along the entire treatment zone. A thrombolytic drug is infused directly into the embolus through side-holes in the catheter, using an infusion pump, along with a flow of saline to serve as a coolant while the ultrasound wire is activated. An electronic device controls the ultrasound power output. The patient is continuously monitored from the start of treatment. Treatment typically lasts for 12- 24 hours.
- 3.4 Follow-up angiographic and echocardiographic assessment is performed at regular intervals after the start of the procedure. Once the embolus has cleared, or there is no further progress, the treatment is stopped and the patient starts standard anticoagulation therapy.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the [interventional procedure overview](#) *[add URL]*.

- 4.1 A retrospective comparative case series of 25 patients with acute massive pulmonary embolism (PE) comparing ultrasound enhanced catheter-directed thrombolysis (UE-CDT; n=11) against catheter-directed thrombolysis alone (CDT; n=14) reported a significant difference between the 2 groups in the rate of complete thrombolysis (>90% removal) at angiography assessment performed 12-48 hours after initiation of treatment (UE-CDT 100% [11/11] and CDT 50% [7/14]; p=0.01). The study also reported that there was a significant difference in the mean overall infusion time between the 2 treatment groups (UE-CDT group 17.4±5.23 hours, CDT group 26.7±8.64 hours; p=0.03).
- 4.2 In a systematic review of 7 studies (n=197), 3 studies assessed the right-to-left ventricular dimension (RV/LV) ratio using a chest computed tomography scan or echocardiography, before and after UE-CDT. The pooled mean RV/LV ratio decreased from 1.36 to 1.03 (no significance test was reported).
- 4.3 In the systematic review of 7 studies, 3 studies reported mean pulmonary artery pressure before and after UE-CDT. The pooled mean pulmonary artery pressure decreased from 31.3±9.0 mmHg before treatment to 22.7±6.9 mmHg after treatment.
- 4.4 In the systematic review of 7 studies, 2 studies reported cardiac index before and after UE-CDT. The pooled mean cardiac index increased from 2.2±0.7 l/min/m² before treatment to 3.1±1.3 l/min/m² after treatment (no significance test was reported).
- 4.5 In the systematic review of 7 studies, 4 studies assessed pulmonary thrombus load before and after UE-CDT using various angiographic scores (Miller index, modified Miller score, and Mastora score). The pooled mean relative reduction in the

pulmonary occlusion score was 41% (scores ranged from 32% to 69%).

- 4.6 In the systematic review of 7 studies, 2 studies reported recurrence of PE in 2 patients at follow-up. A suspected recurrent PE 1 day after UE-CDT was reported in a case series of 24 patients. This was treated with rescue thrombolysis (100 mg rtPA) given intravenously over 2 hours. A recurrent PE 4 months after thrombolysis, arising from noncompliance with anticoagulant treatment, was reported in a case series of 10 patients. This patient died of severe right ventricular failure.
- 4.7 A retrospective case series of 22 patients with a sub-massive or massive PE who underwent UE-CDT reported that 86% (19/22) of patients were alive at 180 day follow-up.
- 4.8 The specialist advisers listed additional key efficacy outcomes as long term reduction in pulmonary hypertension and right ventricle dysfunction, reduction in right ventricle strain, shortened recovery time and hospital stay, symptom relief and vessel patency.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the [interventional procedure overview](#) *[add URL]*.

- 5.1 Overall mortality at 3 month follow-up was 4% (7/197) in a pooled analysis of UE-CDT, in a systematic review of 7 studies with 197 patients. Deaths were mainly in patients with a massive PE and were caused by multi-organ failure (n=1), discontinued

treatment (n=1), acute abdominal haemorrhage with hypovolaemic shock 6 days after treatment (n=1), ovarian cancer and multiple factors (n=1), cardiogenic shock (n=1) and recurrent PE (n=1). Reasons for the other death were not given.

- 5.2 Mortality was 9% (1/11) in the UE-CDT group and 14% (2/14) in the CDT alone group in a retrospective comparative case series of 25 patients. One patient in the UE-CDT group who had a massive PE died of multi-organ failure 7 hours after treatment. One patient in the CDT group died of cardiac arrest and acidosis 2 hours after initiation of treatment, and 1 had severe heart failure and died 13 hours after initiation of treatment.
- 5.3 Acute kidney injury and cardiac arrest were reported in 1 patient (in whom a retracted infusion catheter was replaced and thrombolysis extended) in a case series of 60 patients, in the systematic review of 7 studies. The patient was successfully resuscitated and recovered after a lengthy hospitalisation.
- 5.4 Major bleeding complications were reported in 4% (7/197) of the patients in a pooled analysis of UE-CDT, in the systematic review of 7 studies. These included: bleeding from the access site that needed a blood transfusion (n=4), intra-abdominal haemorrhage (n=1), intra-thoracic bleeding after cardiopulmonary resuscitation that needed a blood transfusion (n=1) and intrapulmonary bleeding that needed a lobectomy (n=1).
- 5.5 Minor bleeding complications were reported in 11% (21/197) of the patients in a pooled analysis of UE-CDT, in the systematic review of 7 studies. These included: puncture site haematomas that needed no intervention (n=6) and non-fatal haemoptysis (n=3).
Details of the other 11 patients were not available.

- 5.6 The specialist advisers listed additional theoretical adverse events as distal embolization, pulmonary artery perforation, extra-cranial haemorrhage, cerebrovascular accident, cardiac dysrhythmias and right ventricle failure.

6 Committee comments

- 6.1 The Committee noted that ultrasound-enhanced, catheter-directed thrombolysis has the potential to reduce the dose of thrombolytic agent and the duration of thrombolysis compared with catheter-directed thrombolysis alone, and this underpinned the recommendation for comparative research.
- 6.2 In considering the risks and benefits of this procedure, the Committee noted that patients with major pulmonary embolism may die without thrombolytic treatment. It also noted the substantial risks of systemic thrombolysis. The Committee noted that NICE's clinical guideline on [management of venous thromboembolic diseases](#) recommends that systemic thrombolytic therapy for pulmonary embolism should be considered for patients who have haemodynamic instability but should not be offered to patients who are haemodynamically stable.

7 Further information

- 7.1 For related NICE guidance, see the [NICE website](#).
- 7.2 This guidance requires that clinicians undertaking the procedure make special arrangements for audit. NICE has identified relevant audit criteria and is developing an audit tool (which is for use at local discretion), which will be available when the guidance is published.

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