NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of 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, which stop 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.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in June 2014.

Procedure name

- Ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism.

Specialist societies

- British Thoracic Society
- British Society of Haematology
- British Society of Interventional Radiologists

Description

Indications and current treatment

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 reduced 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 or hormone replacement therapy, pregnancy and dehydration.

A PE without haemodynamic instability is normally treated with low molecular weight heparin (LMWH) or fondaparinux, followed by oral anticoagulants (typically warfarin). The newer factor X inhibitors may be used without preliminary heparin. PEs with haemodynamic instability 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.

What the procedure involves

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.

The procedure is usually done using local anaesthesia, with imaging guidance using fluoroscopy. Therapeutic doses of heparin are administered through a peripheral catheter before and during the procedure.

With the patient in the supine position, an angiographic catheter is inserted from the femoral vein and 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 transducers that deliver ultrasound waves along the entire treatment zone. A thrombolytic drug is infused directly into the embolus through holes in the side of 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.

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.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism. The following databases were searched, covering the period from their start to 23 June 2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with pulmonary embolism.
Intervention/test	Ultrasound-enhanced catheter-directed thrombolysis.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 272 patients from 1 systematic review of 7 studies[1] (including 1 randomised controlled trial and 1 non-randomised comparative study that have been summarised in detail separately) [2, 3], and 2 additional retrospective case series[4,5].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

Study 1 Engelberger RP (2014)

Details

Study type	Systematic review
Country	Switzerland
Recruitment period	Not reported
Study population and number	n=**197 patients with pulmonary embolism (PE) (from 7 studies: 1 randomised controlled study, 1 non-randomised retrospective case series and 5 retrospective case series)** Acute PE: 82% (160/197) patients; high-risk PE*: 18% (37/197) *(According to European Society of Cardiology (ESC) high-risk PE is defined as PE with sustained systemic arterial hypotension, cardiogenic shock, or the need for cardiopulmonary resuscitation, and is associated with an in-hospital mortality rate >15%).
Age and sex	Not reported Not reported
Patient selection criteria	Not reported
Technique	Ultrasound enhanced, catheter-directed thrombolysis (UE-CDT) was used to treat patients. Recombinant tissue plasminogen activator (rt-PA) was used as thrombolytic drug in 99% (195/197) of patients with a mean total dose ranging from 17.2–35.1 mg. In 2 studies (Engelberger 2013, Engelhardt 2011) an intrapulmonary bolus of rt-PA was administered prior to UE-CDT in high-risk patients. Treatment duration varied widely (range of medians 15–24 hours) between studies and was guided by improvement in clinical or angiographic parameters (Lin 2009, Chamsuddin 2008, Quintana 2013, and Kennedy 2013). Two studies used a fixed-dose treatment regimen with 10 mg of rt-PA per lung over 15 hours (Engelberger 2013, Kucher 2013).
Follow-up	**Varied follow-up periods between studies (range of mean follow-up 90–269 days)**
Conflict of interest/source of funding	The second author is a consultant for EKOS corporation (manufacturer).

Analysis

Follow-up issues: Follow-up period varied between studies (range of mean follow-up 90–269 days)

Study design issues: Methodology used (study selection criteria, search strategies, quality assessment and methods of analysis) for the systematic review and meta-analysis were not described.

Only UE-CDT were analysed in the pooled variance analysis. The comparative efficacy data (from 1 randomised controlled trial and 1 retrospective comparative case series) were not analysed in the systematic review.

Standardised treatment protocols were not used in most of the studies.

Studies used various angiographic scores to measure pulmonary thrombus load pre and post UE-CDT. RV/LV ratio assessed either by echocardiography or chest computer tomography in most of the studies.

Study population issues: Studies mainly included patients with acute massive and sub-massive PE.

Other issues: Safety data were not fully reported in the systematic review and were therefore extracted from the original studies.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **197**

Summary of studies reporting treatment details

Author (year)	No of patients	Total rt-PA dose (mg)	Total thrombolysis duration (hours)
Chamsuddin (2008)	10	21.8	24.8±8.4
Lin (2009)	11	17.2±2.4	17.4±5.2
Engelhardt (2011)	24	33.5±15.5	19.7±8.1
Quintana (2013)	10	18(7-38)[d]	
Kennedy (2013)	60	35.1±11.1	19.6±6.0
Engelberger (2013)	52	21.0±5.7	15.2±1.7
Kucher (2013)	30	20.8±3.0	15.0±1.0
Total[g]	197	26.9[h]	17.8[h]

[d]Median dose and (range)

[g]Pooled means ± standard deviation derived from pooled variance analysis

[h]Pooled mean without study by Qunitana et al.

Summary of studies reporting clinical outcomes (no significance test was reported)

Author (year)	RV/LV ratio		Mean pulmonary artery pressure (mmHg)		Cardiac index (l/min/m^2)		Relative reduction in pulmonary occlusion score (%)
	Before	After	Before	After	Before	After	
Chamsuddin (2008)	R	NR	NR	NR	NR	NR	NR
Lin (2009)	NR	NR	NR	NR	NR	NR	69.0[a]
Engelhardt (2011)	1.33±0.24[b]	1.0±0.13[b]	NR	NR	NR	NR	51.1[c]
Quintana (2013)	NR	NR	NR	NR	NR	NR	41.9[e]
Kennedy (2013)	NR	NR	27±9	20±6	NR	NR	32.0[a]
Engelberger (2013)	1.42±0.21[f]	1.06±0.23[f]	37±9	25±8	2.0±0.7	2.7±0.9	NR
Kucher (2013)	1.28±0.19[f]	0.99±0.17[f]	30±9	24±7	2.5±0.5	3.9±2.3	NR
Total[g]	1.36±0.21	1.03±0.20	31.3±9.0	22.7±6.9	2.2±0.7	3.1±1.3	41.2

Data presented as (%) or mean ± SD if not otherwise stated.

[a]Assessed by angiographic Miller index (MI is the sum of obstruction and perfusion indexes, ranging from 0 [best] to 34 [worst], an MI of >17 is diagnosed as massive PE)

[b]Assessed by chest computed tomography as a sign of right ventricular dysfunction which predicts short term mortality for PE patients

[c]Assessed by modified Miller score (MS is the sum of obstruction and perfusion indexes, ranging from 0 [best] to 34 [worst], an MS of >17 is diagnosed as massive PE)

[e]Assessed by Mastora score

[f]Assessed by echography as a sign of right ventricular dysfunction which predicts short term mortality for PE patients

[g]Pooled means ± standard deviation derived from pooled variance analysis

Recurrence at follow-up (extracted from source papers included in review and data not reported by systematic review)

A suspected recurrent PE 1 day after UE-CDT was reported in a case series of 24 patients (Engelhardt 2011). This was treated with rescue thrombolysis (100 mg rt-PA) intravenously over 2 hours.

A recurrent PE 4 months after treatment due to non-compliance was reported in a case series of 10 patients (Quintana 2014). The patient died due to severe RV failure.

Safety

Author (year)	No of patients	Minor bleeding % (n)	Major bleeding % (n)	Mortality at 3 months % (n)	Late mortality % (n)	Cardiac pulmonary arrest and acute kidney injury % (n)
Chamsuddin (2008)	10	20 (2/10)[a]	0	0		
Lin (2009)	11	0	0	9 (1/11)[b]		
Engelhardt (2011)	24	8 (2/24)[c]	17 (4/24)[d]	0	(5/24)[e]	
Quintana (2013)	10	20 (2/10)[f]	0	0	(1/10)[g]	
Kennedy (2013)	60	2(1/60)[h]	2(1/60)[i]	7(4/60)[j]		2 (1/60)[l]
Engelberger (2013)	52	21 (11/52)	4(2/52)[n]	4(2/52)[m]		
Kucher (2013)	30	10(3/30)[k]	0	0		
Total[g]	197	10.7 (21/197)	3.6 (7/197)	3.6(7/197)		

[a] 1 patient had a small groin haematoma and the other had a non-fatal haemoptysis.

[b] death in a patient who had massive PE, 7 hours after UE-CDT treatment due to multi-organ failure.

[c] patients who had high-dose rt-PA had inguinal puncture site haematoma needing no intervention.

[d] patients who had high-dose rt-PA had access site bleeding requiring blood transfusion.

[e] at mean 269 days, 4 deaths due to cancer and 1 due to pre-existing chronic lung disease.

[f] mild epistaxis and groin haematoma (treated by immediate cessation of thrombolytic therapy and no further intervention).

[g] death at 4 months after treatment (in a patient with recurrent PE due to noncompliance) from severe RV failure.

[h] puncture site haematoma, needed no treatment.

[i] intra-abdominal haemorrhage 6 days after UE-CDT, patient died of hypovolaemic shock.

[j] 3 patients with massive PE (1 died within 2 hours after discontinued UE-CDT, 1 developed an acute intra-abdominal haemorrhage 6 days after UE-CDT and died of hypovolaemic shock, 1 in a patient with undiagnosed ovarian cancer 8 days after UE-CDT due to multiple factors) and 1 in sub-massive PE patient at 90 day follow-up.

[k] 2 patients with transient haemoptysis without medical intervention, 1 patient with access site groin haematoma managed with manual compression.

[l] 1 patient (in whom a retracted infusion catheter was replaced and thrombolysis extended) had cardiac pulmonary arrest and acute renal injury. Patient successfully resuscitated and recovered after lengthy hospital stay.

[m] 1 patient died from cardiogenic shock and 1 patient from recurrent PE

[n] 1 intrathoracic bleeding after cardiopulmonary resuscitation needing transfusion, 1 intrapulmonary bleeding requiring lobectomy

Abbreviations used: NR, not reported; PE, pulmonary embolism; rt-PA, recombinant tissue plasminogen activator; RV; right ventricle; RV/LV-ratio, right-to-left ventricular end-diastolic diameter ratio; UE-CDT, ultrasound-enhanced catheter-directed thrombolysis.

Study 2 Kucher N (2013) [This study is also included in the systematic review above]

Details

Study type	**Randomised controlled trial**
Country	Germany, Switzerland (multicentre)
Recruitment period	2010–13
Study population and number	n=59 patients with intermediate risk PE (acute main or lower lobe PE and RV/LV ratio>1.0) **UE-CDT (n=30/59) vs unfractionated heparin (UFH) alone (n=29/59)** Frequent comorbidities: systemic hypertension (59%), diabetes (17%), renal insufficiency (15%), cancer (12%)
Age and sex	All: mean 63 years; UE-CDT mean 64 years, UFH mean 62 years All: 47% (28/59) male; UE-CDT 37%(11/30) male, UFH 59%(17/29) male
Patient selection criteria	Inclusion criteria: PE (confirmed by contrast enhanced CT) with embolus located in at least 1 main or proximal lower lobe pulmonary artery and echocardiographic RV to left ventricular dimension (RV/LV) ratio >1. Exclusion criteria: <18 or >80 years, PE symptom duration >14 days, insufficient echocardiographic image quality in the apical 4-chamber view that prohibited the measurement of RV/LV ratio, known significant bleeding risk, use of thrombolytic agents within previous 4 days, active bleeding, coagulation disorder, platelet count <100,000 mm^3, previous use of vitamin K, intolerance to administered treatment drugs.
Technique	UE-CDT group underwent treatment with EKOS Endowave catheter system (median procedure time 42 minutes). Treatment performed according to a standard protocol for 15 hours with an rt-PA dose of 20 mg for patients with bilateral device placement 87% (26/30) and 10 mg for patients with unilateral device placement 13% (4/30). Echocardiographic measurements at baseline, 24 hours and 90 days were performed. UFH group were administered UFH immediately after randomisation (intravenous bolus of 80 IU/kg, followed by infusion of 18 IU/kg per hour). For those already receiving heparin or LMWH or fondaparinux initial bolus was omitted. For patients who received a weight adjusted dose, the UFH was delayed up to 8–12 hours after last LMHW and 20 24 hours after last fondaparinux injection. The UFH infusion was adjusted to achieve and maintain activated partial thromboplastin time corresponding to therapeutic heparin levels. The minimum duration infusion was 24 hours. Postoperative anticoagulation therapy was at the discretion of the investigators. Use of vitamin K or a switch from heparin to LMWH was allowed 36 hours after randomisation. The minimum duration of anticoagulation was 3 months. All patients were scheduled for a 90 days follow-up clinical visit and echocardiography.
Follow-up	**3 months**
Conflict of interest/source of funding	The study was funded by EKOS corporation (manufacturer) and first author is a consultant to the manufacturer, also received fees from different pharmaceutical companies.

Analysis

Follow-up issues: 2 patients in the heparin group were lost to follow-up (1 died and 1 hospitalised for major depression).

Study design issues: small study in 8 tertiary care hospitals. Study compared with anticoagulation therapy rather than thrombolysis. Randomisation performed in blocks of 4 without stratification and terminated if estimated sample size were identified (25 patients per group with primary endpoint (RV/LV ratio)).

Standardised fixed dose of thrombolytic treatment regimen was used for UE-CDT. Before the study, 11 patients in UE-CDT group and 9 patients in the UFH group received antithrombotic treatment with LMWH or fondaparinux (p=0.78). The quality of anticoagulation therapy with dose adjustments of UFH and of vitamin K was not monitored.

Instructions were provided for measurement of RV/LV ratio from the echocardiograms. Blind assessment of echocardiograms was done. These were compared with the data obtained by core laboratory to assess inter-observer agreement. Datasets for additional RV echographic analyses were incomplete for 5 patients (4 patients in UE-CDT, 1 UFH) because of the poor quality of the images.

Patient population issues: patients in the study were haemodynamically stable and there was no difference between the 2 groups in comorbidities and baseline vital parameters (heart and respiratory rates, oxygen saturation, arterial pressure, occlusion score and RV/LV ratio).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **UE-CDT (30/59) vs UFH (29/59)**

Clinical outcomes in the UE-CDT and UFH treatment groups

Variable	**Baseline**		**24 hours**		**90 days**		**difference baseline vs 24 hours**		**difference baseline vs 90 days**	
	UE-CDT	**UFH**	**UE-CDT**	**UFH**	**UE-CDT**	**UFH**	**UE-CDT**	**UFH**	**UE-CDT**	**UFH**
RV/LV ratio (mean ± SD)	1.28± 0.19	1.20± 0.14	0.99± 0.17	1.17± 0.20	0.92± 0.15	0.96± 0.16	0.30±0.1	0.03±0.16	0.35±0.22	0.24±.19
n	26	29	28	28	26	27	25	28	23	27
Between group	p=0.07		p=0.31		p=0.36		p<0.001		p=0.07	
Within group	NA		NA		NA		p<0.001	p=0.31	p<0.001	p<0.001
RV systolic dysfunction n										
None/mild/ moderate/ severe	0/4/5/16	0/5/1 1/13	5/10/10 /2	1/9/7/11	19/5/0/0	10/15/1/1	1.1±0.8	0.3±0.4	2.2±0.9	1.5±0.9
Between group	P=0.37		P=0.01		P=0.003		P<0.001		p=0.01	
Within group	NA		NA		NA		p<0.001	p=0.02	p<0.001	p<0.001

PE recurrence at 90 days follow-up

No episodes of haemodynamic compensation or recurrent venous thromboembolism.

Safety

Complications

Variable	**UE-CDT % (n=30/59)**	**UFH % (n=29/59)**	**p value**
Death	0	1^	NR
Major bleeding	0	0	NA
Minor bleeding	10 (3/30)*	(1/29)**	0.61

*2 with transient haemoptysis without medical intervention, 1 with access-site groin haematoma managed with manual compression.
**with muscular haematoma at the injection site of LMWH during initial hospitalisation and transient anal bleeding after endoscopic removal of a colon polyp 80 days after treatment.
^ this death was reported as being from pancreatic cancer

Abbreviations used: CDT, catheter-directed thrombolysis, MS, Miller score; NA, not applicable; NR, not reported; NS, not significant; PE, pulmonary embolism; tPA, tissue plasminogen activator; RV/LV right ventricular to left ventricular; UE CDT, ultrasound-enhanced catheter-directed thrombolysis.

Study 3 Lin PH (2010) [This study is also included in the systematic review above]

Details

Study type	**Retrospective comparative case series**
Country	USA (single centre)
Recruitment period	1999–2010
Study population and number	n=25 patients with massive PE (33 lesions) **UE-CDT (n=11/25) (15 lesions) vs CDT (n=14/25) (18 lesions)**
Age and sex	UE-CDT mean 59 years, CDT mean 62 years UE-CDT 45% (5/11) male; CDT 50% (7/14) male
Patient selection criteria	Patients with massive PE (diagnosed on a variety of imaging and clinical modalities) who had shortness of breath, hypoxia, or haemodynamic instability (systolic arterial pressure <90 mmHg or drop in systolic arterial pressure of at least 40 mmHg for at least 15 minutes); a dilated right ventricle at echocardiography; and electrocardiographic findings of the RV strain.
Technique	UE-CDT performed by placing EKOS Endowave catheter in the pulmonary artery whereas a conventional multi-lumen thrombolytic infusion catheter was used in the conventional CDT treatment group. Bilateral femoral access obtained in patients with PE in bilateral pulmonary vasculature. Interventions were performed by either interventional radiologists or vascular surgeons. Thrombolytic agents used included urokinase and tissue plasminogen activator (tPA). Pre- and post-treatment (after 12–48 hours) angiography done for evidence of thrombus removal based on Miller criteria and chest CT performed where clinical indications were present. IVC filters were placed in all UE-CDT patients (7 retrieved at mean 7.3 months) and only 4 CDT patients (none retrieved) for prevention of recurrence in patients with lower extremity DVT or at the discretion of the physician.
Follow-up	**not clear**
Conflict of interest/source of funding	None

Analysis

Study design issues: Small number of patients in each group. All medical records were reviewed retrospectively.

All CDT procedures were performed during the early phase of the study by interventional radiologists and authors state that no retrieval filters were available during that period. All UE-CDT procedures were done by vascular surgeons with routine use of IVC filers.

Angiographic scores to measure thrombus load pre- and post- treatment were analysed by a blinded interventionist. These were based on Miller score (computed as the sum of obstruction and perfusion indexes, ranging from 0 (best) to 34 (worst). A massive PE was confirmed with an MS>17.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **UE-CDT (11/25) vs CDT (14/25)**

Treatment outcomes in the UE-CDT and CDT treatment groups

Variable	UE-CDT (n=11)	CDT (n=14)	p value
Complete thrombolysis (>90% removal)	100 (11/11)	50 (7/14)	0.01
Partial thrombolysis (50-75%)	0	14.3 (2/14)	0.03
Mean total thrombolytic dosage (urokinase U × 10^6)	NA	2.04±56^	NA
Mean total thrombolytic dosage (tPA, mg)	17.2±2.36	25.43±5.27^^	0.03
Mean thrombolytic infusion time (hours)	17.4±5.23	26.7±8.64	0.03
Pre-intervention Miller score (MS)	18.65±3.25	17.29±3.86	NS
Post intervention Miller score	5.84±1.57*	7.38±2.26*	NS
Relative Miller score[a] improvement	0.63±0.18	0.68±0.26	NS

*comparison of pre and post-intervention Miller score within the groups showed a significant difference with p<0.002.

^ 5 patients received urokinase; ^^ 10 patients received tPA.

[a] defined as pre-MS minus the post-MS divided by the pre-MS.

PE recurrence

No recurrent PE episodes during the follow-up period (even in those who had IVC filter retrieval) and all surviving patients were compliant on long-term oral anticoagulant therapy (warfarin) in both groups.

Safety

Complications

Variable	UE-CDT (n=11)	CDT (n=14)	p value
Mortality	9.1 (1/11)^	14.2 (2/14)*	NS
Haemorrhage complications (major)	0	21.4 (3/14)**	0.02

^occurred in a patient who had massive PE, 7 hours after UE-CDT treatment due to multi-organ failure.
*Occurred in 1 patient who had cardiac arrest and acidosis 2 hours after initiation of treatment; in 1 patient who had severe right heart failure and died 13 hours after initiation of treatment.
**2 groin haematomas and 1 retroperitoneal haematoma, treated non-surgically with immediate cessation of thrombolytic therapy and blood transfusion.

Abbreviations used: CDT, catheter-directed thrombolysis, DVT, deep vein thrombosis; IVC, inferior vena cava; MS, Miller score; NA, not applicable; NS, not significant; PE, pulmonary embolism; RV, right ventricle; tPA, tissue plasminogen activator; UE-CDT, ultrasound-enhanced catheter-directed thrombolysis.

Study 4 Dumantepe M (2014)

Details

Study type	**Retrospective case series**
Country	Turkey (single centre)
Recruitment period	2010–12
Study population and number	**n=22** patients with massive or sub-massive PE (28 lesions) massive PE (26.4%, 5/22); sub-massive PE (73.6%,14/22) 2 patients were on inotropic support before treatment. Symptom duration :<14 days in 86% (19/22) patients.
Age and sex	Mean 53.7 years 59% (13/22) male
Patient selection criteria	Patients with dyspnoea, hypoxia, or haemodynamic instability (systolic arterial pressure <90 mmHg or drop in systolic arterial pressure of at least 40 mmHg for at least 15 minutes, or ongoing administration of inotropes for systemic arterial hypotension); evidence of PE by contrast-enhanced CT; right ventricular dysfunction by electrocardiography or right-to-left ventricular-dimension ratio >0.9 by CT. Exclusion criteria determined according to contraindications for thrombolysis: active bleeding; history of intracranial bleeding; head injury; ischaemic stroke; brain tumour; neurosurgery; surgery; childbirth; organ biopsy; puncture of a non-compressible vessel within 10 days; gastrointestinal bleeding within 15 days; major trauma within 15 days; active cancer; known haemorrhagic risk; platelets<50,000 or INR >2.0; and pregnancy.
Technique	After confirmation of PE and RV dysfunction, all patients were treated with UE-CDT using EKOS Endowave catheter system with recombinant tissue plasminogen activator (tPA) (28 interventions performed). Unilateral treatment in 72.7% (16/22); Bilateral treatment in 28.3% (6/22) No bolus tPA was given before overnight infusion. Patients admitted to ICU for thrombolytic infusion and close monitoring. Follow-up angiography done at 12–24 hours to determine need to continue or stop thrombolysis. After 24–48 hrs infusion, patients had another CT angiography examination. IVC filters were inserted in DVT patients to prevent recurrence and were retrieved after 6 weeks from discharge. Anticoagulation therapy (warfarin) was started prior to discharge and continued for at least 6 months.
Follow-up	**Mean 180 days**
Conflict of interest/source of funding	None

Analysis

Study design issues: Small number of patients. All medical records were reviewed retrospectively. Therefore there may be several confounding factors that could have influenced the results.

Angiographic scores to measure thrombus load pre and post treatment were analysed by 2 cardiologists and cardiovascular surgeons. These were based on Miller score (computed as the sum of obstruction and perfusion indexes, ranging from 0, best to 34, worst). A massive PE was confirmed with an MS>17.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **UE--CDT 22 patients**

Treatment outcomes

Variable	UE-CDT (n=22)
Complete thrombolysis (>90% removal)	77.2 (17/22)
Near complete thrombolysis (50-90%)	22.8 (5/22)
Partial thrombolysis (<50%)	0
Median total thrombolytic dosage (tPA, mg)	23 (16-35)
Median thrombolytic infusion time (hours)	20.5 (25)

Clinical outcomes (n=22)

Variable	Pre-treatment	Post-treatment	p value
Miller score (MS)	24±5	13±4	<0.001
RV/LV ratio	1.29±0.17	0.92±0.11	<0.001
RV end-diastolic diameter(mm)	52.0±7.0	42.5±5.5	<0.001
LV end-diastolic diameter(mm)	37.2±.3	43.4±5.1	<0.001
PAP systolic (mean ± SD, mm Hg)	67±14	34±11	<0.001
PAP diastolic (mean ± SD, mm Hg)	15±8	8±5	<0.001
PAP mean (mean ± SD, mm Hg)	33±6	20±5	<0.001

Respiratory parameters (n=22)

	Pre-treatment	Post-treatment	Day 1	Day 2
Inspiratory pressure (cm H_2O)	39.0±4.0	28.5±2.0	27.2±1.6	25.4±1.3
Respiratory rate	31.0±6.0	20±3.0	18±2.5	15±2.0
Arterial PH	7.16±0.32	7.29±0.19	7.34±0.32	7.38±0.22
$PaCO_2$ (mm Hg)	78.0±22.0	61.0±25.0	45±17.0	33±7.0
PaO_2 (mm Hg)	58.5±17.0	65.3±14.0	79.3±11.2	105±8.5

Survival at 180 days: 86% (19/22)

Safety

Complications

Variable	UE-CDT % (n=22)
Haemorrhage complications (major)	0
Minor bleeding (at access site, controlled by elevation of limb and compressive bandage)	9 (2/22)
Inguinal puncture site haematoma (needed no intervention)	9 (2/22)
Mortality at 180 days (1 sub-massive PE patient died from cancer, 1 with massive PE died of during initial treatment due to cardiogenic shock and multi-organ failure; 1 died of severe RV failure at 3 months after discharge with recurrent PE due to non-compliance)	14 (3/22)

Abbreviations used: CDT, catheter-directed thrombolysis, IVC, inferior vena cava; LV, left ventricle; MS, Miller score; NA, not applicable; NS, not significant; PAP, pulmonary artery pressure; PE, pulmonary embolism; RV, right ventricle; SD, standard deviation; tPA, tissue plasminogen activator; UE-CDT, ultrasound-enhanced catheter-directed thrombolysis.

Study 5 McCabe JM (2015)

Details

Study type	**Retrospective case series (registry data)**
Country	USA (single centre)
Recruitment period	2010–2014
Study population and number	n=**53 patients with intermediate risk PE (defined as haemodynamically stable with evidence of RV strain or failure)** Mean Left Ventricular Ejection Fraction (LVEF): 59.4±7.6 Average PE Severity Index (PESI) score: 73.6±23.6 Moderate or severe right ventricular dysfunction (RVF): 58% (29/53) patients
Age and sex	Mean 57.6 years; 51% (27/53) male
Patient selection criteria	Inclusion criteria: symptoms of <14 days at the time of procedure. Exclusion criteria: patients with symptoms of >2 weeks were not offered therapy. Patients with contraindications to thrombolytics, such as bleeding, major surgical procedures, malignancies were treated at the discretion of the physician.
Technique	Patients underwent treatment with EKOS UE-CDT plus anticoagulation. 20 mg of total alteplase (at a rate of 2 mg/hour) infused, patients also received intravenous unfractioned heparin for a partial thromboplastin time of 40 to 60. After treatment period, pulmonary artery pressures were transduced through the catheters. After removal of catheter, all patients received heparin for a partial thromboplastin time of 60 to 80 followed by transition to a long term anticoagulation strategy decided by the physician.
Follow-up	**Post procedure**
Conflict of interest/source of funding	None

Analysis

Study design issues: all echocardiographic parameters were assessed retrospectively.
Patient population issues: 11% (6/53) patients had a previous PE, 15% (8/53) had cancer, 17% (9/53) had surgery for various conditions in previous 14 days. 8 had other conditions.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **53**

Procedural outcomes

Pressures (mmHg)	**UE-CDT n=53**
Total infusion time (hours)	15.9±3.0
Total lytic dose (mg)	24.6±9
Lytic infusion rate (mg/hour)	1.5 [1.0-1.5]
Peak activated partial thromboplastin time (aPTT) during treatment	42.5 [38.5-55.6]
Fibrinogen during treatment	406±141

Pulmonary artery and right ventricular outcomes

Pressures (mmHg)	**Baseline**	**Post-procedure**	**p value**
Pulmonary artery systolic pressure	51.4±15.5	40.7±10.8	<0.001
Mean pulmonary artery pressure	33.8±10.5	27±7.6	<0.001
Right ventricular diameter: left ventricular diameter ratio	1.12±0.30	0.98±0.20	0.03
Right ventricular end-diastolic dimension	4.66±0.80	4.48±0.88	0.41

Safety

Complications during treatment

	UE-CDT % (n=53)
Inpatient deaths	0
In hospital bleeding (1 had large spontaneous retroperitoneal bleed, 2 had access-site bleeding, 2 had bleeds during postoperative period, 1 had asymptomatic bilateral-intraventricular haemorrhage after treatment, 1 had a rectus sheath haematoma) None required any intervention. One patient's alteplase was prematurely discontinued for access site bleeding.	9.4 (5/53)

Abbreviations used: CDT, catheter-directed thrombolysis; PE, pulmonary embolism; UE-CDT, ultrasound-enhanced, catheter-directed thrombolysis.

Efficacy

Thrombolysis success

A retrospective comparative case series of 25 patients with acute massive pulmonary embolism (PE) compared ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT; n=11) against catheter-directed thrombolysis (CDT; n=14). It reported a significant difference between the 2 groups in the rate of complete thrombolysis (>90% removal) at angiography assessment performed 12–48 hours after the start of treatment (UE-CDT 100% [11/11]) and CDT 50% [7/14]; p=0.01)[3].

A retrospective case series of 22 patients with sub-massive or massive PE who had UE-CDT reported complete thrombus clearance (≥90%) in 77% (17/22) of the patients and near complete (≥50–90%) clearance in 23% (5/22) of the patients after the procedure[4].

Overall infusion time

The retrospective comparative case series of 25 patients comparing UE-CDT (n=11) against CDT (n=14) 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)[3].

A systematic review of 7 studies (197 patients) on UE-CDT for acute PE reported a pooled mean of 17.8 hours for thrombolysis duration[1].

Right-to-left ventricular dimension ratio (RV/LV ratio)

A randomised controlled trial of 59 patients with acute intermediate-risk PE compared UE-CDT (n=30) against unfractionated heparin (UFH) alone (n=29). It reported that the mean right-to-left ventricular dimension ratio (RV/LV) ratio significantly reduced from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (p<0.001) in the UE-CDT group, whereas in the UFH group there was no significant difference in the RV/LV ratio between baseline and 24 hours (1.20±0.14 at baseline to 1.17±0.20; p=0.31). The mean change in the RV/LV ratio between the 2 groups from baseline to 24 hours was statistically significant (UE-CDT 0.30±0.20 versus UFH 0.03±0.16, p<0.001). The mean change in the RV/LV ratio from baseline to 90 days was 0.35±0.22 in the UE-CDT group versus 0.24±.19 in the UFH group (p=0.07)[2].

In the systematic review of 7 studies (n=197), 3 studies assessed the right-to-left ventricular dimension (RV/LV) ratio using a chest CT 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)[1].

The retrospective case series of 22 patients with sub-massive or massive PE who had UE-CDT reported that the RV/LV ratio significantly decreased from 1.9±0.17 to 0.92±0.11 (<0.001) after the procedure[4].

Mean pulmonary artery pressure

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 (no significance test was reported) [1].

The retrospective case series of 22 patients with sub-massive or massive PE who had UE-CDT reported that the mean pulmonary artery pressure (systolic) significantly decreased from 67±14 to 34±11 mmHg (<0.001) after the procedure[4].

A case series of 53 patients with intermediate risk PE who had UE-CDT reported significant reduction in systolic pulmonary artery pressure (from 51.4±15.5 to 40.7±10.8; 95% confidence interval 7.7 to 15.0 mmHg, p<0.001) and mean pulmonary artery pressure (from 33.8±10.5 to 27±7.6; 95% confidence interval 4.7 to 9.7 mmHg, p<0.001) respectively after treatment[5].

Right ventricular (RV) systolic function

In the randomised controlled trial of 59 patients comparing UE-CDT (n=30) against UFH (n=29), right ventricular (RV) systolic function was graded into 4 categories (normal, mild, moderate or severe dysfunction). The study reported that there was a significant improvement in the mean difference in RV systolic function from baseline to 90 days between the 2 groups (UE-CDT 2.2±0.9 versus UFH 1.5±0.9, p=0.01)[2].

Cardiac index

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/m^2 before treatment to 3.1±1.3 l/min/m^2 after treatment (no significance test was reported)[1].

Pulmonary thrombus load

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%; no significance test was reported)[1].

The retrospective case series of 22 patients with sub-massive or massive PE who had UE-CDT reported that the pulmonary clot burden (assessed by the modified Miller score) significantly reduced from 24±5 to 13±4 (p<0.001) in 95% (21/22) patients who survived to discharge[4].

Recurrence

In the systematic review of 7 studies[1], 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 (Engelhardt 2011). This was treated with rescue thrombolysis (100 mg rt-PA) given intravenously over 2 hours. A recurrent PE 4 months after thrombolysis, from non-compliance with anticoagulant treatment, was reported in a case series of 10 patients (Quintana 2014). This patient died of severe right ventricular failure.

Survival

The retrospective case series of 22 patients with a sub-massive or massive PE who had UE-CDT reported that 86% (19/22) of patients were alive at 180 day follow-up[4].

Safety

Mortality

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[1].

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 treatment, and 1 had severe heart failure and died 13 hours after treatment[3].

Acute kidney injury

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[1]. The patient was successfully resuscitated and recovered after lengthy hospitalisation.

Major bleeding complications

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)[1].

Minor bleeding complications

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 were mainly puncture site haematomas that needed no intervention (n=6) and non-fatal haemoptysis (n=3). Details of the other 11 patients were not available[1].

Minor bleeding complications were reported in 10% (3/30) of the patients in the UE-CDT group (2 with transient haemoptysis without medical intervention, 1 with access site groin haematoma managed with manual compression) and 3% (1/29) in the UFH group (with muscular haematoma at the injection site and transient bleeding after endoscopic removal of a colon polyp 80 days after initiation) in a randomised controlled trial of 59 patients (p=0.61)[2].

Validity and generalisability of the studies

- There is a lack of high-quality evidence (randomised controlled studies) and long-term data comparing the procedure with standard catheter-directed thrombolysis.
- Only 1 randomised controlled trial compared ultrasound-enhanced catheter-directed thrombolysis (UE-CDT) with unfractionated heparin (UFH).
- Studies were mainly retrospective case series and the mean follow-up ranged from 90–269 days.
- 1 retrospective comparative case series compared ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) with standard catheter-directed thrombolysis (CDT).
- Studies included patients with: acute; intermediate-risk; high-risk; sub-massive; and massive PE.
- Two studies (Engelberger 2013, Kucher 2014) included in the systematic review[1] used fixed dose and duration for treatment regimens. All other studies used different drug treatment regimens and treatment duration was according to follow-up angiographic assessment results (mean ranging from 15–24 hours).

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Technology appraisals

- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance 261 (2012). Available from http://www.nice.org.uk/guidance/TA261
- Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. NICE technology appraisal guidance 287 (2013). Available from http://www.nice.org.uk/guidance/TA287
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157 (2008). Available from http://www.nice.org.uk/guidance/TA157
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance 245 (2012). Available from http://www.nice.org.uk/guidance/TA245
- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal guidance 327 (2014). Available from http://www.nice.org.uk/guidance/TA327

Clinical guidelines

- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline 144 (2012). Available from http://www.nice.org.uk/guidance/CG144
- Venous thromboembolism – reducing the risk: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (2010). Available from http://www.nice.org.uk/guidance/CG92

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Neil Martin and Dr Syed Hussain (British Thoracic Society); Jeremy Taylor and Mo Hamady (British Society of Interventional Radiologists).

- One specialist adviser stated that he has performed the procedure at least once and 3 specialist advisers stated that they have never performed this procedure but have taken part in patient selection or referral.
- Two advisers considered the procedure to be a minor variation of an existing procedure, which is unlikely to alter the procedure's safety and efficacy, whereas 2 advisers considered it as definitely novel and of uncertain efficacy and safety.
- Comparators listed include anticoagulation therapy (intravenous unfractionated heparin or subcutaneous low molecular weight heparin), peripheral intravenous thrombolysis, catheter-directed thrombolysis, pharmacomechanical or surgical thrombectomy in the pulmonary artery.
- One adviser stated that patient groups for this treatment should be clearly defined in the title or introduction.
- One adviser stated that fewer than 10% of specialists are performing this procedure. One adviser stated that 10–50% of specialists are engaged in this area of work and 2 stated that they could not give an estimate.
- Key efficacy outcomes include: thrombus clearance; reduction in right-to-left ventricular ratio; long-term reduction in pulmonary hypertension and right ventricle dysfunction; reduction in pulmonary artery pressure; reduction in right ventricle strain; shortened infusion time, recovery time and hospital stay; symptom relief; and survival and vessel patency.
- Advisers stated that the main uncertainties relate to the advantage of ultrasound-enhanced, catheter-directed thrombolysis over conventional treatments because there is lack of evidence from randomised clinical trials and also a lack of evidence on cost effectiveness.

- Anecdotal adverse events reported include access site haematoma and procedural deaths.
- Theoretical adverse events listed include: death; systemic bleeding; distal embolisation; bleeding from access sites; access site haematoma; groin haematoma; pulmonary artery perforation; extra-cranial haemorrhage; cerebrovascular accident including haemorrhage and shock; cardiac dysrhythmias; right ventricle failure; cardiac arrest; and death.
- Specialist advisers stated that the procedures should be performed by an interventional radiologist or a cardiologist trained in endovascular techniques (such as interventional radiology and use of ultrasound systems) in a radiology interventional suite or cardiology angiography laboratory with appropriate equipment for cardiopulmonary resuscitation. Training for nursing staff on the use of equipment and access to specialists would be needed.
- Specialist advisers stated that there is uncertainty about patient selection criteria, which patients would derive maximum benefit and whether there should be discussion with cardiothoracic surgeons before starting catheter-based thrombolysis.
- Three advisers stated that the speed of diffusion of this procedure would likely be very slow and only offered in a minority of hospitals, whereas 1 adviser stated that it would likely be very fast and carried out in most district and general hospitals.
- One adviser stated that the impact on the NHS would be major (if the procedure is used as a standard treatment) whereas 1 stated that it would be moderate. One adviser stated that strict patient selection criteria would be needed (such as only offering it to patients with massive or sub-massive PE).

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- The EkoSonic Endovascular system is currently the only commercially available catheter system for intravascular ultrasound-enhanced, catheter-directed thrombolysis. This system received FDA approval in 2008 for the ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism (PE).
- In the European Union it is approved for the treatment of pulmonary embolism patients with ≥50% clot burden in 1 or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥25 mmHg) or echocardiographic evaluation.
- Indications include intermediate and high-risk pulmonary embolism.
- Ongoing studies:
  - NCT01899339- Long-term study looking at the effects of treating sub-massive pulmonary embolism with ultrasound-accelerated thrombolysis (SPEAR); study type: prospective observational study; estimated enrolment: 25; inclusion criteria: patients with acute (14 days or less) symptomatic pulmonary embolism by CT angiogram of the thorax with embolus involving at least 1 main or lower lobe pulmonary artery and RV:LV ratio less than 0.9; primary outcomes: change in right-to-left ventricular ratio at 72 hours post PE; start date: May 2013; completion date: May 2014; location: USA; status: recruiting ; sponsors: EKOS Corp.
  - NCT01513759- A prospective, single-arm, multicentre trial of EkoSonic endovascular system and activase for treatment of acute pulmonary embolism. (SEATTLE II; sub-massive and massive pulmonary embolism treatment with ultrasound-accelerated thrombolysis therapy used in conjunction with recombinant t-PA); study type: observational study; study population: patients with acute, intermediate and high-risk PE; estimated enrolment: 150; inclusion criteria: CT evidence of proximal PE (filling defect

in at least 1 main or segmental pulmonary artery), PE symptom duration ≤14 days, informed consent can be obtained from subject or legally authorised representative, massive PE (syncope, systemic arterial hypotension, cardiogenic shock, or resuscitated cardiac arrest) or sub-massive PE (RV diameter-to-LV diameter 0.9 or less on contrast-enhanced chest CT); primary outcome: ratio of RV to LV diameter within 48 ± 6 hours; location: USA; status: completed; sponsor: EKOS Corp (not published yet).

References

1. Engelberger RP and Kucher N (2014). Ultrasound assisted thrombolysis for acute pulmonary embolism: a systematic review. European Heart Journal Advance Access published February 3, 2014. Doi:10.1093/eurheartj/ehu029
2. Kucher N, Boekstegers P et al (2014). Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 129 (4); 479-486.
3. Lin PH, Annambotla S et al (2009). Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. Vascular.17 (3); s137-147.
4. Dumantepe M, Uyar I et al (2014). Improvements in pulmonary artery pressure and right ventricular function after ultrasound-accelerated catheter-directed thrombolysis for the treatment of pulmonary embolism J Card Surg.29; 455-463.
5. McCabe JM, Huang PH, Riedl L, Eisenhauer AC, and Sobieszczyk P (2015). Usefulness and Safety of Ultrasound-Assisted Catheter-Directed Thrombolysis for Submassive Pulmonary Emboli. Am J Cardiol (Article in press).

Appendix A: Additional papers on ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Amankwah KS, Seymour K.et al Ultrasound accelerated catheter directed thrombolysis for pulmonary embolus and right heart thrombus secondary to transvenous pacing wires. Vascular & Endovascular Surgery 2011 45 (3); 299-302.	Case report n=1 symptomatic PE and extensive atrial and ventricle thrombus formation with transvenous pacing wires UE-CDT	Complete resolution of thrombus in the pulmonary arterial vasculature. Repeated echocardiograms showed resolution of the intra-atrial and ventricular thrombus and improvement of the right heart function. No hypercoaguable states or any complications associated with the procedure.	Larger studies with longer follow-up included in table 2.
Azemi T, Almahasneh F et al (2012). Ultrasound-assisted catheter-directed thrombolytic therapy for management of acute pulmonary embolism. Connecticut Medicine. 76: 197-200.	Case report n=1 Acute PE UE-CDT	Pulmonary angiography showed significant reduction in thrombus burden. Concomitant clinical improvement in haemodynamics as well as oxygenation. Patient discharged on warfarin therapy, at 3 months, was asymptomatic with good functional status.	Larger studies with longer follow-up included in table 2.
Bavare AC, Naik SX et al (2014). Catheter-directed thrombolysis for severe pulmonary embolism in pediatric patients. Annals of Vascular Surgery 28: 1794-1797.	Case series (retrospective) n=5 Paediatric patients with severe PE (main or major branch pulmonary artery occlusion) 4 (UCDT]), 1 CDT without ultrasound.	Complete resolution of PE occurred in 4 (67%) at 24 hr, whereas in 2 cases (33%), there was partial resolution. 1 patient with complete resolution had another successful UCDT after 4 months for recurrence. Clinical parameters and echocardiographic findings improved in all the patients. Median duration of hospital stay was 9 days with no mortality and treatment-related complications. All patients were discharged with long-term anticoagulation.	Larger studies included in table 2.
Chamsuddin A, Nazzal L et al (2008). Catheter-directed thrombolysis with the Endowave system in the treatment of acute massive pulmonary embolism: a retrospective multi-center case series. Journal of Vascular & Interventional Radiology. 19: 372-376	Retrospective case series n=10 patients with massive pulmonary embolism (PE)	Complete thrombus removal was achieved in 13 of the 17 lesions (76%), near complete thrombolysis was achieved in three lesions (18%), and partial thrombolysis was achieved in one lesion (6%). The mean time of thrombolysis was 24.76 hours +/- 8.44 (median, 24 hours). The mean dose of tPA used for the Endowave group was 0.88 mg/h +/- 0.19 (13 lesions).	Study in systematic review included in table 2

Davis C, Declue C, Lewis T et al (2014). Sonothrombolysis of submassive and massive pulmonary embolus with the EkoSonic endovascular system and tissue plasminogen activator. Journal of Vascular and Interventional Radiology 25: 155-155.	Retrospective chart review n=31 Patients with submassive/massive PE. (6 massive PE and 25 submassive PE) Sonothrombolysis and recombinant tPA (rtPA) (with varying infusion times, rates, and total doses)	1. Elevated RV/LV ratio measured on pulmonary embolus protocol CTA had a positive correlation with direct mean pulmonary artery pressures (P=0.0159, Spearman coefficient). 2. There were significant changes in MPAP, SPAP, and DPAP (-12.5+11.4, -6.4+7.6, and -9.6+8.2 mm Hg, respectively) after sonothrombolysis with low doses of tPA (25.5 mg) and less than 21 hours of infusion (P=0.0009, <24 h). 3. Changes in the PAP pre- and post-procedure were correlated with the total tPA infusion dose (P=0.0027, Spearman coefficient). There was no correlation with total time of tPA infusion and change in pulmonary artery pressures. 4. Pre procedure troponin I serum level was not correlated with level of RV/LV ratio (P=0.2990). 5. Bleeding complications were not encountered (0%), but there was a 6.4% mortality rate due to cardiopulmonary arrest. Two of 4 patients who were intubated prior to the procedure died. One patient had cardiopulmonary arrest in the hours prior to the procedure but was stable enough to have the catheters placed; that patient died immediately after placement. Although the sample size is small, patients who received post procedure CT (19%) had a 46% drop in the RV/LV ratio.	Abstract only. Adverse events already reported in table 2.
Engelhardt TC, Taylor AJ et al (2011). Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism. Thrombosis Research. 128: 149-154.	Retrospective case series n=24 PE patients	The right-to-left ventricular dimension ratio (RV/LV ratio) from reconstructed CT four-chamber views at baseline of 1.33 + 0.24 was significantly reduced to 1.00 + 0.13 at follow-up by repeated-measures analysis of variance ($p < 0.001$). The CT-angiographic pulmonary clot burden as assessed by the modified Miller score was significantly reduced from 17.8 + 5.3 to 8.7 + 5.1 ($p<0.001$). All patients were discharged alive, and there were no systemic bleeding complications but 4 major access site bleeding complications requiring transfusion and 1 suspected recurrent massive PE event.	Study in systematic review included in table 2
Kennedy RJ, Kenny HH et al (2013). Thrombus resolution and hemodynamic recovery using ultrasound-accelerated thrombolysis in acute pulmonary	Retrospective case series n=60 53 bilateral PE; 48 sub-massive PE)	Treatment resulted in complete thrombus clearance (>90%) in 57% and near-complete (50%-90%) clearance in 41% of patients after infusion of 35.1 mg+11.1 of recombinant tissue plasminogen activator over 19.6 hours+6.0.	Study in systematic review included in table 2

embolism. Journal of Vascular & Interventional Radiology 24: 841-848.		Measurements before and after treatment showed a decrease in pulmonary artery pressure (47 mm Hg+15 to 38 mm Hg+12 [systolic], p<0.001) and Miller score (25+3 to 17+6, p<0.001). There were 57 patients who survived to discharge. All three patients who died in the hospital presented with massive PE. On 90-day follow-up, 56 patients (93%) were alive.	
Jain SK, Patel B et al (2014). Unloading of right ventricle and clinical improvement after ultrasound-accelerated thrombolysis in patients with sub-massive pulmonary embolism. Case Reports in Medicine 297951.	Case series n=5 Ultrasound-accelerated thrombolysis	5 patients had improvement in symptoms and right ventricular function.	Larger studies included in table 2.
Porres-Aguilar, Burgos JD, Munoz OC et al (2013). Successful pharmacomechanical intervention with ultrasonic-accelerated thrombolytic catheter for massive pulmonary embolism. Indian Heart Journal 65: 699-702	Case report n=1 Massive pulmonary embolism in the right main pulmonary artery extending into the middle and lower lobe branches.	An ultrasonic-accelerated thrombolytic catheter was placed for continuous infusion of alteplase for 20 h. Repeat pulmonary angiogram showed resolution of the large pulmonary emboli, with normal flow in to the distal pulmonary arteries. Significant improvement of hemodynamics, symptoms and hypoxemia.	Larger studies with longer follow-up included in table 2.
Polillo R, Brower J, Benson V et al (2011). Ultrasound-assisted thrombolysis of thrombus and pulmonary embolus. Journal of Vascular Nursing 29: 73-80	case report n=1 life threatening pulmonary embolism UE-CDT	Significant reduction in thrombus. Patient discharged with an IVC filter which was removed after 5 weeks and no further evidence of pulmonary embolism was apparent.	Larger studies with longer follow-up included in table 2.
Quintana D, Salsamendi IJ et al (2014). Ultrasound-assisted thrombolysis in sub-massive and massive pulmonary embolism: assessment of lung obstruction before and after catheter-directed therapy Cardiovascular & Interventional Radiology 37 (2): 420-426.	Retrospective case series n=10 acute sub-massive/massive PE patients.	Median thrombolytic dose was 18.0 mg tissue plasminogen activator infused over 20.8 h. There was a significant decrease in pre-treatment and post-treatment RV pressures (52.0-30.0; p<0.01); there was a significant decrease in pre-treatment and post-treatment Mastora obstructive indices (74-43; p<0.01). All patients improved clinically shortly after treatment onset. All ten patients survived to discharge with a median intensive care (ICU) stay of 4 days and 14 hospital days.	Study in systematic review included in table 2
Shah KJ, Scileppi RM et al (2011). Treatment of pulmonary embolism using ultrasound-accelerated thrombolysis directly into pulmonary	Case report n=1 Bilateral sub-massive pulmonary emboli along with a saddle pulmonary	UE-CDT resulted in rapid substantial clinical improvement, resolution of bilateral pulmonary emboli along with resolution of the saddle pulmonary embolus, restoration of pulmonary blood flow with restoration of	Larger studies with longer follow-up included in table 2.

arteries. Vascular & Endovascular Surgery 45 (6): 541-548	embolus.	pulmonary hypertension, and normalisation of pulmonary embolism related cardiac dysfunction.	
Silvetti S, Pappalardo F et al (2013). Ultrasound-accelerated thrombolysis and extracorporeal membrane oxygenation in a patient with massive pulmonary embolism and cardiac arrest. Circulation: Cardiovascular Interventions. 6 (3): e34-e36	Case report n=1 Patient with massive PE and cardiac arrest. UE-CDT combined with extracorporeal membrane oxygenation.	No bleeding as noted and patient needed only 1 U of blood transfusion. After day 1, TEE showed complete recovery of right ventricular function. Anoxic brain damage as a result of the cardiac arrest was evident and patient was discharged from hospital with severe neurological sequels.	Combined intervention (UE-CDT with ECMO)
Stambo GW and Montague B (2010). Bilateral EKOS EndoWave catheter thrombolysis of acute bilateral pulmonary embolism in a hemodynamically unstable patient. Southern Medical Journal 103:455-457	Case report n=1 Acute massive bilateral pulmonary embolism in a haemodynamically unstable patient. Combination of percutaneous transcatheter directed tPA + mechanical thrombolysis (EKOS device catheters/tPA)	There was complete clearing of the bilateral pulmonary emboli after combination with EKOS/tPA thrombolysis. Patient clinically improved, no bleeding and was discharged from ICU to floor that day and to home in 3 days.	Combined intervention
Yaqoob M, Hamzeh IR et al (2014). Ultrasound-assisted catheter directed thrombolysis in massive and sub-massive pulmonary embolism: A meta-analysis. Journal of the American College of Cardiology. Conference: 26th Annual Symposium Transcatheter Cardiovascular Therapeutics, TCT 2014 Washington, DC United States. Conference Start: 20140913 Conference End: 20140917.	Meta-analysis 7 studies (n=197 patients) Ultrasound-assisted catheter directed thrombolysis (UA-CDT) for massive or sub-massive PE.	130 patients were treated with UCDT. Massive & bilateral PE was reported in 74(30.8%) & 152(63.3%) patients respectively. UCDT resulted in a significant reduction in PA systolic (mean -15.22mmHg; 95% CI -21.01- 9.43) & mean PA pressures (mean -9.35mmHg; 95% CI -13.03- -5.68), in addition to a 24% increase in cardiac index. The ratio of RV to LV was reduced with UCDT (mean -0.35; 95% CI -0.42- -0.28), & the heart rate decreased by 16.9 beats/min (95% CI -26.46 - -7.34). The Miller pulmonary artery occlusion score (in 87 patients) showed a significant reduction of 10.12 points (95% CI -12.21 - -8.02). 30 & 90-day all-cause mortality was 3.1% (6/197) & 4.6 %(7/152) respectively with UCDT. Recurrent events & major bleeding was reported in 2/115 (1.7%) & 7 patients (3.5%) respectively.	Conference abstract only.

Appendix B: Related NICE guidance for ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

Guidance	Recommendations
Technology appraisals	**Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal 261 (2012)** 1.1 Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults. **Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. NICE technology appraisal 287 (2013)** 1.1 Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults. **Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal 157 (2008)** 1.1 Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. **Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal 245 (2012)** 1.1 Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. **Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal 327 (2014)** 1.1 Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.
Clinical guidelines	**Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline 144 (2012)** **1.2 Treatment: Pharmacological interventions**

Deep vein thrombosis or pulmonary embolism

1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism).

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer.

1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[4]. At 6 months, assess the risks and benefits of continuing anticoagulation[5].

1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 1.2.4 and 1.2.5 below).

1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

1.2.5 Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

Rivaroxaban

NICE developed technology appraisal guidance on rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism TA261(2012)

1.1 Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.

Thrombolytic therapy

Pulmonary embolism

1.2.7 Consider pharmacological systemic thrombolytic therapy for patients

	with PE and haemodynamic instability (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). 1.2.8 Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). **Mechanical interventions** **Proximal deep vein thrombosis or pulmonary embolism** 1.2.9 Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[6], and: • advise patients to continue wearing the stockings for at least 2 years • ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions • advise patients that the stockings need to be worn only on the affected leg or legs. 1.2.10 Offer temporary inferior vena caval filters to patients with proximal DVT or PE who cannot have anticoagulation treatment, and remove the inferior vena caval filter when the patient becomes eligible for anticoagulation treatment. 1.2.11 Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as: • increasing target INR to 3–4 for long-term high-intensity oral anticoagulant therapy or • switching treatment to LMWH. 1.2.12 Ensure that a strategy for removing the inferior vena caval filter at the earliest possible opportunity is planned and documented when the filter is placed, and that the strategy is reviewed regularly. **Venous thromboembolism - reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (2010)** This guidance covers assessing and reducing the risk of VTE and using VTE prophylaxis in different patient groups. It does not cover thrombolytic therapy.

Appendix C: Literature search for ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/02/2015	Issue 2 of 12, February 2015	37
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	04/02/2015	Issue 1 of 4, January 2015	7
HTA database (Cochrane Library)	04/02/2015	Issue 1 of 4, January 2015	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/02/2015	Issue 1 of 12, January 2015	118
MEDLINE (Ovid)	04/02/2015	1946 to January Week 4 2015	7
MEDLINE In-Process (Ovid)	04/02/2015	February 03, 2015	52
EMBASE (Ovid)	04/02/2015	1974 to 2015 Week 05	12
CINAHL (NLH Search 2.0)	04/02/2015	n/a	71
PubMed	04/02/2015	n/a	16
JournalTOCS	04/02/2015	n/a	4

Trial sources searched on 20/06/2014:

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 20/06/2014:

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites <<add details>>
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Venous thromboembolism/
2	(Venous adj4 (thrombo-embolism* or thromboembolism* or "thrombo embolism*")).tw.
3	VTE.tw.
4	Pulmonary embolism/
5	(Pulmonary* adj4 embol*).tw.
6	Venous thrombosis/
7	((venous* or vein*) adj4 thromb*).tw.
8	DVT.tw.
9	(bloodclot* or blood-clot* or "blood clot*").tw.
10	Postthrombotic syndrome/
11	((Postthrombotic or post-thrombotic or "post thromobotic") adj4 syndrome).tw.
12	(femoropopliteal* adj4 (venous* or vein*) adj4 occlusion*).tw.
13	(Vascular adj4 occlusion).tw.
14	or/1-13
15	Thrombolytic therapy/
16	(Thrombolytic adj4 (drugs or medicine* or therap* or treat*)).tw.
17	Mechanical Thrombolysis/
18	(thrombolysis or clot-busting or "clot busting" or clotbusting).tw.
19	or/15-18
20	Ultrasonic Therapy/
21	(Ultraso* adj4 (wave* or therap* or procedur* or stimul* or nhance* or facilitate* or boost* or augment* or advance* or accelerat*)).tw.
22	(Tissue* adj4 plasminogen* adj4 activat*).tw.
23	or/20-22
24	19 and 23
25	14 and 24
26	Endowave.tw.
27	EKOS*.tw.
28	or/25-27
29	animals/ not humans/
30	28 not 29
31	limit 30 to english language