NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of Interventional procedure overview of ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis

A blood clot (thrombus) in a vein is usually treated with anticoagulant drugs. This stops further clotting but does not dissolve the thrombus. For severe deep vein thrombosis (DVT) thrombolysis is sometimes used: a catheter (tube) is inserted into a vein (usually in the leg) 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 deep vein thrombosis

Specialist societies

- British Society of Interventional Radiologists
- The Vascular Society of Great Britain and Ireland.

Description

Indications and current treatment

Deep vein thrombosis (DVT) occurs most commonly in the deep veins of the legs. Signs and symptoms include pain swelling, tenderness and colour change, but some DVTs cause no symptoms. Risk factors for DVT include surgery, immobility (due to acute illness such as stroke), malignancy, acquired or inherited hypercoagulable states, pregnancy and dehydration.

DVT is associated with the risk of potentially life-threatening pulmonary embolism (PE) and in the longer term with post-thrombotic syndrome due to chronic venous insufficiency, which is associated with pain, swelling, and sometimes chronic leg ulcers.

A DVT 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. Extensive DVT is sometimes treated by systemic thrombolysis or by endovascular interventions such as catheter-directed and percutaneous mechanical thrombectomy. Thrombolysis is associated with a risk of haemorrhagic complications including stroke. Surgical thrombectomy is an option in patients with DVT that is refractory to thrombolytic therapy, or for whom thrombolysis is contraindicated, but it is rarely used.

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

With the patient in the supine position, a diagnostic catheter is inserted into the area of the thrombosis via the femoral, jugular or popliteal vein and a venogram is done. A guide wire is passed through the thrombosed segment of vein under X-ray guidance and the diagnostic catheter is removed. A multi-lumen infusion catheter is passed over the guide wire into the thrombosed venous segment and the guide wire is replaced with an ultrasound core 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 thrombus through holes in the side of the catheter, using an infusion pump, along with a flow of

saline to act as a coolant while the ultrasound is activated. An electronic device controls the ultrasound power output. The patient is continuously monitored from the start of the treatment. Treatment typically lasts for 12–24 hours.

Follow-up venographic and echocardiographic assessment is performed at regular intervals after the start of the procedure. Once the thrombus has cleared, or there is no further progress, the treatment is stopped and the patient starts standard anticoagulant 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 deep vein thrombosis. 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 deep vein thrombosis.
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 384 patients from 1 randomised controlled trial[1], 2 retrospective comparative case series [2,3], 3 prospective case series[4, 5, 9] and 4 retrospective case series[6-8].

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 deep vein thrombosis

Study 1 Engelberger RP (2015)

Details

Study type	**Randomised controlled trial (BERNUTIFUL)**
Country	Switzerland (single centre)
Recruitment period	2011–13
Study population and number	n=**48 patients with acute iliofemoral DVT (24 UE-CDT versus 24 conventional CDT)** Thrombus extension: distal extension to femoropopliteal deep veins in 67% (32/48), proximal extension into inferior vena cava in 4% (2/48), both proximal and distal extension in 13% (6/48). Bilateral DVT: 6% (3/48), right leg DVT: 25% (12/48), left leg DVT: 69% (33/48). Symptom duration: UE-CDT group mean 5 days; CDT group mean 4.5 days. Adjunct procedures: thrombectomy and prolonged thrombolysis in 29% (7/24) UE-CDT group, 46% (11/24) in CDT group (p=0.37); angioplasty and stenting in 80% (19/24) UE-CDT group and 83% (20/24) CDT group (p>0.99).
Age and sex	Mean 50 years; 48% (23/48) male
Patient selection criteria	Inclusion criteria: symptomatic proximal DVT of iliac or common femoral veins, symptom duration of <2 weeks confirmed by Duplex sonography. Exclusion criteria: age<18 or>75 years, DVT symptom duration>14 days, established post thrombotic syndrome or previous symptomatic DVT within 2 years, limb threatening circulatory compromise, hypotension, inability to tolerate catheter procedure, allergy to iodinised contrast, bleeding risk, coagulation disorders, renal impairment, liver dysfunction, major surgery, stroke, trauma, invasive procedures<10 days, aneurysm, severe hypertension, pregnancy, lactation, thrombolytic therapy <1 month, life expectancy <24 months.
Technique	Patients in UE-CDT and conventional CDT groups initially received intravenous bolus of unfractionated heparin or low-molecular-weight heparin. Fixed dose UE-CDT was performed using a recombinant human tissue plasminogen activator (Actilyse 20 mg for15 hours without bolus) using the EKOS Endowave system. Conventional CDT performed using the same standardised thrombolysis without ultrasound. Compression devices were applied during thrombolysis. Post procedure venography was repeated, UE-CDT continued for 10–24 hours or additional thrombectomy performed in case of thrombotic obstructions. Adjunctive angioplasty and stenting performed for residual venous stenosis (defined as residual luminal narrowing >50%, absent antegrade flow, or presence of collateral flow at the site of suspected stenosis). After CDT, anticoagulation therapy was given for a minimum of 3 months.
Follow-up	**3 months**
Conflict of interest/source of funding	1 author is consultant to EKOS corporation (company). Study supported by Swiss National Science Foundation.

Analysis

Follow-up issues: one patient in each group was lost to follow-up at 3 months.

Study design issues: study was powered to detect a 50% increase in the reduction of thrombus load (for UA-CDT over CDT) therefore a small sample size used. Simple random allocation (1 to 1 ratio) and concealed allocation to either the intervention or control group used. Venograms assessed by independent assessors blinded to group allocation. Standardised treatment protocol (fixed dose regimen, duration) used. Degree of thrombolysis assessed after 15 hours of UE-CDT/CDT in comparison to baseline and prior to adjunctive procedures. A validated venogram scoring system (Lengths Adjusted Thrombus load score system) obtained from standardised venograms and evaluated by blinded assessors was used to quantify changes in thrombus load pre and post intervention.

Patient population issues: Baseline characteristics were similar between groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **UE-CDT 24 versus conventional CDT 24**

Primary treatment success (defined as successful restoration of antegrade inline flow in the treated vein with elimination of any underlying obstructive lesion at the end of the final endovascular procedure) obtained in all but one patient in the UE-CDT group (p>0.99).

Thrombus load (according to LAT score)

Variable	UE-CDT n=24	CDT n=24	p value
Thrombus load at baseline (LAT score^)	59±26	58±22	0.86
Thrombus load after 15 hours (LAT score)	27±24 (p<0.01)	25±16 (p<0.01)	0.68
Percentage of thrombus load reduction* (baseline to 15 hours)	55±27	54±27	0.91
Thrombus load reduction of >50%	58 (14/24)	63 (15/24)	>0.99

^calculated by the sum of the ultrasegment scores (ranging from 0-2 points assigned to each segment, 0 for free of thrombus, 1 for partially thrombosed, 2 for completely thrombosed) multiplied by the length of the ultrasound segment in centimetres.

*calculated according to formula [(LAT score baseline-LAT score after thrombolysis)/LAT score baseline]x100

Clinical follow-up at 3 months

Variable	UE-CDT (n=24)	CDT (n=24)	p value
Mean hospital stay (days)	2.7±1.4	2.8±1.3	0.83
Primary patency* at 3 months (%)	100	96	0.33
Secondary patency^ at 3 months(%)	100	100	
Early rethrombosis** at day 1 (loss of patency within 30 days)	0	4.2 (1/24)	-
Severity of PTS (Villalta score) at 3 months	3.0±3.9	1.9±1.9	0.21
Mean revised venous clinical severity score	3.8±3.3	3.4±1.9	0.63
Clinical Etiologic Anatomic Pathophysiological class	1.2±1.9	1.1±1.2	0.91
Disease specific quality of life (according to Chronic Venous Insufficiency Questionnaire)	28.0±11.6	26.2±7.5	0.55

*defined as percentage of patients with primary success and without the occurrence of either thrombosis of the treated segment or a reintervention to maintain patency of the treated segment.

^defined as percentage of patients with primary treatment success and without permanent loss of flow in the treated segment, irrespective of any interval therapies.

**defined as loss of primary assisted patency within 30 days after the intervention.

Safety

Complications during treatment

	UE-CDT n=24	CDT n=24	p value
Total complications	12.5 (3/24)	8.3 (2/24)	>0.99
Major bleeding* (retroperitoneal haematoma needing 4 units of blood)	4.2 (1/24)	0	>0.99
Minor bleeding*	4.2 (1/24) access-related haematoma	8.3 (2/24) access-related haematoma and transient haemoglobinuria	>0.99
Sub-segmental pulmonary embolism (low risk) at 1 month	4.2 (1/24)		

No bleeding complications at 3 months was noted.

*classified according to the International Society on Thrombosis and Haemostasis

Abbreviations used: CDT, catheter directed thrombolysis, DVT, deep vein thrombosis; LAT score, lengths-adjusted thrombus score; PTS, post-thrombotic syndrome; UE-CDT, ultrasound enhanced catheter directed thrombolysis.

Study 2 Baker R (2012)

Details

Study type	**Retrospective comparative case series**
Country	USA (single centre)
Recruitment period	2004–11
Study population and number	n=**83 (64 UE-CDT vs 19 CDT) patients with iliofemoral DVT** Adjunctive procedures: UE-CDT 68.8% (44/64); CDT 63.2% (12/19), p=42
Age and sex	All=mean 45 years (UE-CDT 44 years; CDT 48 years) All=male 37.3% (31/83) (UE-CDT 40.6% [20/64]; CDT 26.3% [5/19])
Patient selection criteria	Adult patients who underwent CDT or UE-CDT for iliofemoral lower limb DVT (with or without extension into the inferior vena cava) as a primary treatment between 2004 and 2011.
Technique	UE-CDT venous access obtained based on standard practice. The selection of the thrombolysis catheter, drug, and the rate was at the discretion of the physician. Lysis progress was monitored with repeated venography at varying intervals determined by the operator. Treatment was terminated if lysis was achieved, otherwise continued until complete lysis. Any underlying lesions were treated with adjunct procedures (stent placement or percutaneous transluminal angioplasty). Patient remained hospitalised until condition stabilised with anticoagulant therapy. Warfarin administered before discharge and continued for at least 6 months.
Follow-up	**Median 35 months (IQR 20–55 months)**
Conflict of interest/source of funding	One author was supported by a grant by cook medical, 3 authors are shareholders of stocks in EKOS (manufacturer of the device).

Analysis

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

Several lytic agents were also used according to operators' preferences. Target vein patency was reviewed and graded according to a reporting standard by an independent interventional radiologist.

Ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) was used more frequently after 2008.

Study population issues: The baseline parameters and DVT characteristics, including duration of symptoms, location, and extension did not differ significantly between groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **83 (64 vs 19)**

Procedure outcomes

	All (n=83)	UE-CDT (n=64)	CDT (n=19)	p value
Overall infusion time (hours)	26 (21–41)	27(21–27)	25 (22–39)	0.39
Thrombus score**				
At lysis start	10 (7–12)	10 (7–12)	10 (7–13)	0.823
At first lysis check*	3 (16)	3 (1–6)	3 (1–6)	0.574
At lysis stop^	2 (2–3)	2 (1–4)	2 (1–4)	0.658
Percent thrombus resolution				
At first lysis check*	71 (46–91)	71 (40–89)	78 (50–100)	0.269
At lysis stop^	83 (60–100)	82 (55–92)	89 (70–100)	0.560
Substantial lysis (>50%)				
At first lysis check*	74.7 (62/83)	73.4 (47/64)	78.9 (15/19)	0.628
At lysis stop^	89.2 (74/83)	89.1 (57/64)	89.5 (17/19)	0.960
Median inpatient length of stay (days)		6 (3–8)	6 (4–9)	0.331

*median 23 hours; ^ median 26 hours;

** The total thrombus score at lysis start and lysis stop (after lysis) were calculated by adding the scores of the venous segments (0 when the vein was patent and completely free of thrombus, 1 when non-occlusive thrombus was present, 2 when the vein was occluded) before and after thrombolysis

Recurrent thrombosis: 19.2% (16/83) patients.

Kaplan Meier curves for repeated thrombosis

The estimated mean event-free survival time for repeated thrombosis was longer after CDT (69 months, 95% CI 55 to 84 months) compared with UE-CDT (33 months, 95% CI 26 to 41 months) (log-rank test p=0.310).

Safety

Complications

	All % (n=83)	UE-CDT % (n=64)	CDT % (n=19)	p value
Major bleeding*	8.4 (7/83)	7.8 (5/64)	10.5 (2/19)	.709
Minor bleeding**	4.8 (4/83)	4.7 (1/64)	5.3 (1/19)	.918

*defined as clinically overt blood loss with a decrease in haemoglobin level of more than 3g/dL, transfusion of at least 2 units of red blood cells, or the presence of intracranial or retroperitoneal haemorrhage.

**included all haematomas, transfusion of less than 2 units of packed red blood cells, or other sites of bleeding not specified as major.

Deaths in the entire cohort: 3.6% (3/83)

Abbreviations used: CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; tPA, tissue plasminogen activator; UE-CDT, ultrasound enhanced catheter directed thrombolysis; U, units.

Study 3 Lin PH (2010)

Details

Study type	**Retrospective comparative case series**
Country	USA (single centre)
Recruitment period	2000–10
Study population and number	n=**178** patients with symptomatic lower extremity DVT (iliofemoral or femoropopliteal DVT) **UE-CDT (n=46/178), PMT (n=105/178), combined PMT + UE-CDT (n=27/178)** Sub groups: acute DVT 65% (n=116), chronic DVT 35% (n=62) Mean thrombus age (from time of diagnosis to intervention) 24 days (0–65 days) Adjuvant procedures % (n) : Acute DVT group: UE-CDT 84% (27/32), PMT 84.5% (71/84) Chronic DVT group: UE-CDT 100% (14/14) PMT 81% (17/21) combined PMT+ UE-CDT 100% (27/27)
Age and sex	All=mean 47 years All= 55% (98/178) male
Patient selection criteria	Patients with overwhelming symptoms of lower extremity swelling, incapacitating pain, or phlegmasia dolens, with acute DVT (thrombus age <14 days), chronic DVT (>14 days).
Technique	UE-CDT using EKOS Endowave system and/or PMT using tissue plasminogen activator with either Angiojet or Trellis mechanical thrombectomy devices were performed. Procedural-related venograms performed and graded for quantity of thrombus extraction. Following intervention procedures, all patients were continued on fractioned or low molecular weight heparin, with subsequent conversion to warfarin.
Follow-up	**Mean 35±9.8 months (range 1–65 months)**
Conflict of interest/source of funding	None

Analysis

Study design issues: All medical records were reviewed retrospectively.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 178
Outcomes with different catheter based interventions
<table>
<tr><th></th><th>UE-CDT</th><th>PMT</th><th>Combined treatment (PMT+UE-CDT)</th></tr>
<tr><td>Acute DVT (n=116)</td><td>28 (32/116)</td><td>72.4 (84/116)</td><td></td></tr>
<tr><td>Complete treatment success* % (n)</td><td>88 (28/32)</td><td>82 (69/84)</td><td>0</td></tr>
<tr><td>Partial treatment success^ % (n)</td><td>12 (4/32)</td><td>18 (15/84)</td><td>0</td></tr>
<tr><td>Immediate clinical improvement^^ % (n)</td><td>91 (29/32)</td><td>90 (76/84)</td><td>0</td></tr>
<tr><td>No improvement % (n)</td><td>9 (3/32)</td><td>10 (8/84)</td><td>0</td></tr>
<tr><td>Chronic DVT (n=62)</td><td>34 (21/62)</td><td>23 (14/62)</td><td>43 (27/62)</td></tr>
<tr><td>Complete treatment success* % (n)</td><td>64 (9/14)</td><td>33 (7/21)</td><td>74 (20/27)</td></tr>
<tr><td>Partial treatment success^ % (n)</td><td>36 (5/14)</td><td>67 (14/21)</td><td>26 (7/27)</td></tr>
<tr><td>Immediate clinical improvement^^ % (n)</td><td>64 (9/14)</td><td>28 (6/21)</td><td>63 (17/27)</td></tr>
<tr><td>No improvement % (n)</td><td>36 (5/14)</td><td>52 (11/21)</td><td>37 (10/27)</td></tr>
</table>
*complete thrombus removal based on angiographic evidence
^presence of residual thrombus following treatment;
^^ decrease in pain/swelling of the affected extremity within 24 hours of intervention.

Recurrent DVT (needing retreatment): 7% patients (13/178).</td><td>Complications
No deaths</td></tr>
<tr><td colspan="2">Abbreviations used: CDT, catheter directed thrombolysis, DVT, deep vein thrombosis; PMT, pharmacomechanical thrombectomy; tPA, tissue plasminogen activator; UE-CDT, ultrasound enhanced catheter directed thrombolysis.</td></tr>
</table>

Study 4 Engelberger RP (2014)

Details

Study type	**Prospective case series**
Country	Switzerland (single centre)
Recruitment period	2010–13
Study population and number	n=**87 patients with acute iliofemoral DVT** Thrombus location: in 66% (57) patients with distal extension to the femoropopliteal deep veins, 3% (3) with proximal extension into the IVC, 11% (10) in both proximal and distal extension. Bilateral DVT: 9% (8/87), unilateral DVT: 91% (79/87) Symptom duration: Acute (<14 days) in 66% (57/87) patients, sub-acute (15-28 days) in 10% (9/87), acute on-chronic (>28 days) in 24% (21/87) Provoked DVT: 78% (68/87), unprovoked DVT: 22% (19/87) Adjunct procedures: venous stenting (mean 1.9±1.3 stents) in 80% (70/87) patients, frequent site: common iliac (83%).
Age and sex	Mean 46 years; 40% (35/87) male
Patient selection criteria	Inclusion criteria: leg pain or swelling for <28 days and thrombus in the iliac or common femoral vein (lower extremities classification, LET class III) (18), or in the IVC (LET class IV) confirmed by duplex sonography or computed tomography, as ascending or descending thrombosis. Exclusion criteria: patients with femoropopliteal DVT without involvement of the common iliac or femoral veins.
Technique	Fixed dose UE-CDT was performed using a recombinant human tissue plasminogen activator (20 mg for15 hours) which was delivered using the EKOS Endowave system. Extended UE-CDT performed in 7% (6/87) patients with residual thrombosis for a mean additional duration of 18.7 hours, and a total rt-PA dose of 21.7 mg. This was followed by routine stenting for underlying venous stenosis (defined as residual luminal narrowing >50%, absent antegrade flow, or presence of collateral flow at the site of suspected stenosis). Post procedure venography was repeated after treatment and before stenting. Routine follow-up visits were done at 3 months, 6 months and 12 months.
Follow-up	**Mean 273±201 days (range 1–819 days)**
Conflict of interest/source of funding	The first author is a consultant to EKOS corporation (company).

Analysis

Follow-up issues: 18% (15/87), 40% (34/87) and 60% (51/87) patients were lost to follow-up at 3 months, 6 months and 12 months respectively.

Study design issues: standardised treatment protocol used.

Degree of thrombolysis assessed after 15 hours of UE-CDT in comparison to baseline and prior to adjunctive procedures.

Patient population issues Majority of the patients had descending DVT.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **87**

Re-canalisation, mean drug dose and infusion time

Variable	
Mean total drug dose (mg)	20.0±3.0
Mean infusion time (hours)	15.1±0.8
Complete thrombolysis (grade III^^: >95% thrombus removal)	16% (14/87)
Partial thrombolysis (Grade II^^: 50-90% thrombus removal)	61% (53/87)
Minimal/no thrombolysis (Grade I^^: <50% thrombus removal)*	23% (20/87)

^^ grades classified according to Venous Registry Index scoring system.

* 2 patients had no lysis and no further revascularization was done.

The rate of grade II or III thrombolysis was significantly higher in patients with acute DVT (89%, 95% CI, 78-96%) than in patients with sub-acute DVT (56%, 95% CI, 21-86%) or on acute on chronic DVT (57%, 95%CI, 34-78%) (p=0.002).

Clinical follow-up outcomes at mean 273±201 days (range 1–819 days)

Variable	**% (n)**
Venous patency (calculated using Kaplan-Meier survival analysis)	
Primary patency at 1 year[1] (n=36)	87%
Secondary patency at 1 year[2] (n=36)	96%
Re-thrombosis	
Early rethrombosis (loss of patency within 30 days) ^	6% (5/87)
Late thrombosis[3] (reintervention in 1 with hypoplasia of the IVC after 111 days and 1 after 333 days due to stent kinking, successfully treated with UE-CDT and stent placement/thrombectomy)	3% (3/87)
Recurrent DVT (at another site at 6 months)	1(1/87)
Free from post-thrombotic syndrome (PTS 0-4 points on Villalta scale)	
at 3 months (n=72)	88% (63/72)
at 1 year (n=36)	94% (34/36)
Clinical success (calculated using Kaplan-Meier survival analysis)	
Primary clinical success rate at 1 year[4]	78%
Secondary clinical success rate at 1 year[5]	90%

[1]defined as percentage of patients with primary treatment success without thrombosis of treated segment.

[2] defined as % of patients with primary treatment success without the occurrence of permanent loss of flow in treated segment.

[3]defined as loss of primary patency 30 days after intervention

[4]defined as absence of PTS without the need for repeated intervention

[5]defined as the need for interval therapy

^ in 3 UE-CDT and stenting was done and patency achieved.

Safety

Complications during treatment

	% (n)
Major Bleeding (retroperitoneal haematoma due to a wire perforation needing 4 units of blood transfusion)	1 (1/87)
Minor bleeding (4 due to access-related haematoma)	7 (6/87)
Transient foot drop (in a patient who had an access-related popliteal haematoma)	1 (1/87)
Transient asymptomatic haemoglobinuria	2 (2/87)
Transient fever (of unknown origin, negative cultures)	2 (2/87)
Severe phlegmasia coerulea dolens (due to extensive IVC and bilateral iliac thrombosis, needed fasciotomy of lower leg)	1 (1/87)

No pulmonary embolism, local infection at the puncture site was noted.

Thromboembolic events during follow-up mean 273±201 days (range 1–819 days)

	% (n)
Sub-segmental pulmonary embolism (34 days after UE-CDT)	1(1/87)

Abbreviations used: CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IVC, inferior vena cava; PTS, post-thrombotic syndrome; UE-CDT, ultrasound enhanced catheter directed thrombolysis,

Study 5 Strijkers RHW (2012)

Details

Study type	**Retrospective case series**
Country	Germany, Netherlands
Recruitment period	2008–2012
Study population and number	n=**37 patients with acute symptomatic iliofemoral DVT** DVT location: unilateral 87% (33/37) and bilateral 13% (4/37) Thrombus stage: femoropopliteal=1, iliofemoral=32, IVC=4 Thrombus age: 0–6 days=5; 7–13 days=21; 14–20 days=11 Adjunctive procedures (angioplasty, stenting, AV fistula or surgical thrombectomy): 54% (20/37) patients with mainly May–Thurner syndrome.
Age and sex	Mean 42 years ; 49%(18/37) male
Patient selection criteria	Exclusion criteria: patients with >21 days old thrombus, stent thrombosis or thrombosis of the arm, contraindications and high risk bleeding.
Technique	Diagnosis of iliofemoral DVT confirmed using duplex sonography and MR-venography. 45 UE-CDT procedures performed, thrombolytic agents used were rt-PA and urokinase. After thrombolysis, patients received standard DVT therapy with oral anticoagulation, compressive stockings and mobilization according to ACCP guidelines. In addition, additional procedures (angioplasty, stenting, AV fistula or surgical thrombectomy) done to ensure patency of the treated vein. All patients assessed with MR venography combined with Doppler sonography. Follow-up visits planned at 6-8 weeks, after stent placement, then at 3 months, 6 months and 1 year.
Follow-up	**Mean 14 months**
Conflict of interest/source of funding	None

Analysis:

Study design issues: Retrospective study

Key efficacy and safety findings

Efficacy

Number of patients analysed: **37**

Variable	**% (n)**
Average thrombolysis time (hours)	43±17
Success rate of thrombolysis*	95 (35/37)
Grade 3 lysis (<50%)^	5 (2/37)
Primary patency at 1 year (patients at risk, n =14)	70%
Secondary patency at 1 year (patients at risk, n=16)	87%

*Grade I (>90% lysis) in 19, Grade II (50-90% lysis) in 16

^after 72 hours, 2 patients had an occluded segment without signs of recanalisation and thrombolysis was stopped.

Recurrent thrombosis (within first 2 weeks after thrombolysis): in 30% (11/37) of patients. These were due to failed/ delayed stent placements in 6 and due to failure of anticoagulation in 3 (of which 2 were due to heparin-induced thrombocytopenia) patients. Additional UE-CDT and/or stenting/PTA were done in 9 patients and 2 were switched to other anticoagulation therapy.

Safety

Complications

	% (n)
Major bleeding (at catheter insertion site, required blood transfusion)	3 (1/37)
Minor bleeding (at catheter insertion site)	8 (3/37)
Pulmonary embolism (2 weeks after UE-CDT, caused by heparin-induced thrombocytopenia)	3(1/37)
Fever with positive cultures for staphylococcus aureus (recovered after treatment with antibiotics for 6 weeks)	3 (1/37)
Aortic aneurysm (needed acute surgical repair) unrelated to UE-CDT	3 (1/37)

Abbreviations used: ACCP, American college of chest physicians; AV, arteriovenous; CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IVC, inferior vena cava; MR, magnetic resonance; PTA, percutaneous transluminal angioplasty; rt-PA, recombinant tissue plasminogen activator; UE-CDT, ultrasound enhanced catheter directed thrombolysis.

Study 6 Dumantepe M (2013)

Details

Study type	**Prospective case series**
Country	Turkey (single centre)
Recruitment period	2009–12
Study population and number	n=**26 patients with DVT** Thrombus location: 80.8% (21) in the lower extremities (3 IVC, 6 iliac veins, 12 femoral veins) and 19.2% (5) in the upper extremities. Risk factors: postpartum (3), post-surgery (5), trauma (4), prolonged immobilization (3), malignancy (2), idiopathic (9) Symptom duration: Acute (<14 days) in 23% (6/26) patients, sub-acute (15-28 days) in 30.8% (8/26), chronic (>28 days) in 46.2% (12/26) Mean symptom duration: 54.9 days (range 6-183) Adjunct procedures (balloon angioplasty and stenting after thrombolysis): 8% (2/26) patients with iliac vein stenosis
Age and sex	Mean 50.6 years; 46% (12/26) male
Patient selection criteria	Inclusion criteria: Presence of acute or chronic DVT in the upper or lower extremities for 6 months or less without any history or diagnostic evidence (duplex scans) of previous episodes of DVTs Exclusion criteria: contraindications to use of thrombolytic agents and contrast media, recent delivery or major surgery, neurological intervention, significant trauma, disease with known risk of haemorrhagic complications, patients with isolated infrapopliteial thrombosis, recurrent ipsilateral DVT, pre-existing leg ulcers, short life expectancy.
Technique	UE-CDT was performed using a recombinant human tissue plasminogen activator (alteplase for 24 hours) which was delivered using the EKOS Endowave system. Angioplasty and adjunctive procedures (such as stenting) were performed if any underlying stenosis. Post procedure venography was repeated after treatment. Warfarin started before discharge and continued for at least 6 months, adjuvant compression therapy recommended for more than 1 year.
Follow-up	**Mean 12.4 months (range 6–22 months)**
Conflict of interest/source of funding	None

Analysis

Study design issues: Small numbers of patients

Recanalisation calculated after completion of UE-CDT and additional adjunct procedures.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **26**

Re-canalisation, mean drug dose and infusion time

Variable	
Mean total drug dose (mg)	37±9.2 (range, 20-54)
Mean infusion time (hours)	25±5.3 (range 16-39)
Overall clot lysis^ (% of patients)	92.3%
Complete clot lysis (>95% restored patency)	53.8% (14/26)
Partial lysis (50-90% restored patency)	38.4% (10/26)
Minimal clot lysis (<50%)*	8% (2/26)

^sum of partial and complete thrombolysis

*patients had a chronic thrombus that did not respond to thrombolysis.

Thrombosis versus clinical improvement

Clinical response	**percentage of thrombus removal (mean [range])**
Complete (n=13)	93.4 (76–100)
Significant (n=9)	81.9 (65–100)
Poor (n=2)	59 (35–65)
Absent (n=2)	32.5 (28–55)

Clinical follow-up outcomes at mean 12.4 months (range 6-22 months)

Variable	**% (n)**
Venous patency (on Doppler ultrasound)	
Patent	84.7 (22/26)
Early rethrombosis	7.6 (2/26)
Restenosis/occlusion (7 months after treatment in 1 patient with protein C deficiency who achieved complete lysis; in another patient due to left-sided common iliac vein stenosis unmasked after lysis, patient refused early angioplasty and developed rethrombosis 2 months after lysis before stenting)	7.6 (2/26)
Valve function	
Normal	80.8 (21/26)
reflux in limbs	19.2 (5/26)
Post-thrombotic syndrome	
No	88.5 (23/26)
Mild (with pain, heaviness, oedema of the affected limbs after activity)	11.5 (3/26)

Safety

Complications during treatment

	% (n)
Minor bleeding at catheter insertion site (resolved by elevation of limb or compressive banding)	11.5 (3/26)
Haematuria (after 25 hours in a patient with minor bleeding, resolved spontaneously after interruption of lysis)	4 (1/26)
Slight pain in the affected knees	23 (6/26)

No pulmonary embolism, intracranial haemorrhage, death or other procedure-related complications.

Adverse events at follow-up (mean 12.4 months)

	% (n)
Mild pruritus (none of the limbs had severe PTS)	15 (4/26)

Abbreviations used: CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; IVC, inferior vena cava; PTS, post-thrombotic syndrome; UE-CDT, ultrasound enhanced catheter directed thrombolysis,

Study 7 Parikh S (2008)

Details

Study type	**Retrospective case series+ comparison with historical controls**
Country	USA (8 centres)
Recruitment period	2004–06
Study population and number	n=**47 DVT patients (with 53 venous occlusions)** Thrombus location: 60% (32) occlusions in lower extremities, 36% (19) in upper extremities, and 4% (2) were hepatic. Symptom duration: acute (<14 days) in 47% (25) patients, sub-acute (15-28 days) in 8% (4), chronic (>28 days) in 17% (9), acute on chronic in 17% (9) and not specified in 11%. Adjunct procedures (PTA, stent placement, mechanical thrombectomy and surgery): 75.5 (40/53 occlusions). Chronic occlusions and high grade venous stenosis treated with PTA (49%, n=26), and/or stent placement (24.5%, n=13). Mechanical thrombectomy in 22.6% (n=12) and surgical arteriovenous fistula in 3.8% (n=2) patients. Multiple adjunct procedures in 24% (13/53) cases.
Age and sex	Mean 50.8 years; 55.3% (26/47) male
Patient selection criteria	All patients with DVT of the upper and lower extremities treated with UE-CDT for primary thrombolysis between 2004–06.
Technique	Patients were treated with UE-CDT (EKOS Endowave system) in the ICU; thrombolytic drugs used were urokinase, tPA, rPA, or tenecteplase. Follow-up venography performed on all patients at the discretion of the radiologist with first check ranging from 2–29 hours after treatment initiation. Treatment was terminated if complete lysis was achieved, otherwise continued until complete lysis. After thrombus clearance, adjunct procedures (including PTA, stent placement) were performed to treat any underlying lesion. Patients remained hospitalised until stabilised with anticoagulation therapy and after discharge followed as per site standard practice.
Follow-up	**Median 35 months (IQR 20–55 months)**
Conflict of interest/source of funding	5 authors are consultants for EKOS corporation (manufacturer of the device).

Analysis

Study design issues:

Thrombolytic drugs and follow-up checks were not standardised. Infusion times were based on standard practice patterns rather than actual time to achieve clot lysis.

Mean thrombus size was not reported. DVT classified according to symptom duration in the society of Interventional Radiology reporting standards for endovascular treatment of lower-extremity DVT.

Thrombolytic drug dose, infusion times were compared with the findings of a historical cohort study on standard CDT for iliofemoral DVT (National venous thrombolysis registry).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **47 (53 occlusions)**

Median total drug dose and infusion times between UE-CDT and CDT (historical controls)

Median total drug dose				
	n	**UE-CDT**	**n**	**Standard CDT for iliofemoral DVT -National venous thrombolysis registry**
UK	14	2.0×10^6 U	38	4.4×10^6 U
tPA	9	14.0 mg	32	21.6 mg
rPA	22	6.9 units	12	21.4 units
Tenecteplase	8	9.5 mg	0	
Median infusion time (h)				
UK	14	19.3	38	40.6
tPA	9	18.0	32	30.8
rPA	22	24.0	12	24.3
Tenecteplase	8	24.3	0	

The median infusion time for all patients was 22.0 hours (range, 6-69 hours).

Resolution of thrombus by duration of symptoms

Symptom duration	**Complete lysis (≥90%)**	**Partial lysis (50-90%)**	**No lysis^^**	**Overall lysis^**
All occlusions (n=53)	69.8 (37/53)	20.8 (11/53)	9.4 (5/53)	90.6 (48/53)
Acute (n=25)	72 (18/25)	NR	NR	96 (24/25)
Sub-acute (n=4)	75 (3/4)	NR	NR	100 (4/4)
Chronic (n=9)	77.8 (7/9)	NR	NR	77.8 (7/9)
Acute-on-chronic (n=9)	66.7 (6/9)	NR	NR	77.8 (7/9)

^complete (at least 90%) and partial lysis (less than 90%) confirmed through venography assessment

^^4 chronic thrombus, 1 acute occlusion did not respond to thrombolysis.

Safety

Complications

Haematoma (at surgical site in patients who underwent surgery for bleeding complications, removed surgically and 2-unit blood transfusion done, resolved with no sequelae) 3.8% (2/47)

No incidence of intracranial or retroperitoneal haemorrhage occurred.

Abbreviations used: CDT, catheter directed thrombolysis, DVT, deep vein thrombosis; IQR, interquartile range; PTA, percutaneous transluminal angioplasty; rPA, recombinant plasminogen activator; tPA, tissue plasminogen activator; UE-CDT, ultrasound-enhanced, catheter-directed thrombolysis; UK, urokinase.

Study 8 Motarjeme MD (2007)

Details

Study type	**Retrospective case series + comparison with historical controls**
Country	USA (single centre)
Recruitment period	2005–06
Study population and number	n=**33 (with 36 occlusions- 12 venous and 24 arterial) patients with acute and chronic arterial and venous occlusions.** Thrombus location: subclavian (2), isolated iliac (3), iliofemoral (3), femoral (3), and femoropopliteal veins (1) and 1 inferior vena cava occlusion.
Age and sex	Range 39–90 years; 70% (23/33) male
Patient selection criteria	Not reported
Technique	In patients with chronic occlusion of the IVC and iliac veins, pre-dilation with a 3–4 mm balloon catheter was needed for insertion of the lysis catheter. All patients were treated with UE-CDT (EKOS Endowave system) with urokinase (80,000–120,000 IU/h). Systemic heparin was used throughout the course of treatment. Patients examined at 6 months, 12 months and 18 months after initiating lytic therapy. After completion of thrombolysis, the IVC and iliac veins were stented.
Follow-up	**12 months**
Conflict of interest/source of funding	First author is a consultant for EKOS corporation (manufacturer of the device).

Analysis

Study design issues: Small numbers of patients, only venous occlusions are considered for review. Findings of arterial occlusions (n=24) are outside the scope of this report.

Final angiograms were taken after overnight treatment. Complete lysis was defined as >90% clot removal for acute or >75% for chronic DVT. Thrombolytic infusion times and lysis rates were compared with the findings of a historical cohort study on standard CDT for iliofemoral DVT (National venous thrombolysis registry (n=287).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **12 venous occlusions** **Technical success** (defined as catheter positioning within the occlusions and simultaneous ultrasound delivery with lytic infusion): 100% **Comparison of clinical results with historical controls**	**Complications** There were no device-related adverse events or failures, no major complications including bleeding.

	UE-CDT current study (12 venous occlusions)	**CDT for iliofemoral DVT - National venous thrombolysis registry (n=287)**
Average lytic infusion time (hours) for complete lysis	21.2 (range 6–43)	53.4
Complete lysis (>90%) at final angiography	83% (10/12)	31%

Recurrence: in 2 chronic DVT patients were refractory to lytic therapy

- 1 re-occlusion at 2 months in the iliac vein
- 1 re-thrombosis in the femoropopliteal graft.

Abbreviations used: CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; IVC, inferior vena cava; UE-CDT, ultrasound enhanced catheter directed thrombolysis,

Study 9 Grommes J (2011)

Details

Study type	**Prospective case series**
Country	Germany, Netherlands
Recruitment period	2008–10
Study population and number	n=**12 patients with DVT (13 occlusions)** (7 caval-iliofemoropopliteal, 3 iliofemoropopliteal, 1 femoropopliteal, 1 superior caval vein thrombosis) Age of thrombus (days between symptom onset and intervention): 0–6 days in 3 patients, 7–13 days in 5 patients, 14–20 days in 1 patient, >21 days in 4 patients. Adjunctive procedures (balloon angioplasty and stent insertion) to treat underlying lesions:25% (3/12)
Age and sex	Median 44 years ; 58% (7/12) male
Patient selection criteria	Inclusion criteria: Patients with symptomatic, duplex and computed tomography confirmed DVT, life expectancy exceeding 6 months, receiving standard anticoagulant and compression therapy. Exclusion criteria: gastrointestinal bleeding or cerebrovascular haemorrhage in the previous year, severe hypertension (>180/100 mm Hg), active malignancy, surgery in previous 6 weeks, pregnancy.
Technique	Patients were treated with UE-CDT procedures using the EKOS Endowave system with recombinant tissue plasminogen activator (rtPA) (10/13) or urokinase (3/13) combined with standard DVT therapy. Follow-up phelbograms were performed every 24 hours thereafter. Thrombolysis was stopped, if clot lysis was achieved or the maximum infusion period of 72 hours was reached. Additional angioplasty with or without stents was performed to treat underlying lesions. After discharge, anticoagulation was given according to international guidelines (ACCP 2008) with duration planned for 6 months for idiopathic DVT and 3 months for provoked DVT.
Follow-up	**Mean 7 months (range 3–17 months)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: patients followed-up every 3 months after discharge.

Study design issues: small study

Study population issues: in 5 patients pulmonary embolism was present before the procedure.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **12**

Thrombolysis outcomes

Variable	% (n)
Complete clot lysis (>90% restored patency)	85 (11/13)
Partial lysis (50–90% restored patency)	8 (1/13)
No lysis*	8 (1/13)

*in a 5-year-old boy who developed DVT and PE as a consequence of an undetected thrombophilia (factor V Leiden) and immobilisation after orthopaedic surgery. 3 month and 6 month follow-up revealed spontaneous re-canalisation of the IVC up to the origin of the left renal vein. The iliac vein remained occluded.

No relationship observed between successful thrombolysis and age of thrombus.

Patency at 7 months follow-up

At a mean of 7 months follow-up, no further occlusions occurred in all patients.

Recurrence

Variable	% (n)
Recurrent DVT	46% (6/13) occlusions
Early recurrent thrombosis (3 due to inadequate treatment of underlying residual venous obstruction (May–Thurner syndrome): 1. Within day 1 in a patient developed bleeding necessitating 50% reduction in hourly drug dose (50% recanalisation of femoral and iliac vein was found after 6 months, this was dilated and stented). 2. 4 days after initial treatment in whom iliac stenosis was not treated immediately, thrombolysis repeated with success, followed by angioplasty and stenting and construction of an AV fistula in the femoral vein. 3. 1 day after successful treatment and inadequately treated with angioplasty alone (remained occluded at follow-up). 1 due to a heparin-induced thrombocytopenia (HIT type II) caused by enoxaparin 4. At 14 days after treatment, 50% recanalisation of the femoral and iliac veins at 6 months noted.	31 (4/13)

Safety

Complications

	% (n)
Bleeding (at catheter insertion site in whom catheterisation of the popliteal vein achieved by open access)	8% (1/13)

Abbreviations used: AV, arteriovenous; CDT, catheter directed thrombolysis, CI, confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; IVC, inferior vena cava; UE-CDT, ultrasound enhanced catheter directed thrombolysis.

Efficacy

Thrombolysis success

A randomised controlled trial (RCT) of 48 patients with acute iliofemoral deep vein thrombosis (DVT) comparing ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT, n=24) against catheter-directed thrombolysis (CDT, n=24) with a fixed-dose thrombolysis regimen in all patients, reported that there was no significant difference in the percentage of thrombus load reduction (according to Length-Adjusted Thrombus score, obtained from venograms) between the 2 treatment groups (UE-CDT 55±27% and standard CDT 54±27%; p=0.91)[1].

A retrospective comparative case series of 83 patients with deep vein thrombosis (DVT) comparing UE-CDT, (n=64) against CDT (n=19) reported no significant difference between the 2 groups in the rate of substantial thrombolysis lysis (>50% removal) at the last angiography assessment at a median follow-up of 26 hours (UE-CDT 89.1% [57/64] and CDT 89.5% [17/19]; p=0.96)[2].

A retrospective comparative case series of 178 patients with DVT comparing UE-CDT (n=46) against pharmacomechanical thrombectomy (PMT) alone (n=105) and against PMT plus UE-CDT (n=27) reported that in patients with chronic DVT (n=62), the combined intervention achieved complete treatment success more frequently (74% [20/27]) than either UE-CDT or PMT alone (64% [9/14] and 33% [7/21] respectively; p values not reported). Complete treatment success was similar in patients with acute DVT (n=116) who had UE-CDT or PMT alone (88% [28/32] and 82% [69/84] respectively)[3].

The retrospective comparative case series of 83 patients with DVT comparing UE-CDT (n=64) against CDT (n=19) reported no significant difference in of percentage resolution of thrombus load between the two groups (UE-CDT 82%, [interquartile range 55–92%], CDT 89%, [interquartile range 70-100%]; p=0.56)[2].

A prospective case series of 87 patients with acute iliofemoral DVT treated with a fixed dose UE-CDT (20 mg rt-PA during 15 hours) reported that thrombolysis success ≥50% was achieved in 77% (67/87) of patients[4].

Overall infusion time

The retrospective comparative case series of 83 patients comparing UE-CDT (n=64) against CDT alone (n=19) reported that there was no significant difference in overall infusion time between the 2 treatment groups (UE-CDT 27 hours [range 21–27], CDT 25 hours [range 22–39]; p=0.39)[2].

Median total drug dose

A retrospective comparative case series of 47 patients with 53 occlusive DVTs comparing UE-CDT against historical controls who had CDT alone (n=82)

reported that median total dose of each thrombolytic drug was lower in UE-CDT compared with CDT alone (respectively, urokinase 2.0×10^6 units and 4.4×10^6 units; tissue plasminogen activator 14 mg and 21.6 mg; recombinant plasminogen activator 6.9 units and 21.4 units)[7].

Clinical improvement

The retrospective comparative case series of 178 patients with acute and chronic DVT comparing UE-CDT against PMT alone and combined UE-CDT plus PMT reported that in patients with chronic DVT (n=62) immediate clinical improvement occurred more often in the UE-CDT and combined intervention group (64% [9/14] and 63% [17/27] respectively) compared against PMT alone (28% [6/21], p values not reported). In the patients with acute DVT (n=116), clinical improvement was similar in the 2 treatment groups: UE-CDT 91% (29/32); PMT 90% (76/84)[3].

Patency at 1 year

The RCT of 48 patients with acute iliofemoral DVT comparing UE-CDT against standard CDT reported no significant difference in the primary venous patency between the 2 treatment groups at 3-month follow-up (UE-CDT 100% and standard CDT 96%; p=0.33)[1].

The prospective case series of 87 patients with acute iliofemoral DVT reported that primary and secondary patency rates (calculated using Kaplan–Meier survival analysis) at 1 year were 87% and 96% respectively[4].

A prospective case series of 26 patients with DVT reported that 85% (22/26) of the patients treated successfully remained patent at 12 months follow-up (on Doppler ultrasound)[6].

Recurrent thrombosis/ stenosis

The retrospective comparative case series of 83 patients with DVT comparing UE-CDT (n=64) against CDT (n=19) reported that the mean event-free survival time for repeated thrombosis was (not significantly) shorter after UE-CDT (33 months, 95% confidence interval [CI] 26–41 months) compared with CDT (69 months, 95% CI 55 to 84 months) (log rank test p=0.310)[2].

A case series of 12 patients with DVT reported that early recurrent thrombosis (within 1–14 days) after treatment occurred in 31% (4/13) occlusions. These were due to inadequate treatment of underlying residual venous obstruction (May–Thurner syndrome) in 3 patients and heparin-induced thrombocytopenia (HIT type II) in 1 patient. Additional UE-CDT and/or angioplasty or stenting procedures were performed to achieve patency[9].

The case series of 12 patients who underwent UE-CDT reported that recurrent DVT needing treatment occurred in 46% (6/13) occlusions at a mean follow-up of 7 months[9].

The case series of 26 patients reported restenosis/occlusion in 8% (2/26) of the patients. One patient with protein C deficiency who achieved complete lysis after initial UE-CDT treatment had restenosis 7 months after UE-CDT treatment. In another patient, left-sided common iliac vein stenosis was unmasked after lysis, and patient refused early angioplasty and developed rethrombosis 2 months after lysis before stenting[6].

Valvular reflux

The case series of 26 patients reported valvular reflux in 19% (5/26) of the patients (further details were not reported)[6].

Post-thrombotic syndrome

The RCT of 48 patients with acute iliofemoral DVT comparing UE-CDT against standard CDT reported no significant difference in the severity of the post-thrombotic syndrome between the 2 treatment groups (mean Villalta score: UE-CDT 3.0+/-3.9 versus standard CDT1.9+/-1.9; p=0.21), respectively at 3-month follow-up[1].The case series of 26 patients who underwent UE-CDT reported mild post-thrombotic syndrome in 11.5% (3/26) of patients: this mainly manifested as pain, heaviness and oedema of the affected limbs after activity. The median post-thrombotic syndrome score in these patients was 2 (range 0–7)[6].

Safety

Major bleeding

Major bleeding (retroperitoneal haematoma needing 4 units of blood) was reported in 1 patient in the UE-CDT group (n=24) in the RCT of 48 patients[1].

Major bleeding (at catheter insertion site, needing blood transfusion) was reported in 1 patient in the case series of 37 patients[5].

Major bleeding (retroperitoneal haematoma due to a wire perforation) was reported in 1 patient in the case series of 87 patients. This was treated with 4 units of blood transfusion[4].

Pulmonary embolism

Pulmonary embolism (2 weeks after UE-CDT, caused by heparin-induced thrombocytopenia) occurred in 1 patient in a case series of 37 patients with acute iliofemoral DVT. Further details were not reported[5].

Sub-segmental pulmonary embolism (34 days after UE-CDT) was reported in 1 patient in a case series of 87 patients[4].

Aortic aneurysm (unrelated to UE-CDT)

Aortic aneurysm unrelated to UE-CDT was reported in 1 patient in the case series of 37 patients. The patient was treated with acute surgical repair[5].

Haematoma

Haematoma at the access site was reported in 1 patient in the UE-CDT group (n=24) and 2 patients in the standard CDT group (n=24) in the RCT of 48 patients[1].

Severe phlegmasia coerulea dolens (due to extensive IVC and bilateral iliac thrombosis) was reported in 1 patient in the case series of 87 patients with acute iliofemoral DVT. Fasciotomy of the lower leg was performed to relieve symptoms[4].

Minor bleeding

Minor bleeding at the site of catheter insertion (resolved by elevation of the limb or compressive banding) was reported in 12% (3/26) of patients in a case series of 26 patients[6].

Haematuria

Haematuria (25 hours after minor bleeding during thrombolysis) was reported in 1 patient in the case series of 26 patients (further details were not reported)[6].

Fever

Fever with positive cultures for staphylococcus aureus was reported in 6% (2/37) of patients in the case series of 37 patients. Both patients recovered after treatment with antibiotics for 6 weeks[5].

Mild pruritus

Mild pruritus was reported in 15% (4/26) patients in the case series of 26 patients (further details were not reported)[6].

Transient foot drop

Transient foot drop was reported in 1 patient who had an access-related popliteal haematoma in the case series of 87 patients (further details were not reported)[4].

Transient asymptomatic haemoglobinuria

Transient asymptomatic haemoglobinuria was reported in 2 patients in the case series of 87 patients (further details were not reported)[4].

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 other treatments for DVT.
- Evidence is mainly from 1 randomised controlled trial[1], 2 retrospective comparative case series[2,3], 3 small retrospective case series[5,7,8] and 3

prospective case series[4,6,9]. Therefore there may be several confounding factors that could have influenced the results.

- A retrospective comparative case series[2] comparing UE-CDT against standard CDT showed similar efficacy and safety.
- Two small retrospective case series[7,8] showed greater thrombolysis success and shorter treatment times with UE-CDT.
- Follow up ranged from 1 month to 3 years.
- The majority of the studies used different drug treatment regimens and treatment duration was according to follow-up venographic assessment results (mean ranging from 21.2–47 hours). Only 1 prospective case series[4] used fixed dose and duration for treatment regimens.
- Stenting rate for underlying venous stenosis varied widely between different studies.

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 261 ([2012]). Available from http://www.nice.org.uk/guidance/TA261
- Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolic events. NICE technology appraisal 287 ([2013]). Available from http://www.nice.org.uk/guidance/TA287
- Rivaroxaban for the prevention of venous thromboembolism. NICE technology appraisal 170 ([2009]). Available from http://www.nice.org.uk/guidance/TA170

- Dibigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal 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 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 327 ([2014]). Available from http://www.nice.org.uk/guidance/TA327

Clinical guidelines

- Management of venous thromboembolic diseases. NICE clinical guideline 144 ([2012]). Available from http://www.nice.org.uk/guidance/CG144
- 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 is not intended to represent the view of the society.

Mr Isaac K Nyamekye, Dr Julian Hague, Mr Holdsworth Richard, Dr Lasantha Wijesinghe, Mr Simon Ashley and Mr David Cooper (The Vascular Society of Great Britain and Ireland); Mr Jeremy Taylor (British Society of Interventional Radiology).

- One adviser stated that he has performed the procedure at least once. Six specialist advisers stated that they have never performed this procedure but most of them referred patients for standard catheter thrombolysis (CDT) and mechanical thrombolysis.
- Three advisers considered the procedure to be definitely novel and of uncertain efficacy and safety while 1 adviser considered it as an established practice and no longer new. Three advisers considered that it is a minor

variation of an existing procedure which is unlikely to alter that procedure's safety and efficacy.

- One adviser stated that the procedure will be mainly performed by interventional vascular radiologists but patients will be under the care of vascular surgeons.
- Comparators listed include oral anticoagulation, systemic thrombolysis, standard catheter directed thrombolysis (CDT), pharmacomechanical thrombectomy and in exceptional circumstances surgical thrombectomy.
- Six advisers 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.
- Key efficacy outcomes include duration of lysis (enhanced lysis over shorter period of time), reduced dose of thrombolytic drug, recanalisation of deep veins (resolution of thrombus), DVT symptom relief, prevention of long-term sequelae of DVT (that is, free from post thrombotic syndrome), rethrombosis, recurrent DVT, long term patency and improved quality of life. Advisers stated that the main uncertainties relate to lytic dose needed, duration of lysis compared to standard catheter directed thrombolysis and the long term efficacy of the procedure.
- Anecdotal adverse events listed include puncture site bleeding and pulmonary embolus.
- Theoretical adverse events listed include: bleeding (puncture site and systemic); pulmonary embolism; failure of lysis; thermal damage to surrounding structures; potential nerve damage; septic thrombophlebitis; vessel perforation; access site haematoma; haemorrhage (both locally and systemically) and death.
- Specialist advisers stated that the procedures should be performed by interventional radiologist or cardiologist trained in endovascular techniques (interventional radiology, use of ultrasound systems) in a radiology interventional suite or cardiology angiography laboratory with appropriate equipment for cardiopulmonary resuscitation. Training for operators, nursing

staff on the use of equipment and access to specialists is needed during overnight lysis. For monitoring post-procedure, high-dependency units or dedicated bays on vascular wards are required. Surgical support will be necessary in the event of haemorrhagic complications. For those trained in standard catheter-directed thrombolysis, mentoring from clinicians and manufacturer's training courses is adequate.

- Four advisers stated that the uptake of the procedure is likely to be slow in a minority of hospitals and the impact on the NHS will be moderate. Three advisers stated that the standard CDT procedure is already in use in a number of centres and if UE-CDT (minor variation of CDT) is safe and efficacious it is likely to be carried out in district and general hospitals that routinely use venous thrombolysis for DVT and the potential impact on the NHS will be minor.

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 UE-CDT. This system received FDA approval in 2008 for the infusion of thrombotic drugs.
- Ongoing studies:
  - NCT00970619: DUTCH CAVA-trial: Ultrasound-accelerated, catheter-directed thrombolysis for primary iliofemoral deep vein thrombosis (IFDVT) Compared to non-invasive conventional anticoagulant therapy alone: a Dutch randomised controlled multicentre clinical trial. Study design: prospective, non-blinded, randomised, controlled, multicentre, intervention study. Study population: patients with acute primary IFDVT (thrombus not older than 14 days). Primary outcome: percentage of patients with post thrombotic syndrome 1 year following the acute thrombotic event. Estimated

enrolment:180; location: Netherlands. Estimated completion: January 2015. Status: currently recruiting.

- NCT02159521: Treatment of patients with chronic deep vein thrombosis (DVT) and post-thrombotic syndrome (PTS) with the EkoSonic Endovascular System (ACCESS PTS). Study design: open-label single-group assignment. Study population: patients with chronic DVT (proximal DVT>6 months). Primary outcome: Villalta score at 30 days. Secondary endpoints: Villalta score (a measure of severity of PTS) and patency at 1 year. Estimated enrolment: 200. Completion date: 2016. Location: USA. Sponsor: manufacturer; Status: currently recruiting.

References

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2. Baker R, Samuels S et al. (2012) Ultrasound-accelerated vs standard catheter-directed thrombolysis--a comparative study in patients with iliofemoral deep vein thrombosis. Journal of Vascular & Interventional Radiology 23: 1460-1466
3. Lin PH, Ochoa LN et al. (2010) Catheter-directed thrombectomy and thrombolysis for symptomatic lower-extremity deep vein thrombosis: review of current interventional treatment strategies. Perspect Vasc Surg Endovasc Ther. 22: 152-163
4. Engelberger RP, Fahrni J, Wilenberg T et al. (2014) Fixed low-dose ultrasound assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis. Thrombosis and haemostasis 111: 1153-1160
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6. Dumantepe M , Tarhan A et al. (2013) US-accelerated catheter-directed thrombolysis for the treatment of deep venous thrombosis. Diagnostic & Interventional Radiology 19: 251-258
7. Parikh S, Motarjeme A et al. (2008) Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience Journal of Vascular & Interventional Radiology 19: 521-528
8. Motarjeme A (2007). Ultrasound-enhanced Thrombolysis Journal of Endovascular Therapy. Journal of Endovascular Therapy 14: 251-256
9. Grommes J, Strijkers R et al. (2011) Safety and feasibility of ultrasound-accelerated catheter-directed thrombolysis in deep vein thrombosis. European Journal of Vascular & Endovascular Surgery 41: 526-532

Appendix A: Additional papers on ultrasound enhanced, catheter-directed, thrombolysis for deep vein thrombosis

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
Crouch SD, Hill D et al. (2008) New Technology for the Treatment of Peripheral Arterial and Venous Occlusions: Ultrasound Accelerated Thrombolysis. Journal of Radiology Nursing 27: 14-21	Case report n=1 patient with occluded right femoral-tibial peroneal bypass graft symptomatic for 12 months UE-CDT	Lytic check at 24 hrs showed a patent bypass graft with minimal residual thrombus. Moderate atherosclerotic irregularity at the anastomosis of the graft in the common femoral artery resulted in stenosis which was treated with angioplasty resulting in excellent angiographic results and improved blood flow. There was complete resolution of symptoms post procedure. And 1 month visit patient was not experiencing any leg pain.	Larger studies with longer follow-up included in table 2.
Dumantepe M, Arif TI et al. (2013) Endovascular treatment of postpartum deep venous thrombosis: Report of three cases. Vascular 21: 380-385	Case report n=3 Patients with postpartum iliofemoral DVT UE-CDT using a rt-PA (alteplase) using EKOS endowave system.	The treatment was successful in all three cases of iliofemoral DVT and symptom relief was achieved in all cases. Minor bleeding at the catheter insertion site in 1 patient was observed but none of the patients suffered from major bleeding or symptomatic pulmonary embolism.	Larger studies with longer follow-up included in table 2.
Dumantepe M, Tarhan IA et al. (2013) Ultrasound-accelerated catheter-directed thrombolysis for the management of postpartum deep venous thrombosis. Journal of Obstetrics & Gynaecology Research 39: 1065-1069	Case report n=1 (26 years) Patient with symptomatic postpartum iliofemoral DVT UE-CDT using EKOS endowave system rtPA Alteplase	Recanalisation of the totally occluded vein was revealed at post procedure venography. There was no bleeding complication due to treatment, patient discharged on 2nd day on Vitamin K therapy for 6 months with graduated compression stockings fo 6–12 months. Further follow-up ultrasonography showed patency of iliac and femoral vein without thrombotic changes after 6 and 12 months.	Larger studies with longer follow-up included in table 2.
Dommernik DE, Schrijver AM et al. (2011) Advancements in catheter –directed ultrasound-accelerated thrombolysis. Journal of endovascular specialists18:418-434	Systematic review on UE-CDT for peripheral arterial occlusions, stroke, DVT and pulmonary embolism.	UE-CDT seems to be a promising concept in the treatment of various thromboembolic conditions. The technique has shown to be safe and effective in vitro, in vivo and in clinical studies. Randomised trials are warranted before considering UE-CDT as a new standard treatment.	Narrative review that summarised evidence on UE-CDT. Primary studies on DVT are included in table 2.
Ganguli S, Kalva S et al. (2012) Efficacy of lower-extremity venous thrombolysis in the setting of congenital absence or atresia of the inferior vena cava. Cardiovascular & Interventional Radiology 35: 1053-1058	Retrospective case series n=6 Patients with acute lower-extremity DVT and congenital agenesis or atresia of the inferior vena cava (IVC). Mean follow-up= 25.8 months	Pharmacomechanical CDT (PCDT) + systematic thrombolysis + systemic heparinization and use of compression stockings. All PCDT procedures were technically successful, no venous stenting or angioplasty was performed. Average thrombolysis time was 28.6hrs, 2 patients had heparin-induced thrombocytopenia, 1 patient developed a self-limited knee haemarthrosis, and no patients were lost to follow-up. No incidence of recurrent DVT or manifestation of post thrombotic syndrome.	Combined interventions.

Mewissen MW (1999). Catheter directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 211 (1), 39-49.	Case series n=287 Patients with symptomatic lower DVT. Standard catheter directed thrombolysis	IFDVT and FPDVT treated with urokinase infusions for a mean 53.4 hours. After thrombolysis 99 iliac and 5 femoral vein lesions were treated with stents. Complete lysis was achieved in 96 (31%) infusions, partial lysis (50-99%) in 52% (162), no lysis (<50%) in 17% (54). For acute thrombosis complete lysis in 34% cases and in 19% of chronic DVT (p<.01). Major bleeding occurred in 11% (54) patients at puncture site. 6 developed pulmonary emboli. 2 deaths due to PE and intracranial haemorrhage. At 1 year patency rate was 60%. Lysis grade was predictive of 1 year patency rate (grade III 79%, grade II 58%, grade I 32%; p<.001).	Standard CDT
Owens CA (2008). Ultrasound-Enhanced Thrombolysis: EKOS EndoWave Infusion Catheter System. Seminars in Interventional Radiology 25 (1) 37-41.	UE-CDT		Review on concepts and early clinical studies.
Raabe RD (2010). Ultrasound-accelerated thrombolysis in arterial and venous peripheral occlusions: fibrinogen level effects. Journal of Vascular & Interventional Radiology. 21 (8); 1165-1172	n=38 (with 38 occlusions- 9 venous and 29 arterial) patients with peripheral arterial occlusions and DVT in the upper and lower extremities. UE-CDT (EKOS endowave system) Follow-up 30 days	Treatment success 89% (8/9). Mean drug dose 40.6 mg. Mean infusion time 42.3 hours. No lysis 11.1% (1/9). Slightly longer infusion times and higher lytic dose was needed for venous occlusions. Fibrinogen depletion was more pronounced among patients with venous occlusions (26.4% from baseline) than those with arterial occlusions (15.8% from baseline). Access site bleeding event (resolved by compressive dressing) -1. Re-occlusion (2 months after treatment) in 1 patient with an acute-on- chronic venous occlusion who achieved complete lysis.	Larger studies with longer follow-up included in table 2.
Stanley GA, Murphy EH et al (2013). Midterm results of percutaneous endovascular treatment for acute and chronic deep venous thrombosis Journal of Vascular Surgery: Venous and Lymphatic Disorders.1 (1) 52-58.	Retrospective chart review n=80 Patients with acute and chronic DVT Endovascular techniques : percutaneous pharmacomechanical thrombectomy and/or UE-CDT,	65% (52) were treated for acute DVT 53% (28) were treated for chronic DVT. Patients were treated with PMT (n=43, 53.8%), UE-CDT (n=14, 17.5%) or both (n=32, 28.7%). Clot lysis (>90%) achieved in 90% (72/80). Tnecteplase used for all cases, mean dose 8.6mg. Adjunctive procedures were used in 90% (47/52) acute DVT cases and 96% (27/28) chronic cases. 3.8% (3) had bleeding events requiring transfusion. At mean follow-up of 3.8 years, venous patency was present in 94% (49/52) patients, 82% (23/28) chronic patients (p=.12). Valve function preserved in 79% (41/52) acute patients and 39% (11/28) chronic patients (p<0.001).	Clinical outcomes presented according to acute and chronic DVT groups and not according to the interventions used.

Appendix B: Related NICE guidance for ultrasound enhanced, catheter-directed, thrombolysis for deep vein thrombosis

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 Guidance 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 thromboembolic events. NICE technology appraisal 287 ([2013])** 1 Guidance 1.1 Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults. **Dibigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal 157 ([2008])** 1 Guidance 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 Guidance 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 Guidance 1 Guidance

	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	**Management of venous thromboembolic diseases. NICE clinical guideline 144 ([2012]). Available from http://www.nice.org.uk/guidance/CG144** **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 Guidance 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** **Deep vein thrombosis** 1.2.6 Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have: • symptoms of less than 14 days' duration and • good functional status and • a life expectancy of 1 year or more and • a low risk of bleeding. **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. **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** This guidance covers assessing and reducing the risk of VTE and using VTE prophylaxis in different patient groups. It doesn't cover thrombolytic therapy.

Appendix C: Literature search for ultrasound enhanced, catheter-directed, thrombolysis for deep vein thrombosis

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
- 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