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[Intervention Review]

Interventions for restoring patency of occluded central venous catheter lumens

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ABSTRACT

Background

Central venous catheters (CVCs) facilitate the administration of intravenous drugs, fluids, blood products and parenteral nutrition to patients with either chronic disease or critical illness. Despite a pivotal role within medical management, a common complication associated with CVC use is occlusion of the CVC lumen(s). CVC occlusion can interrupt and cause serious delays in administration of treatment interventions.

Objectives

The primary objective of this review was to assess the efficacy and safety of different interventions used to restore patency of occluded CVC lumens, in adults and children.

Search methods

We identified trials by searching the Cochrane Central Register of Clinical Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 9); OvidSP MEDLINE (1950 to September 2011); OvidSP EMBASE (1980 to September 2011) and NHS Evidence CINAHL (1982 to September 2011). We also searched clinical trial registers, handsearched reference lists, contacted pharmaceutical companies and authors of publications that met the inclusion criteria to identify trials.

Selection criteria

We selected randomized controlled trials which investigated the efficacy of an intervention (chemical, surgical or drug) used to restore patency to an occluded CVC lumen, in either adults or children.

Data collection and analysis

Three authors independently assessed those studies that met the inclusion criteria for quality and extracted the relevant data using a standardized form.

Main results

No studies were found that investigated the efficacy and safety of either chemical or surgical interventions.

Seven studies (eight papers) with a total of 632 participants were identified from the search. They investigated different comparisons, strengths of thrombolytic or anticoagulant drug interventions for treating CVC lumen occlusion thought to be caused by a thrombus.

There was low quality evidence from a meta-analysis of two studies suggesting that urokinase (various strengths) was more effective than placebo for restoring patency to occluded CVC lumens in adults and children with underlying medical conditions (relative risk (RR) 2.09, 95% confidence interval (CI) 1.47 to 2.95), with a number needed to treat of 4 (95% CI 2 to 8). There was insufficient evidence to draw conclusions on the safety of urokinase.

The overall quality of the evidence provided by these studies was low to very low due to one or more domains being assessed as either at 'unclear risk of bias' or 'high risk of bias'. Furthermore, the total number of participants in these studies was small and consequently may lead to spurious results.

Authors' conclusions

There is inadequate evidence to draw strong conclusions on the efficacy or safety of the drug interventions included in this review. There is some low quality evidence from a meta-analysis of two studies investigating urokinase (various strengths) and some very low evidence from two single studies investigating alteplase 2 mg/2 mL that suggest that these two drug interventions may be effective in treating withdrawal or total occlusion of CVC lumens caused by thrombosis. Further high quality, sufficiently powered research is still required to look at the efficacy and safety of urokinase, alteplase and other chemical, surgical and drug interventions for treating CVC lumen occlusion. Research studies which exclusively include child participants are especially warranted.

PLAIN LANGUAGE SUMMARY

Interventions for restoring patency of occluded central venous catheter lumens

A central venous catheter is a small, hollow tube that is inserted into a large vein in either the chest, neck or groin. Central venous catheters enable healthcare professionals to administer drugs and other fluids directly into the blood stream, in order to treat critically ill patients or those patients with a long-term condition. In certain chronic conditions, patients or their carers may also be involved with the administration of treatment interventions via the central venous catheter.

Occasionally, the catheter lumens can become blocked with either a blood clot or a treatment intervention solidifying in the tube, or due to the position of the tube inside the vein. If the catheter does become blocked it may mean that the patient has to undergo further surgery to remove and replace the blocked catheter.

No studies were found investigating the efficacy and safety of surgical interventions (brush, snare or guidewire exchange) or chemical interventions (hydrochloric acid, sodium bicarbonate, 70% ethanol solution) to unblock the catheter.

Our search identified seven studies (eight papers), with a total of 632 participants, that investigated different drug comparisons or compared different strengths of drug therapies for treating catheters that were either completely or partially blocked with a blood clot.

This review has found low to very low quality evidence suggesting that thrombolytic drugs (urokinase and alteplase) could be effective in unblocking central venous catheter lumens blocked by blood clots. However, the total number of participants included in these trials was small and consequently the results of the analysis may well be over exaggerated. There were also issues with the way the studies were conducted that could possibly have introduced bias.

In conclusion, more research is required to establish the efficacy and safety of different treatment interventions used to unblock occluded central venous catheter lumens. Particularly, there is a need for studies exclusively in children.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Urokinase (any strength) compared with placebo

Urokinase (any strength) compared with placebo

Patient or population: patients with occluded central venous catheter

Settings: Hospital (USA)

Intervention: Urokinase (any strength)

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Urokinase (any strength)				
Restored patency Follow-up: 72 hours	Study population		RR 2.09 (1.47 to 2.95)	287 (2 studies)	⊕⊕⊕⊕ low ^{1,2}	
	286 per 1000	597 per 1000 (420 to 843)				
	Moderate					
Adverse effects Follow-up: 72 hours	Study population		RR 02.88 (0.38 to 21.93)	72 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	Only includes data from trial, with a sum total of 35 participants for urokinase 25 000 and 37 participants for urokinase 15 000 IU compared with placebo.
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 Insufficient information on randomisation, allocation concealment and assessed as high risk of bias for 'other bias'
- 2 Total number of participants were small

BACKGROUND

Description of the condition

Central venous catheters (CVCs) facilitate the administration of intravenous drugs, fluids, blood products and parenteral nutrition to patients with either chronic disease or critical illness. They can also be used to obtain blood samples and for haemodynamic monitoring. [Elliot 1993](#) and [Hockenhull 2008](#) provide an approximate figure of between 200,000 and 240,000 CVCs being used annually in the United Kingdom (UK), with an estimated cost to the National Health Service (NHS) in excess of £100 million ([Hamilton 1993](#)). In the United States of America (USA) approximately five million CVCs are used annually ([Wheeler 1997](#)). Despite a pivotal role within medical management, a common complication associated with CVC use is occlusion of the CVC lumen(s).

CVC lumen occlusion is a frequently encountered problem, affecting up to 25% of CVCs that are placed ([Stephens 1995](#)). CVC lumen occlusion can be either partial or complete ([Jacobs 2003](#)) and has been defined as a decreased ability to infuse solutions into or withdraw solutions from a cardiovascular access device ([Herbst 1998](#)). Clinical characteristics of CVC lumen occlusion include increased resistance felt with manual administration of drugs or fluids; reduced flow rates; a sustained increase in pressures observed with infusion devices or occlusion alarms being activated; and complete inability to infuse fluid into or withdraw fluid from the CVC lumen.

CVC lumen occlusion can predispose the individual to further risk of morbidity and mortality due to delays in treatment regimens or nutritional support. Additionally, the patient may have to undergo further invasive surgical interventions to replace the CVC. CVC lumen occlusion, therefore, is not only disruptive to the patients and their treatment regimens but also creates potential additional costs for the hospital. CVC occlusion can fall into the three distinct categories of drug precipitation or lipid residue; anatomical or mechanical; and thrombotic.

Drug precipitation and lipid residue

The infusion of preformed precipitates or the formation of a precipitate within the catheter can result in catheter occlusion ([Hardy 2005](#)). Calcium phosphate, diazepam, phenytoin, heparin, bicarbonate, mannitol, pentobarbital and phenobarbital are all drugs that have been reported to be associated with precipitation ([Hardy 2006](#); [Jacobs 2003](#); [McKinnon 1996](#)). The pH of these drugs is associated with the evolution of precipitates ([Hadaway 1998](#)). Precipitation occurs when exposing the drugs to flushing solutions and other drugs which have an opposing pH. However, many of these drugs are not in use anymore and healthcare professionals are more aware of the issues with precipitation.

Parenteral nutrition is an intravenous solution administered to patients who are unable to feed orally or via a feeding tube due to the nature of their medical or surgical condition. All-in-one parenteral nutrition solutions or total nutrient admixtures can produce a waxy lipid residue that can result in CVC lumen occlusion. Variables that favour the growth of lipid residues include the type of lipid emulsion; the age of the lipid at compounding; the age of the all-in-one admixture; the container material; the nature of

the catheters and any concomitant catheter-related therapy ([Hardy 2005](#)).

Anatomical or mechanical occlusion

Anatomical or mechanical obstructions can occur as a result of malpositioning of the catheter, catheter damage or fracture due to traumatic insertion, defective catheter material, increased pressures inside the catheter lumen or 'pinch off' syndrome. 'Pinch off' syndrome occurs when the subclavian vein (with the CVC in situ) becomes trapped between the first rib and clavicle, which in turn leads to compression and occlusion of the CVC lumen.

Thrombotic occlusion

Several studies report thrombotic occlusion, caused by fibrin build-up in the CVC, with an incidence ranging anywhere between 3% and 79% ([Moureau 2002](#); [Walshe 2002](#); [Wingerter 2003](#)). Thrombus formation occurs when there are changes to the blood vessel wall, alteration in blood flow and changes in the chemical composition of the blood ([Bertina 1997](#); [Mammen 1992](#)). Shortly after a catheter is placed in the vessel lumen, it begins to accumulate a fibrinous coating on its surface ([Jacobs 2003](#)). Fibrin can be deposited inside the CVC (intraluminal deposition), as a tail of fibrin at the distal tip of the CVC (fibrin tail), around the wall of the blood vessel (mural thrombus), or as a layer around the outside of the catheter (fibrin sheath) ([Hardy 2005](#)), mimicking the action of a one way valve. [Moureau 2002](#) identified a number of important outcomes in patients undergoing home infusion associated with catheter dysfunction secondary to thrombotic occlusion. These outcomes comprise interruption in therapy caused by loss of patency (43%); device replacement (29%); device removal (14%); an emergency room visit (9%) and an unscheduled hospital visit (6%).

Diagnosing which 'type' of occlusion is causing the obstruction usually involves both clinical judgement based on recent medical history, including a review of medications and fluids received, and radiological investigations such as chest x-ray, linogram, venogram and ultrasound ([Jacobs 2003](#); [Yacopetti 2008](#)) ('Glossary of terms', [Appendix 1](#)).

Description of the intervention

Chemical interventions

Several case series and non-randomized studies report successful restoration of patency for CVCs occluded with either drug precipitate or lipid residue using chemical interventions such as hydrochloric acid, sodium bicarbonate or 70% ethanol ([Breux 1987](#); [Duffy 1989](#); [Goodwin 1991](#); [Sando 1997](#); [Shulman 1988](#); [Werlin 1995](#)). For occlusions where drug precipitate is suspected, hydrochloric acid and sodium bicarbonate are used to alter the pH in order to try to dissolve the drug precipitate. Drugs with a pH > 7 are more soluble in an alkaline solution whereas drugs with a pH < 6 are more soluble in an acid solution. A 70% ethanol solution has been used to try and dissolve occlusions attributed to lipid residue.

Surgical interventions

A number of surgical interventions, for instance intraluminal brushing, snaring and guidewire exchange, have reportedly been used to clear occluded CVC lumens. An intraluminal brush is a surgical device for obtaining biofilm samples and for removing debris from inside the CVC lumen. [Bouza 1999](#) found intraluminal brushing to be unreliable and reported a number

of side effects such as cardiac arrhythmias, embolization and bacteraemia following its use in CVCs. A snare is a surgical device with a preformed loop for retrieval of intraluminal foreign bodies, including thrombi, from CVC lumens; whilst guidewire exchange involves using the Seldinger technique to exchange a malfunctioning CVC with a new CVC over a guidewire (Cook 1997).

Drug interventions

Systemic anticoagulant drugs, for example either unfractionated heparin (UFH), low-molecular weight heparin (LMWH) or warfarin, have traditionally been used for treating CVC-related thrombosis. UFH exerts its effect by binding to antithrombin III, accentuating its retardant effect on clot formation (Nazario 2002). UFH infusions require patients to be admitted to hospital for frequent monitoring of the activated partial thromboplastin time (aPTTs). Conversely, LMWH and warfarin do not require the same level of monitoring so may be advantageous for treating occluded CVCs in outpatient and community settings. Thrombolytic agents dissolve thrombi by activating plasminogen to form the active agent plasmin (Nazario 2002), which degrades fibrin to soluble peptides (1970). There are many publications of non-randomized, single arm, clinical studies and case series that suggest thrombolytic drugs such as urokinase, alteplase and reteplase are both safe and effective in treating CVC lumen occlusion caused by a thrombus, in adults and children (Atkinson 1989; Blaney 2006; Bussieres 2001; Chesler 2002; Choi 2001; Deitcher 2002; Jacobs 2001; Lawson 1982; Liu 2004; Molinari 2004; Ng 2004; Schindler 1999; Shen 2003; Svoboda 1990; Wachs 1990; Whigham 2002).

How the intervention might work

The interventions work through either dissolving or manually clearing or retrieving the object causing the occlusion, as described in the [Description of the intervention](#).

Why it is important to do this review

All three types of occlusion occur in both adult and child populations. There appears to be a piecemeal approach in the management of these complications. Many different strategies described within the literature have evolved through attempts to try to salvage occluded CVC lumens. Restoring patency of occluded CVC lumens does not appear to have been subjected to a comprehensive systematic review of the evidence to ascertain the safest and most effective method for treating each of the three types of CVC lumen occlusion in adults and children.

OBJECTIVES

The primary objective of this review was to assess the safety and efficacy of different interventions used to restore patency of occluded central venous catheter (CVC) lumens in adults and children. For this review CVC lumen occlusion has been defined as follows.

- Total occlusion: complete inability to either infuse blood or fluid into the CVC lumen or withdraw blood or fluid from the CVC lumen.
- Partial occlusion: decreased ability to either infuse blood or fluid into the CVC lumen or withdraw blood or fluid from the CVC lumen.

- Withdrawal occlusion: blood and fluid are able to be infused into the CVC lumen however withdrawal of blood and fluid from the CVC lumen is not possible.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel group randomized controlled trials (RCTs) and parallel group quasi-randomized controlled trials.

Types of participants

We included adults and children from the age of one month that required a CVC for medical treatment or management in either the hospital or the community setting.

We included all makes of long-term and short-term CVCs irrespective of size and number of lumens (Appendix 2).

We included CVCs bonded with either heparin or impregnated with antibiotics.

We excluded any studies that included dialysis catheters or pulmonary artery catheters from the review unless the study presented any data on CVCs separately.

Types of interventions

1. Chemical interventions for drug precipitates or lipid residue: sodium bicarbonate; hydrochloric acid; ethanol.
2. Surgical interventions for any type of CVC lumen occlusion: intraluminal brush; snare; guidewire exchange.
3. Drug interventions for thrombotic occlusions:
 - anticoagulant drugs, heparin (UFH or LMWH), warfarin;
 - thrombolytic drugs, urokinase, alteplase, tenecteplase, reteplase, streptokinase, alteplase.

All different comparisons were looked at separately. An example of the types of comparisons we anticipated finding were where one of the aforementioned drug interventions was compared with either:

- same drug, different strength;
- same drug, different administration protocol (e.g. infusion versus bolus);
- another of the aforementioned drugs;
- placebo;
- no treatment;
- chemical intervention;
- surgical intervention.

Types of outcome measures

Primary outcomes

The primary outcome of this review was restoration of patency to the occluded CVC lumen(s). This was defined as either: 1) being able to aspirate blood from, or 2) infuse fluids through the CVC lumen(s).

Secondary outcomes

The secondary outcomes of this review were to determine what effect these interventions had on the following.

1. Adverse effects following the intervention: catheter-related thrombosis; abnormal coagulopathy; allergic reactions associated to the intervention; thrombocytopaenia; biochemical abnormalities; cerebral or pulmonary embolus; and any other adverse effects documented within the studies that have not been included here.
2. The development of catheter-related blood stream infection (CRBSI) following intervention. CRBSI can be defined as isolation of the same organism (i.e. identical species with the same antibiograms) from a peripheral blood culture and a semi-quantitative or quantitative culture of a catheter segment (Chaiyakunapruk 2002).
3. Duration of patency following intervention.
4. Mortality.

Search methods for identification of studies

Electronic searches

We identified trials by searching the Cochrane Central Register of Clinical Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 9); OvidSP MEDLINE (1950 to September 2011); OvidSP EMBASE (1980 to September 2011) and NHS Evidence CINAHL (1982 to September 2011). We exploded all index terms. Please refer to the Appendices for a comprehensive list of our search terms: [Appendix 3](#) (CENTRAL); [Appendix 4](#) (MEDLINE); [Appendix 5](#) (EMBASE); [Appendix 6](#) (CINAHL).

We searched the following clinical trials registers:

- Current Controlled Clinical Trials (www.controlled-trials.com/);
- Clinical Trials (www.clinicaltrials.gov/);
- Centre Watch (www.centrewatch.com/);
- Trials Central (www.trialscentral.org/ClinicalTrials.asp);
- National Research Register (<https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx>).

Searching other resources

We also identified trials by:

1. manual searching, we scrutinized reference lists of all identified trials and relevant review articles;

2. contacting relevant trial authors to identify additional trials;
3. contacting relevant pharmaceutical companies to identify published and unpublished trials.

We did not restrict the search by language or publication status.

Data collection and analysis

Selection of studies

Three authors (CvM, RH and LJ) independently reviewed all the initial titles and abstracts to identify potentially relevant studies from the search. We ordered the full publication of those abstracts identified as potentially relevant and independently assessed them for eligibility. We used a standardized eligibility form which contained the review inclusion criteria for types of study, participants, interventions and outcomes. We resolved any disagreements through discussion.

Data extraction and management

Three authors (CvM, RH and LJ) independently extracted data using a form specially devised by the Cochrane Cystic Fibrosis and Genetic Disorders Group ([Appendix 7](#)). We resolved any disagreements through discussion. If a disagreement remained unresolved or published results made data extraction difficult then we contacted the study authors for further clarification. We entered data into, and analysed it on, [RevMan 5.1](#).

Assessment of risk of bias in included studies

Three authors (CvM, RH and LJ) independently assessed the methodological quality of the trials which met the inclusion criteria. We assessed the methodological quality using the six domains (sequence generation; allocation concealment; blinding of participants, investigators and outcome assessors; incomplete outcome data; selective reporting; and other threats to validity) described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)) for assessing risk of bias. We made the following judgements for each included trial: low risk of bias; unclear risk of bias; or high risk of bias. These judgements were then included in the 'risk of bias' tables ([Figure 1](#); [Figure 2](#)).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dietcher 2004	?	+	+	+	+	-
Fink 2004	+	+	-	?	?	-
Haire 1994	+	+	+	+	+	?
Haire 2004	?	?	+	+	+	?
Horne III 1997	?	?	?	?	?	?
Moll 2006	?	?	?	+	+	-
Ponec 2001	?	+	?	?	+	-

Measures of treatment effect

Where dichotomous outcomes were reported, we calculated a pooled treatment effect for each outcome using relative risk (RR), number needed to treat (NNT) and, if appropriate, number needed to harm (NNH). These data were accompanied by 95% confidence intervals (CI). We planned to present continuous data as mean difference (MD) or standardized mean difference (SMD), as appropriate, and calculate the pooled MD or SMD along with the 95% confidence interval. However, continuous data were not presented in any of the studies and so have not been used in this review. An available case analysis was executed for every

participant with available outcome data as described by [Higgins 2011b](#).

Unit of analysis issues

A number of unit of analysis issues were identified whilst extracting data from the included studies.

i) CVC: this unit of analysis was used with one study ([Haire 1994](#)), which reported having 48 participants with a total of 50 CVCs inserted. Therefore, a number of participants had more than one CVC inserted and more than one installation of the treatment intervention.

ii) CVC lumen: CVCs can have up to four individual lumens. One study (Fink 2004) reported that the participants were randomized for the study; however, the individual patient data provided by Fink 2004 suggested that CVC lumen was used as the unit for analysis. These data reported a number of participants with CVCs having two or more lumens. All lumens on each CVC had an installation of the study drug under investigation. The individual patient data appears to indicate that each lumen was included in the analysis as a separate event. The review authors were unable to obtain further clarification of the unit of analysis issues from the study authors. The review authors have chosen to analyse and present the data using the participant as the unit of analysis as opposed to the lumen.

In future updates of this review those studies that use either CVCs or CVC lumens as the unit of analysis will be included in a sensitivity analysis to identify any substantive differences. This is required to take into account the effects of 'clustering' from an individual participant having more than one installation of the study drug under investigation, which could lead to spurious conclusions through inappropriate weighting.

iii) Multiple treatment groups: two studies (Dietcher 2004; Moll 2006) each had four intervention groups with one group being 'shared', e.g. Dietcher 2004 had three urokinase groups and these were compared to a 'shared' placebo group.

Dealing with missing data

All authors from the included studies were approached via e-mail and letter for further information and clarification on key aspects of their study methods. Three contact authors for four of the studies responded (Fink 2004; Haire 1994; Haire 2004; Horne III 1997). One author (Horne III 1997) informed the review authors that he could not provide the information we requested. Haire (Haire 1994; Haire 2004) initially agreed to provide information on these two studies but then did not make any further communication with the review authors despite follow-up e-mails. Only one author (Fink 2004) provided further information on both the study methods and individual patient data.

Assessment of heterogeneity

Sources of heterogeneity include: methodological differences between studies; study quality; different types of CVCs; types of interventions; drug administration methods; drug dosage; age of participants; and type and severity of illness or disease. After considering the likelihood of clinical heterogeneity based on comparisons of the included studies, we visually inspected forest plots to investigate the possibility of statistical heterogeneity. We planned to use the fixed-effect model for data synthesis unless significant heterogeneity was observed, then a random-effects model would be used. We assessed statistical heterogeneity using the Chi² test with a statistical significance level of 10% ($P < 0.10$). We calculated the value of the I^2 statistic to provide an estimate of the percentage of variability due to heterogeneity rather than chance alone. An I^2 value of less than 25% is considered low risk of heterogeneity, an I^2 value less than 50% is considered moderate risk and an I^2 value greater than 75% indicates high levels of heterogeneity (Higgins 2003).

Assessment of reporting biases

Publication bias

We intended to use outcome data from the trials to plot a funnel graph to investigate the likelihood of overt publication bias. Any asymmetry of the funnel plot may indicate possible publication bias. We intended to explore other reasons for asymmetry such as selection bias, methodological quality, heterogeneity, artefact or chance as described in Section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Due to insufficient number of studies, a funnel graph was not possible to explore publication bias.

Duplicate (multiple) publication bias

A possible duplicate publication of one study (Ponec 2001) was identified. The authors were contacted for clarification but they did not respond. Until we receive clarification from the authors an assumption has been made that it is a duplicate publication and for that reason the data from the second publication was not used in this review.

Outcome reporting bias

All studies were assessed for the suggestion of selective outcome reporting. This was undertaken by ensuring there were results reported for all the outcomes listed in the methods section of the study report.

Data synthesis

A meta-analysis was performed when sufficient data were available from two or more studies that were similar in terms of population, intervention, comparison and outcomes. A summary statistic with 95% CI was calculated for each outcome. A fixed-effect model was used unless significant statistical heterogeneity was observed, in which case a random-effects model was used. For studies with multiple intervention groups, the events in the 'shared' group were evenly split in order to avoid 'double counting' and to allow an overall summary statistic to be calculated for the analysis, as suggested by Higgins 2011b. This enabled us to make reasonable, independent comparisons.

Subgroup analysis and investigation of heterogeneity

We intended to investigate possible statistical heterogeneity in the following subgroups:

- age (one month to five years; 6 to 12 years; 13 to 18 years; and 19 years and above);
- CVCs bonded with heparin or impregnated with antibiotics.

A subgroup analysis was not undertaken due to insufficient data.

Sensitivity analysis

We intended to include studies that were described as 'double blind' but did not describe the method of randomization and quasi-randomized studies (for example, participants allocated by date of birth; odd or even; day of week) in a sensitivity analysis. If there were no substantive differences within the primary outcomes we intended to include these studies in the final analysis. If there was a substantive difference, we planned to include only studies that clearly described methods for randomization. The results of the sensitivity analysis would be described within the text. A narrative

description of these studies would be presented with the help of the 'Appendices'. We did not undertake a sensitivity analysis due to insufficient studies.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#)

Results of the search

See [Figure 3](#)

Figure 3. Study flow diagram.

The yield from the electronic database search was 4623 studies. We independently screened the titles and abstracts of all these studies for potential inclusion and excluded 4605 studies. These studies were excluded due to either overlap between databases or not fulfilling the inclusion criteria. We identified 18 studies as potentially eligible for inclusion. Two studies are currently awaiting assessment for inclusion into this review ([Gabrail 2010](#); [Muller 2010](#)). We obtained the full publications for 16 studies. Following further scrutiny of the full publications we excluded a further eight studies that did not fulfil the inclusion criteria.

We examined the bibliography lists of all identified studies and relevant review articles and searched the trial registers. We approached all contact authors for the included studies and pharmaceutical companies. We identified a further two studies from trial registers ([Levine R](#); [NCT00073515](#)). The data from these two studies are not currently available, so for that reason they are currently awaiting assessment for inclusion into this review (see [Characteristics of studies awaiting classification](#)).

Included studies

Seven studies (eight papers), with a sum total of 632 participants, fulfilled the inclusion criteria for this review ([Dietcher 2004](#); [Fink 2004](#); [Haire 1994](#); [Haire 2004](#); [Horne III 1997](#); [Moll 2006](#); [Ponec 2001](#)). A potential duplicate publication was identified for [Ponec 2001](#).

Please refer to the table [Characteristics of included studies](#) for more detailed information on all of these studies.

Participants

Five studies ([Fink 2004](#); [Haire 1994](#); [Horne III 1997](#); [Moll 2006](#); [Ponec 2001](#)) included only adult participants. Two studies ([Dietcher 2004](#); [Haire 2004](#)) included both adults and children, with a sum total of 108 child participants. Three studies ([Fink 2004](#); [Haire 1994](#); [Horne III 1997](#)) included only participants with either oncological or haematological pathologies. Two studies ([Dietcher 2004](#); [Haire 2004](#)) included participants with serious underlying medical conditions including anaemia, thrombocytopenia and oncological or haematological pathologies. Two studies ([Moll 2006](#); [Ponec 2001](#)) did not report on the disease status of participants. Only three studies ([Dietcher 2004](#); [Haire 2004](#); [Ponec 2001](#)) specified the types of CVCs that were included. [Dietcher 2004](#) and [Haire 2004](#) only included participants with any type of semi-permanent or temporary CVC, while [Ponec 2001](#) included only long-term CVCs such as peripherally inserted catheters, catheters with valves and implanted ports. All seven studies were conducted in the USA, with some studies recruiting from additional sites in Canada.

Interventions

None of the included studies investigated chemical or surgical interventions for treating occluded CVCs. The seven studies

investigated different comparisons or strengths of thrombolytic or anticoagulant therapies for treating either withdrawal occlusion or total occlusion caused by a thrombus. [Haire 1994](#) and [Horne III 1997](#) were the only studies to definitively prove that CVC malfunction was due to a thrombus, by using linograms. Six studies assessed patency by attempting to aspirate blood and infuse either 0.9% saline ([Dietcher 2004](#); [Fink 2004](#); [Haire 2004](#); [Moll 2006](#); [Ponec 2001](#)) or urokinase ([Horne III 1997](#)) into the lumen. If the lumen was found to have either withdrawal or total occlusion it was treated as a thrombolytic occlusion. The types of thrombolytic therapy under investigation were urokinase, alteplase and alteplase, and the anticoagulant therapy was unfractionated heparin.

[Dietcher 2004](#) compared different strengths of urokinase (25,000; 15,000; 5000 IU) with placebo. [Fink 2004](#) compared two strengths of alteplase (1 mg/1 mL; 2 mg/2 mL). [Fink 2004](#) wanted to establish clinical equivalence of effectiveness for these two strengths of alteplase. [Haire 1994](#) compared urokinase (10,000 IU) with alteplase (2 mg/2 mL). [Haire 2004](#) compared urokinase (5000 IU) with placebo. [Horne III 1997](#) compared urokinase infusion (250,000 IU in 0.9% normal saline, 50 mL) with urokinase infusion (250,000 IU in 0.9% normal saline) plus heparin (2000 IU). [Moll 2006](#) compared different strengths of alteplase (0.3, 1.0 and 3.0 mg) with alteplase (2 mg/2 mL). [Ponec 2001](#) compared two treatment regimens, Group 1: placebo, alteplase (2 mg/2 mL), alteplase (2 mg/2 mL); Group 2: alteplase (2 mg/2 mL), alteplase (2 mg/2 mL), placebo. Three studies ([Dietcher 2004](#); [Haire 2004](#); [Ponec 2001](#)) used a placebo as the comparator. None of these studies reported what the placebo was.

Outcomes

The primary outcome for all seven studies was restoration of patency of the occluded CVC lumen(s). Five studies ([Dietcher 2004](#); [Fink 2004](#); [Haire 2004](#); [Moll 2006](#); [Ponec 2001](#)) reported results for outcomes on safety, adverse effects and mortality. One study ([Horne III 1997](#)) reported on an outcome for duration of patency. Other outcomes reported in these studies included: cost effectiveness ([Fink 2004](#)); thrombus reduction or resolution ([Haire 1994](#)); relationship of CVC location and type to the rate of success with urokinase infusions ([Horne III 1997](#)).

Excluded studies

We excluded the following eight studies that did not fulfil the inclusion criteria: [Barrett 1990](#), [Lawson 1982](#), [Molinari 2004](#), [Ng 2004](#), [Owens 2002](#), [Study 1974](#), [Svoboda 1990](#), [Zeitler 1976](#) (see [Characteristics of excluded studies](#) for further details).

Risk of bias in included studies

We approached all contact authors for further clarification on individual trial methodology in order to make an accurate assessment of 'risk of bias'. [Fink 2004](#) was the only author who responded to this request and provided both information on the trial protocol and individual patient data. The following 'risk of bias' domains for all included studies are summarized and presented in [Figure 1](#) and [Figure 2](#).

Sequence generation

Two studies ([Fink 2004](#); [Haire 1994](#)) used computers to generate a randomization sequence. The remaining five studies ([Dietcher 2004](#); [Haire 2004](#); [Horne III 1997](#); [Moll 2006](#); [Ponec 2001](#)) did

not provide sufficient information on methods used for sequence generation.

Allocation

Four studies reported appropriate methods for allocation concealment. [Dietcher 2004](#) and [Haire 1994](#) used drugs with identical packaging issued from pharmacy departments. [Fink 2004](#) used sealed, numbered envelopes; and [Ponec 2001](#) used an interactive voice randomization service. There was insufficient information to make a judgement on the remaining three studies ([Haire 2004](#); [Horne III 1997](#); [Moll 2006](#)).

Blinding

Three studies ([Dietcher 2004](#); [Haire 1994](#); [Haire 2004](#)) reported blinding of both participants and clinicians to the interventions. In addition, [Haire 1994](#) ensured outcome assessors were blind. Three studies ([Horne III 1997](#); [Moll 2006](#); [Ponec 2001](#)) also reported being double-blind. However, there was insufficient information available on who was blinded and the method of blinding to make a judgement. One study reported no blinding ([Fink 2004](#)). This was due to differences between the volumes of the drugs administered.

Incomplete outcome data

Two studies ([Haire 1994](#); [Moll 2006](#)) reported all participants being followed up and included in the analysis. Three studies ([Dietcher 2004](#); [Haire 2004](#); [Ponec 2001](#)) reported a small number of attritions or exclusions (six, seven and 10 participants respectively). All three studies included these participants in an intention-to-treat analysis. [Dietcher 2004](#) and [Haire 2004](#) reported that these participants were included as failures in the analysis. [Fink 2004](#) reported three participants being excluded from the analysis. The reasons for these exclusions were not reported.

[Horne III 1997](#) did not report on how many participants were enrolled and randomized into the study, therefore it was difficult to ascertain if there were any attritions or exclusions. The results section only provided information on the number of participants who were actually treated with the interventions. All these participants appeared to be included in the analysis for restoration of patency of the CVC. For duration of patency outcome, however, the observations from both treatment arms were pooled for successfully treated CVCs and three CVCs were excluded from the analysis.

Selective reporting

Five studies ([Dietcher 2004](#); [Haire 1994](#); [Haire 2004](#); [Moll 2006](#); [Ponec 2001](#)) reported prespecified outcomes in the methods section of the study. All five studies provided results for all the prespecified outcomes. Two studies ([Fink 2004](#); [Horne III 1997](#)) did not pre-specify any outcomes in the publications. Both authors were approached for further information. [Fink 2004](#) was able to provide information on the primary and secondary outcomes for the study. Results were obtained for all outcomes with the exception of one of the secondary outcomes, 'incremental cost-effectiveness of 1 mg/mL alteplase versus 2 mg/2 mL alteplase'. [Horne III 1997](#) was unable to provide further information.

Other potential sources of bias

Study design

[Dietcher 2004](#) provided information for the baseline characteristics of included participants. However, this information was not separated into groups and an assessment could not be made to determine any baseline imbalance. [Fink 2004](#) stopped the study early before reaching the target of 226 CVC lumens due to low accrual rates. [Haire 2004](#) reported that if function was not restored in treated lumens after one hour, the treatment was considered unsuccessful. In all unsuccessful cases, physicians could administer a further two instillations of open-label urokinase. The safety data for 72 hours and 30 days included participants who received both the 'blind' intervention and open-label urokinase. [Horne III 1997](#) pooled the successful events from both treatment arms when investigating duration of patency. [Ponec 2001](#) compared two regimens of study drugs. Participants randomized to Group one received an installation of alteplase 2 mg followed, if required, by a second installation of alteplase 2 mg and a third installation of placebo. Participants randomized to Group two received one installation of placebo followed, if required, by a second and a third installation of alteplase 2 mg. This study appeared to be parallel in design, however, only the participants with persistent dysfunctional CVCs, in both Groups, received all three installations of the study drugs in the regimen.

Unit of analysis

The unit of analysis was not always clearly reported in the included studies. Five studies reported the unit of analysis being the participant ([Dietcher 2004](#); [Haire 2004](#); [Horne III 1997](#); [Moll 2006](#); [Ponec 2001](#)). [Fink 2004](#) initially described how the participants were randomized to receive one of the interventions. The study drug was instilled into all blocked lumens for each individual CVC. However, the results section of this study reported "a total of 61 lumens in 45 patients were enrolled" and "37 lumens were randomized to receive alteplase 1 mg/1 mL". Individual patient data provided by [Fink 2004](#) presented 26 participants with a total of 36 lumens treated with alteplase 1 mg/1 mL with one exclusion. Five participants in this group had multi-lumen CVCs that were all treated with the study drug and function was assessed. In the alteplase 2 mg/2 mL group there were 21 included participants with a total of 22 lumens and two exclusions. The one participant with the double lumen CVC in this group only had function assessed for one lumen. [Haire 1994](#) appeared to include CVCs as the unit of analysis as 50 thrombosed CVCs in 48 patients were randomized.

Sample size calculation

[Fink 2004](#) was the only study to report using a sample size calculation. In order to demonstrate equivalence in clearance rates between the study drugs, within 10% of each other, [Fink 2004](#) calculated that 226 occluded CVC lumens were required to ensure 80% statistical power with an α level of 0.05.

Funding and conflicts of interest

Four studies ([Dietcher 2004](#); [Haire 1994](#); [Haire 2004](#); [Moll 2006](#)) documented being either partly or completely supported by commercial grants from the pharmaceutical companies who manufacture the drugs under investigation. It was not possible to ascertain how much control the pharmaceutical companies exerted over the publication of the study results. Nevertheless, all four studies produced positive results for the study drugs manufactured

by these pharmaceutical companies. Moreover, [Dietcher 2004](#) and [Moll 2006](#) both reported having authors who were either consultants, employees or stockholders in the pharmaceutical companies which manufacture the drugs under investigation. [Ponec 2001](#) also declared a conflict of interest but did not elaborate on what this conflict might be.

Effects of interventions

See: [Summary of findings for the main comparison Urokinase \(any strength\) compared with placebo](#)

1.0 Restored patency of occluded CVC lumen(s)

1.1 Chemical interventions

No studies were found investigating the efficacy and safety of chemical interventions.

1.2 Surgical interventions

No studies were found investigating the efficacy and safety of surgical interventions.

1.3 Drug Interventions

1.3.1 Thrombolytic drug interventions

We selected the following groups based on what data were available as opposed to being selected a priori.

Urokinase compared with placebo

[Dietcher 2004](#) compared urokinase 25,000 IU with placebo in 35 participants and urokinase 15,000 IU with placebo in 37 participants. There was no difference between the two treatments. Two studies ([Dietcher 2004](#); [Haire 2004](#)), compared urokinase 5000 IU with placebo in a sum total of 215 participants. The two studies ([Dietcher 2004](#); [Haire 2004](#)) gave either one or two instillations of the study drugs and assessed function at five, 15 and 30 minutes; 82/144 participants in the urokinase 5000 IU group and 20/71 participants in the placebo group had restored patency of occluded CVCs. The RR favoured the urokinase 5000 IU group (RR 2.01, 95% CI 1.35 to 3.01; NNT 4 (95% CI 2 to 11) ([Analysis 1.1](#); [Table 1](#)). The overall pooled treatment effect estimate favoured urokinase (any strength) when compared with placebo for restoring patency to occluded CVCs (RR 2.09, 95% CI 1.47 to 2.95); tests for heterogeneity (χ^2 test 0.88 ($P = 0.35$), $I^2 = 0\%$); NNT of 4 (95% CI 2 to 8) ([Analysis 1.1](#); [Table 1](#)).

Urokinase compared with alteplase

One study with 50 participants ([Haire 1994](#)) compared urokinase 10,000 IU with alteplase 2 mg/mL. The RR favoured alteplase 2 mg/mL for restoring function to occluded CVCs (RR 1.51, 95% CI 1.04 to 2.19) ([Table 1](#)).

Alteplase compared with placebo

One study with 149 participants ([Ponec 2001](#)) compared alteplase 2 mg with placebo. Due to the drug regimen used in the study, the data used for this analysis were taken following the first instillation of study drug where a direct comparison could be made between alteplase 2 mg and placebo. Alteplase restored function to occluded CVCs (RR 4.19, 95% CI 2.44 to 7.20 in favour of alteplase) ([Table 1](#)).

Alteplase compared with alteplase

Individual patient data were available for one study (Fink 2004) with a total of 50 participants comparing alteplase 1 mg/1 mL versus alteplase 2 mg/2 mL. Three of these participants, one participant from the alteplase 1 mg/1 mL group and two participants from the alteplase 2 mg/2 mL group, were excluded from the analysis. There was no difference after single instillation of study drugs in restoring function to occluded CVCs (RR 0.95, 95% CI 0.69 to 1.29) or a second instillation (RR 0.94, 95% CI 0.71 to 1.24).

Alfimeprase compared with alteplase

Moll 2006 compared alfimeprase with alteplase. Alfimeprase 3.0 mg was compared with alteplase 2 mg/2 mL in 14 participants, alfimeprase 1.0 mg was compared with alteplase 2 mg/2 mL in 20 participants, and alfimeprase 0.3 mg was compared with alteplase 2 mg/2 mL in 21 participants. One or two instillations were given but failed to show any significant advantage of one treatment over the other (Table 1).

1.3.2 Anticoagulant drug interventions

Urokinase compared with urokinase plus heparin

Data were available from one study (Horne III 1997) with a total number of 42 participants. Horne III 1997 randomised participants to receive either an infusion of urokinase 250,000 IU in 0.9% saline up to 50 mL (40,000 IU/hour) or urokinase 250,000 IU plus heparin 2000 IU and 0.9% saline (40,000 IU / 320 IU/hour). CVC patency was assessed at one hour, three hours, six hours and 12 hours and failed to produce any statistically significant results (Table 1).

2.0 Adverse effects

Six studies reported on this outcome (Dietcher 2004; Fink 2004; Haire 1994; Haire 2004; Moll 2006; Ponc 2001). The details of the adverse effects are given in Table 2.

Urokinase compared with placebo

Both Dietcher 2004 and Haire 2004 reported on haemorrhagic and non-haemorrhagic adverse effects within 72 hours of study drug exposure. Haire 2004 also reported on adverse effects occurring within 30 days. However, Haire 2004 included in the safety data 155 participants that had received both the blinded study drug and open-label urokinase.

Dietcher 2004 reported adverse effects (comparing urokinase 25,000 IU with placebo): haematuria (one participant), injection site haemorrhage (three participants) and subarachnoid haemorrhage (one participant). Dietcher 2004 reported that one participant had two events of major severity both of which were probably not related to the study drug (subarachnoid haemorrhage after a fall, and injection site haemorrhage in the setting of thrombocytopenia requiring platelet transfusion). Dietcher 2004 also reported adverse effects: epistaxis (one participant) and metorrhagia (one participant) in the comparison between urokinase 15,000 IU and placebo, but failed to report any adverse effects occurring in the comparison between urokinase 5000 IU and placebo (Analysis 3.1; Table 2).

Haire 2004 reported on 19 participants who were initially randomized to receive up to two instillations of placebo and then received up to two further instillations of open-label urokinase. Due to the 'pooling' of participants for this outcome, it was not possible

to make direct comparisons for adverse effects between urokinase 5000 IU and placebo.

2.2 Urokinase compared with alteplase

Haire 1994 did not observe any adverse effects such as bleeding, embolization or septicaemia in either group.

2.3 Alteplase compared with alteplase

Fink 2004 did not observe any adverse effects occurring within either group.

2.4 Alteplase compared with placebo

Ponc 2001 did not observe any adverse effects occurring within either group.

2.5 Alfimeprase compared with alteplase

Moll 2006 assessed safety by evaluating the incidence of major haemorrhagic events, stroke (intracranial haemorrhage (ICH)), and embolic events for up to five days after treatment with the study drug. Major haemorrhage was defined as severe blood loss (> 5 mL/kg) or blood loss requiring transfusion or causing hypotension. All other non-serious adverse events were recorded up to 24 hours after the first study drug instillation; all deaths and serious adverse events that were reported up to 30 days after study drug exposure were recorded. Moll 2006 reported that three participants in the alfimeprase 3.0 mg group and one participant in the alteplase 2 mg group had experienced adverse effects (Table 2). Moll 2006 also described the following adverse effects that were possibly or probably related to alfimeprase 3.0 mg: pyrexia and dizziness; and that were possibly or probably related to alteplase 2 mg: fatigue and malaise.

Moll 2006 reported five participants in the alfimeprase 1.0 mg group and one participant in the alteplase 2 mg group who experienced adverse effects (Table 2). Moll 2006 described the following adverse events that were possibly or probably related to alfimeprase 1.0 mg: generalized pruritus, nausea, fungaemia and urticaria. Moll 2006 described the following adverse effects that were possibly or probably related to alfimeprase 0.3 mg: depressed level of consciousness and renal failure.

3.0 Catheter-related blood stream infection

No studies report on catheter-related bloodstream infection (CRBSI) as a separate outcome. However, Horne III 1997 and Moll 2006 described CVC removal as a consequence of CRBSI. Neither author provided either definitions or criteria for diagnosing CRBSI. Only one study (Moll 2006) provided data on which groups had events for CRBSI (Table 3).

4.0 Duration of patency

Only one study (Horne III 1997) provided data on this outcome. Due to the 'pooling' of both treatment arms it was not possible to make direct comparisons between urokinase 250,000 IU in 0.9% saline up to 50 mL with urokinase 250,000 IU plus heparin 2000 IU and 0.9% saline up to 50 mL.

5.0 Mortality

Two studies (Haire 2004; Ponc 2001) reported on this outcome.

[Haire 2004](#) described how one participant from the placebo group died at 72 hours, but the authors reported that this adult patient had end-stage cystic fibrosis and respiratory failure ([Table 4](#)). [Ponec 2001](#) described one death occurring at 29 days following administration of the study regimen. The authors reported that the death was not related to the study drugs but was from complications of a bone marrow transplantation.

DISCUSSION

Summary of main results

The objective of this review was to assess the efficacy and safety of chemical, surgical and drug interventions for treating occluded CVCs in adults and children. No suitable studies were found investigating the efficacy and safety of either chemical or surgical interventions. This review included seven studies (eight papers), with a total of 632 participants, that investigated the efficacy of different anticoagulant and thrombolytic therapies for treating occluded CVCs. These comprised six different comparisons; urokinase (various strengths) compared with placebo ([Dietcher 2004](#); [Haire 2004](#)), urokinase compared with alteplase ([Haire 1994](#)), alteplase compared with placebo ([Ponec 2001](#)), alteplase compared with alteplase ([Fink 2004](#)), alfineprase (various strengths) compared with alteplase ([Moll 2006](#)), urokinase compared with urokinase plus heparin ([Horne III 1997](#)). The primary outcome reported in all these studies was restored patency to occluded CVC lumen(s), whilst secondary outcomes included safety, adverse effects, mortality, duration of patency, cost-effectiveness, thrombus reduction or resolution and relationship of CVC location and type to the rate of success.

Low quality evidence (one meta-analysis of two studies, 307 adult and child participants) ([Dietcher 2004](#); [Haire 2004](#)) comparing urokinase (25,000 IU; 15,000 IU; 5000 IU) with placebo appears to indicate that urokinase (various strengths) may have a beneficial effect in treating occluded CVC lumens. There was insufficient evidence to draw conclusions on the safety of urokinase in these patient groups. [Dietcher 2004](#) reports on treatment-emergent haemorrhagic events which occurred within 72 hours of study drug exposure for urokinase 25,000 IU (haematuria (one participant), injection site haemorrhage (three participants), subarachnoid haemorrhage (one participant)) and urokinase 15,000 IU (epistaxis (one participant), metrorrhagia (one participant)), with no haemorrhagic events being reported in either the urokinase 5000 IU or placebo groups. [Haire 2004](#) presented 'pooled' data from patients that received both 'blinded' and 'open-label' urokinase at 72 hrs and 30 days and for that reason no comparison between urokinase 5000 IU and placebo could be made for this study.

Very low quality evidence from two single studies suggests that alteplase 2 mg/2 mL may also be effective for treating occluded CVC lumens. One study ([Haire 1994](#)) involving 50 adult participants shows a beneficial effect of alteplase 2 mg/mL over urokinase 10,000 IU which was only just statistically significant, whereas [Ponec 2001](#) (149 adult participants) demonstrated that alteplase 2 mg/2 mL was significantly better than placebo. Both [Haire 1994](#) and [Ponec 2001](#) report no complications or adverse events occurring during the period of follow-up.

Very low quality evidence from one study ([Fink 2004](#)) involving 50 adult participants showed that there was little or no difference between alteplase 1 mg/1mL and alteplase 2 mg/2 mL. No

adverse events were observed in either group. There was also very low quality evidence from another study ([Moll 2006](#)) with 55 adult participants which showed little or no difference between alfineprase (3.0 mg, 1.0 mg, 0.3 mg) and alteplase 2 mg/2 mL. [Moll 2006](#) identified a number of adverse events that were possibly or probably related to alfineprase (pyrexia, dizziness, generalized pruritus, nausea, fungaemia, urticaria, depressed level of consciousness and renal failure) and alteplase (fatigue and malaise).

Finally, there was very low quality evidence from one study ([Horne III 1997](#)) involving 42 adult participants which showed little or no difference between an infusion of urokinase 250,000 IU compared with an infusion of urokinase 250,000 IU with heparin 2000 IU. [Horne III 1997](#) evaluated duration of patency for successfully treated CVC lumens at least once per month until the CVC re-occluded or was removed for evidence of recurrent malfunction. Unfortunately, the observations from both treatment arms were pooled for the analysis.

Overall completeness and applicability of evidence

This review includes seven studies published over the last 17 years in the English language. All seven studies were conducted in hospital settings across the USA and Canada, with six of the studies having a number of authors and medical institutions in common ([Dietcher 2004](#); [Fink 2004](#); [Haire 1994](#); [Haire 2004](#); [Moll 2006](#); [Ponec 2001](#)). There was a sum total of 632 participants and of these 108 participants were children. A subgroup analysis of children was not undertaken due to only one study ([Haire 2004](#)) providing differential data for age groups. The majority of the included participants had underlying oncological and haematological pathologies. The types of CVCs reported within individual studies included tunnelled CVCs, implanted ports, peripherally inserted central catheters (PICCs) and non-tunnelled semi-permanent or temporary CVCs. None of the studies reported on which venous sites were used when placing the CVCs. Consequently the applicability of the review findings may well be restricted to similar populations and healthcare settings.

Quality of the evidence

The overall quality of the evidence provided by individual studies included in this review is very low for two reasons. Firstly, the studies included in this review had small sample sizes, therefore they were probably underpowered to detect important clinical differences. Secondly, there appears to be significant methodological issues with the way the studies were conducted, for instance the balance of group characteristics were not reported, and issues relating to the unit of analysis and the effects of 'clustering', pooling of data, participants receiving both blinded and open-label drug interventions, participants receiving both study drug and a placebo. Nonetheless, the evidence provided by the meta-analysis of two studies comparing urokinase (various strengths) with placebo has been upgraded to low using the Grade system ([Guyatt 2008](#)) ([Summary of findings for the main comparison](#)). This is due to one or more domains being assessed as either 'unclear risk of bias' due to insufficient information in the publications or high risk of bias. Due to the small number of trials that were included in the meta-analysis, a sensitivity analysis excluding poor quality trials was not possible.

Potential biases in the review process

The strength of this review is with the rigorous approach in which systematic review methodology as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) was applied. A comprehensive search was undertaken to find both published and unpublished studies which address the review objectives. We included a search for non-English language studies to limit publication bias and one study was found, which is currently awaiting translation. All titles and abstracts were independently assessed for inclusion by the three review authors. Additionally all three review authors independently extracted data and assessed the quality of the included studies.

There are two limitations highlighted in this review. Firstly, the relatively small number of studies with small numbers of participants identified. Secondly, this review had to deviate from the original published protocol. The changes in the systematic review reflect the updates in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), especially the changes for assessing risk of bias for included studies. The search strategy also had to be changed due to authors no longer being able to directly access clinical databases (MEDLINE, EMBASE, CINAHL) via Dialog Datastar. Access to these databases, via OvidSP and NHS Evidence, had to be sought. Additionally, it became apparent that the review authors had to consider how to analyse data where the unit of analysis was an issue.

Agreements and disagreements with other studies or reviews

Only one other systematic review (Simon 2008) was identified that investigated the efficacy of urokinase for either preventing or treating occluded CVC lumens or for treating CRBSI in paediatric oncology patients. This review identified only one randomized trial (Haire 2004) plus a number of non-randomized clinical trials for CVC lumen occlusion. These studies were not subjected to rigorous quality assessment and there was no commentary on the possibility of bias occurring within these studies. Simon 2008 concluded that urokinase can safely and effectively be used with malfunctioning CVCs caused by intraluminal occlusion in a dose of 5000 IU or as a salvage three-hour infusion with 1000 IU/kg/hour. These conclusions are similar to the conclusions reached in this review for urokinase 5000 IU, although we highlight that these studies provide low quality evidence so could lead to spurious results and conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

There is inadequate evidence to draw strong conclusions on the efficacy or safety of the drug interventions included in this review. That said, there is some low quality evidence that appears to

suggest that urokinase (various strengths) may be effective in treating withdrawal occlusion or total occlusion of either a semi-permanent or temporary CVC caused by a thrombosis in adults and children with underlying medical conditions.

Implications for research

There is a need for good quality multi-centre, randomized, controlled clinical trials that are sufficiently powered to investigate the safety and efficacy of the following interventions for treating occluded CVCs in adults and children.

1. Chemical interventions.
2. Surgical interventions.
3. Drug interventions.

These studies need to be mindful of the methodological issues that have been highlighted in this review. Unit of analysis issues need careful thought, especially with the effects of clustering and how to deal with this in the analysis. Furthermore, there needs to be more head-to-head trials to determine which pharmacological intervention is superior in terms of safety and efficacy, rather than just drawing comparisons with placebo. The primary outcome for these studies should be restored patency of an occluded CVC, whilst secondary outcomes should include adverse effects, CRBSI (with a clear definition and criteria for diagnosis), duration of patency and death. An economic evaluation would be justified in order to assess the cost-effectiveness of these different treatment interventions. For studies that include long-term CVCs, investigators may wish to consider periods of follow-up greater than 30 days, especially when looking at duration of patency. Investigators should also consider designing studies that include participants from community settings with CVCs. In order to improve the reporting of randomized clinical trials future authors should follow the recommendations that are outlined in the CONSORT (Consolidated Standards of Reporting Trials) statement (Schultz 2010). Finally, there is a vital need for studies that exclusively include child participants rather than children being included in a combined study with adults, due to pathophysiological differences. Thrombolytic drugs are not currently licensed for use in children in the UK, furthermore there are only some anticoagulant preparations that have obtained a license in children. Therefore, additional research in children needs to be undertaken to provide the necessary evidence on the benefits, harms and dosages of these drugs in this population group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dietcher 2004

Methods	<p>Design: Phase II, randomized, double blind, parallel, placebo-controlled trial</p> <p>Duration: May 2000 - September 2001</p> <p>Number of centres: Multi-centre (n=25)</p> <p>Country: USA</p>
Participants	<p>Participants: n=108</p> <p>Age (mean): 23yrs (Age categories: 1 year n= 6; 2-11yrs n=45; 12-18yrs n= 21; >18 yrs n=36)</p> <p>Gender: female n=50; male n=58</p> <p>Ethnicity: Black n= 11; white n= 95; other n= 5</p> <p>Eligibility Criteria:</p> <ul style="list-style-type: none"> Adults and children with a CVC, with either withdrawal occlusion (inability to withdraw blood but able to infuse fluids) or a total occlusion (inability to either withdraw or infuse) were eligible for enrolment There was no restriction on the duration of CVC occlusion or CVC age <p>CVC Type: Semi-permanent or temporary CVC (single or double lumen)</p>

Interventions for restoring patency of occluded central venous catheter lumens (Review)

Dietcher 2004 (Continued)

Site of CVC Placement: Not reported

Exclusion Criteria:

- Haemodialysis catheters
- Occlusion was suspected to be caused by incorrect catheter placement or drug precipitation
- Pregnant or nursing
- Sustained hypertension
- Less than 1 year of age or under 10 kg
- Significant risk for bleeding
- Patients with triple-lumen catheters and those receiving treatment intensity anticoagulation were excluded

Disease Status:

- n=59 (54%) haematological malignancies
- n= 50 (47%) had solid tumours
- n=1 had two primary cancers
- n=1 had no cancer

Interventions

- Recombinant urokinase 25,000 IU/mL (n=25)
- Recombinant urokinase 15,000 IU/mL (n=27)
- Recombinant urokinase 5000 IU/mL (n=26)
- Placebo (n=30)

Study medication was slowly instilled at a volume to slightly overfill the occluded catheter lumen(s).

Treatment success was assessed by attempting to aspirate the study drug and residual clot with an empty, sterile syringe. Up to three (5, 15 and 30 minutes) attempts were made to aspirate the CVC after each installation of study medication. If this was unsuccessful, any aspirated study drug was re-instilled. If aspiration was successful, flushing of the lumen was attempted.

If one instillation of study medication was not successful in establishing CVC function after 30 minutes, then a second instillation of the same study medication was administered in the same manner for the 5,000 IU/mL, 15,000 IU/mL and placebo groups. The second installation in the 25,000 IU/mL group was placebo.

Outcomes

Efficacy Endpoint

- Re-establishment of function of CVC after one or two installations of study medication
- Re-establishment of function of CVC after one installation of study medication

Safety Endpoint

- Incidence, causality, and severity of haemorrhagic and non-haemorrhagic adverse events within 72 hrs of the study drug exposure. Haemorrhages were classified as major (intracranial haemorrhage, retroperitoneal haemorrhage, any haemorrhage resulting in death, or overt bleeding associated with transfusion of two units of blood or haemoglobin decrease of at least 2.0 g/dL) or minor (all other haemorrhagic events).

Notes

Funding: "Study supported in part by Abbott Laboratories, Illinois, USA"

Five study authors were consultants and two authors were employees for Abbott Laboratories at the time of the study.

Risk of bias

Bias

Authors' judgement

Support for judgement

Dietcher 2004 (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Low risk	"Randomization was stratified by site. Information from the randomization schedule was incorporated into the drug packaging by labelling the proper blinded study medication kits with the subject numbers. Blind breaker envelopes were provided to the sites for use in an emergency, although none were used during the course of the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, participants and outcome assessors appear to have been blind to the intervention - see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Participants who were randomized but not treated were classified as failures in an Intention To Treat analysis for CVC patency." "Safety analysis was performed on all treated patients."
Selective reporting (reporting bias)	Low risk	Study reports on all expected outcomes
Other bias	High risk	Authors' reported a 'potential conflict of interest' Balance of group characteristics not reported

Fink 2004

Methods	Design: Randomized unblinded parallel controlled trial Duration: May 2001 - May 2002 Number of Centres: Single centre Country: USA
Participants	Participants: n=50 Age (mean): 50 yrs (SD 17 yrs (alteplase 1mg/1mL)); 51 yrs (SD 14 yrs (alteplase 2mg/2mL)) Gender: male n=16 / female n=10 (alteplase 1mg/mL); male n=9 / female n=12 (alteplase 2mg/2mL) Ethnicity: Not reported Eligibility Criteria: <ul style="list-style-type: none"> CVC (single, double, or triple lumen Hickman catheter or implanted port) dysfunction defined as: <ol style="list-style-type: none"> Inability to withdraw blood from CVC Inability to infuse through CVC Haematology/oncology patients Patients ≥ 18 years of age Completion of informed consent process CVC type: Tunnelled CVC (Hickman) or implanted port Site of CVC Placement: Not reported Exclusion Criteria:

Fink 2004 (Continued)

- Active bleeding that is associated with haemodynamic instability at the time of CVC occlusion
- Peripherally-inserted central catheters (PICC lines), because the volume of the catheter is greater than 1mL
- Recent stroke (< 3 months ago)
- Anticoagulation at the time of the CVC occlusion
- Inability to obtain informed consent

Disease Status: Haematology/oncology patients

Interventions	<ul style="list-style-type: none"> • Alteplase 1mg/1mL • Alteplase 2mg/2mL
Outcomes	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Rate (%) of CVC clearance for 1 mg/mL alteplase versus alteplase 2 mg/2mL after administration of one study dose <p>Secondary Endpoint:</p> <ul style="list-style-type: none"> • Rate (%) of CVC clearance for alteplase 1mg/mL versus alteplase 2mg/2mL after administration of one or two study doses • The incremental cost-effectiveness of alteplase 1 mg/mL versus alteplase 2 mg/2mL • The incidence of adverse effects among the groups
Notes	Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The randomization sequence was provided by the department of biostatistics. The study investigators were removed from this process. Random numbers were computer-generated and investigators were provided with sealed, numbered envelopes which contained the treatment group assignment."</p> <p>Comment: Probably done</p>
Allocation concealment (selection bias)	Low risk	"The sealed, numbered randomization envelopes were kept in a central location (where the drug was stored). At the time of enrolment, envelopes were opened to reveal the treatment group assignment. If patients had more than one occluded lumen, each lumen received the same dose. (Patients, rather than lumens were randomized to received either 1mg/ml or 2mg/2ml). Therefore, the sequence was concealed until interventions were assigned."
Blinding (performance bias and detection bias) All outcomes	High risk	"The study was not blinded due to the difference in volumes of study drugs."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of exclusions to make judgement
Selective reporting (reporting bias)	Unclear risk	Did not report on outcome for incremental cost-effectiveness
Other bias	High risk	Study stopped early due to low subject accrual rate

Interventions for restoring patency of occluded central venous catheter lumens (Review)

Haire 1994

Methods	<p>Design: Double-blinded randomized trial</p> <p>Duration: Not reported</p> <p>Number of centres: Not reported</p> <p>Country: USA</p>
Participants	<p>Participants: n=48 participants (n=50 CVCs)</p> <p>Age (mean): Urokinase group: 45 yrs (SD 12.8 yrs; range 22-79yrs); alteplase group: 43 yrs (SD 13.7 yrs; range 19 -74 yrs)</p> <p>Gender: Urokinase group:13 female; 9 male; t-PA group: 13 female; 15 male</p> <p>Ethnicity: Not reported</p> <p>Eligibility Criteria:</p> <ul style="list-style-type: none"> Acquired CVC dysfunction characterized as <ul style="list-style-type: none"> i) inability to withdraw blood from the CVC after at least one successful attempt at doing so, and/or ii) inability to infuse through the CVC or the need for inordinately high pressure for successful infusion. Radiograph contrast injection demonstrating: <ul style="list-style-type: none"> i) presence of thrombus obstructing the tip of the CVC ii) no evidence of subcutaneous kinking suture constricting the CVC or of intravascular CVC tip malposition. Age greater than 19 yrs <p>CVC Type: Not reported</p> <p>Site of CVC Placement: Not reported</p> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> History of severe allergic reaction to radiograph contrast material <p>Disease Status:</p> <p>Patients had CVCs placed for cancer chemotherapy or for apheresis of haematopoietic stem cells</p>
Interventions	<ul style="list-style-type: none"> Urokinase 10,000 IU/2mL Alteplase 2mg/2mL <p>Study drug was injected into the dysfunctional CVC and allowed to remain undisturbed for two hours. At the end of two hours, attempts were made to withdraw and infuse through the CVC. If normal CVC function was restored, blood was drawn for fibrinogen level, a second contrast injection was performed, and study completed.</p>
Outcomes	<p>Function Endpoint:</p> <ul style="list-style-type: none"> CVC function was determined before and after completion of the study. CVC function was considered normal if blood could be withdrawn and solution infused without resistance or discomfort. <p>Anatomic Endpoint:</p> <ul style="list-style-type: none"> Degree of reduction in thrombus size. The degree of reduction was determined by comparing the pre and post treatment contrast injection films of the dysfunctional CVC. Total thrombus resolution was

Haire 1994 (Continued)

defined as the unimpeded flow of contrast material from the catheter rip into the central venous circulation.

Notes Funding: "Study supported by a research grant from Genetech."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized using a computer generated randomization sequence
Allocation concealment (selection bias)	Low risk	The study drugs were reconstituted in a total volume of 2mL and dispensed from pharmacy in identical syringes, which were not labelled with the actual drug content
Blinding (performance bias and detection bias) All outcomes	Low risk	CVC function was determined before and after the study by one individual blinded to the study drug administered. Degree of reduction in thrombus size was determined by a board certified interventional radiologist blinded to the study drug administered
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Unclear risk	"Two of the patients included in the study received treatment for thrombosis of two different catheters at two separate times."

Haire 2004

Methods	<p>Design: A phase 3, double-blind, multi-centre, placebo-controlled trial</p> <p>Duration: December 2001 - July 2002</p> <p>Number of Centres: n=43</p> <p>Country: USA and Canada</p>
Participants	<p>Participants: n=180</p> <p>Age (mean): Urokinase group 45yrs (SD 25yrs, range 33 days - 80yrs); Placebo group 48 yrs (SD 25yrs, range 52 days - 83 yrs)</p> <p>Gender: Urokinase group female n=65 (55%) / male n=54 (45%); Placebo group female n=39 (64%) / male n=22 (35%)</p> <p>Ethnicity: Urokinase group caucasian n=89 (75%), black n=24 (20%), other 6 (5%); Placebo group caucasian n=46 (75%), black n=14 (23%), other 1(2%)</p> <p>Eligibility Criteria:</p> <ul style="list-style-type: none"> Any type of semi-permanent or temporary CVC, with either withdrawal occlusion (inability to withdraw blood but able to infuse fluids) or a total occlusion (inability to either withdraw blood or infuse fluids) The CVC must have been properly placed and successfully used at least once

Interventions for restoring patency of occluded central venous catheter lumens (Review)

Haire 2004 (Continued)

- There was no restriction on the duration of CVC occlusion, on the age of patients or catheters enrolled

CVC Type: Implanted ports (80); PICCs (47); non-tunnelled percutaneous (33); tunnelled CVC (18); unspecified (1)

Site of CVC Placement: Not reported

Exclusion Criteria:

- Haemodialysis catheters
- If occlusion was due to incorrect placement or suspected drug precipitation
- Pregnant or nursing
- Sustained systolic hypertension
- Undergone puncture of a non-compressible vessel within the previous 48hr
- Sustained a known or suspected haemorrhagic event within the previous 7 days
- Undergone major surgery, organ biopsy, major trauma, obstetrical delivery, bloody subarachnoid puncture, CPR, or intraocular surgery within previous 7 days
- Sustained a cerebral vascular accident within the previous six months
- Significant risk for bleeding, including active internal bleeding

Disease Status:

- Serious underlying medical conditions were prevalent including malignancy (51%), anaemia (53%), and thrombocytopenia (14%)

Interventions

- Urokinase 5000 IU/1mL
- Placebo

Instillation for withdrawal occlusions consisted of slightly overfilling (0.2mL) the occluded CVC lumen with study medication. For total occlusions, an attempt was made to aspirate fluid from the CVC lumen, and then as much dedication as possible was instilled up to but not exceeding the maximum lumen volume plus 0.2mL.

The maximum volume of urokinase or placebo instilled was determined according to the internal lumen volume specified by the CVC manufacturer.

If unspecified, the following volumes were utilized:

- 1.5mL - peripherally inserted central catheters, 7-9 French CVC and low-profile port CVCs
- 2mL - 10 - 13 French CVCs
- 2.5mL - implanted subcutaneous ports

The use of a 3-way stopcock for instillation was permitted with total occlusions in order to maximize the amount of instilled study drug.

Outcomes

Efficacy

- Restoration of CVC function to all treated lumens (i.e. total CVC patency) after one or two instillations

Assessments of function were made at 5, 15 and 30 minutes following installation by trying to aspirate blood and infuse fluids. If function was not restored after 30 min, the lumen was flushed with normal saline (withdrawal occlusion) and a second installation was performed with repeat assessments after 5, 15 and 30 minutes.

CVCs were considered functional if both withdrawal of blood and infusion of normal saline were possible through treated lumens. If function was not restored in all treated lumens of multi-lumen CVCs after one hour, the treatment was considered unsuccessful.

In unsuccessful cases, further treatments for restoration of CVC patency were left to the discretion of the treating physician. If additional thrombolytic therapy was chosen, then up to two instillations of open-label urokinase were allowed.

Haire 2004 (Continued)

Safety

- Haemorrhagic and non-haemorrhagic adverse events within 72 hours after instillation

Notes

Funding: "This study was sponsored by Abbot Laboratories, Illinois, USA"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information on allocation concealment - although study investigators report blinding of study drugs
Blinding (performance bias and detection bias) All outcomes	Low risk	Study drugs were blind - an assumption can be made that investigators, participants and outcome assessors were blind to intervention. However, if the treatment was unsuccessful further treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>One patient in the urokinase group was treated for two separate occluded catheters. This was considered a protocol deviation and the results were excluded from the efficacy analysis.</p> <p>Six patients (n=4 urokinase, n=2 placebo) did not receive study drug after enrolment because the catheter was found to be patent on re-examination (n=3), no volume of drug could be instilled (n=2) or a medical event precluded participation in the study (n=1).</p> <p>The statistical analysis for efficacy was performed by intention-to-treat, these six patients were included as failures in their respective randomized treatment groups even though they received no treatment.</p>
Selective reporting (reporting bias)	Low risk	No missing outcome data
Other bias	Unclear risk	<ul style="list-style-type: none"> • Safety data at 30 days includes participants who had open-label urokinase

Horne III 1997
Methods

Design: Double-blinded randomized controlled trial

Duration: Not reported

Number of Centres: n=1

Country: USA

Participants

Participants: n=42

Age: Urokinase (median 54; range 23-68); Urokinase plus heparin (median 53; range 23-73)

Gender: Urokinase (male 7; female 14); Urokinase plus heparin (male 8; female 13)

Ethnicity: not reported

Eligibility Criteria:

Horne III 1997 (Continued)

A patient must have developed impairment of catheter withdrawal that was refractory to urokinase instillation. Refractoriness was defined as the failure of two successive instillations of urokinase (each consisting of 2ml of drug instilled into each obstructed lumen and left undisturbed for 30 mins) to relieve the obstruction or as the recurrence of obstruction within 7 days after successful treatment with one or two urokinase instillations.

CVC malfunction was defined as the inability to fill a 5mL Vacutainer (Beckon Dickinson) through a lumen within 10 seconds. That the malfunction was related to the presence of a fibrin sleeve had to be documented by cathetergram. The distance between the tip of each CVC and the carina was measured on the (supine) cathetergram and expressed as negative cephalad to the carina and positive below it.

Catheter Type: Tunnelled CVC (Hickman or Groshong; Bard) or implanted port CVC (Port-A-Cath; Bard)

Site of Placement: Not reported

Exclusion Criteria:

- Evidence of active gastrointestinal or other internal bleeding
- Neurosurgery within 2 months
- Intracranial metastases

Disease Status: Advanced malignancies that include: breast; prostate; lymphoma; colon; ovary; renal; basal cell

Interventions	<ul style="list-style-type: none"> • Urokinase 250,000 IU/normal saline 50 mL infusing at 8 mL/hour (Urokinase 40,000 IU/hour) • Urokinase 250,000 IU/sodium heparin 2,000 IU/normal saline 50 mL (Urokinase 40,000 IU/sodium heparin 320 IU/hour)/ <p>The intravenous tubing (volume 24 mL) was primed with the infusate. After 1,3,6 and 12 hours of infusion, CVC function was reevaluated. Whenever function was restored, the infusion was stopped and the patient underwent another cathetergram to assess the status of the fibrin sleeve. If the sleeve was still visible by x-ray, the infusion was continued until the next scheduled evaluation.</p> <p>If the obstruction had not been relieved after 12 hours of infusion, the treatment was discontinued and scored as a failure.</p> <p>Seven days before treatment and immediately following each urokinase infusion, peripheral blood was obtained for measurement of prothrombin time, activated partial thromboplastin time and fibrinogen concentration.</p>
Outcomes	<p>Primary and secondary outcomes were not clearly reported in the methods section of the study. Results have been produced for the following:</p> <ul style="list-style-type: none"> • Restored function • Persistence of successful treatment • Influence of the length of prior CVC refractoriness to urokinase instillations on the outcome of treatment with urokinase infusions • Relationship of CVC location and type to the rate of success with urokinase infusions <p>Participant coagulopathy was not reported despite obtaining peripheral blood samples.</p>
Notes	Funding: Source not reported although the study reports being "US government work"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation

Horne III 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information on outcomes
Selective reporting (reporting bias)	Unclear risk	Insufficient information on outcomes to make a judgement for selective reporting
Other bias	Unclear risk	? baseline imbalance with regards to types of malignancy

Moll 2006

Methods	<p>Design: Phase II, randomized, double-blind, active-control, multi-centre, dose-ranging study</p> <p>Duration: May 2003 - August 2004</p> <p>Number of Centres: n=20</p> <p>Country: USA</p>
Participants	<p>Participants: n=55</p> <p>Age: Alfimeprase 0.3 mg 57yrs (13); 1.0 mg 52yrs (11); 3.0 mg 52 (16); Alteplase 2 mg 48 yrs (9)</p> <p>Gender: Alfimeprase 0.3 mg male (n=14) / female (n=2); 1.0 mg male (n=13) / female (n=3); 3.0 mg male (n=4) / female (n=6); Alteplase 2 mg male (n=8) / female (n=5)</p> <p>Ethnicity:</p> <p>Alfimeprase 0.3 mg: White (n=12); Black (n=3); Hispanic / other (n=1)</p> <p>Alfimeprase 1.0 mg: White (n=12); Black (n=4); Hispanic / other (n=0)</p> <p>Alfimeprase 3.0 mg: White (n=10); Black (n=0); Hispanic / other (n=0)</p> <p>Alteplase 2.0 mg: White (n=10); Black (n=2); Hispanic / other (n=1)</p> <p>Eligibility Criteria:</p> <ul style="list-style-type: none"> • 18 yrs or age or older • Clinically stable • Occluded indwelling CVC, defined as the inability to withdraw 3.0 mL of blood from at least one CVC lumen • The ability to infuse at least 2ml of fluid into the CVC lumen with withdrawal occlusion • Peripherally inserted central catheters, CVCs with valves and implanted ports were allowed • Multiple-lumen catheters, only one lumen of the catheter (chosen at the discretion of the investigator) was to be used throughout the study for the assessment of CVC function • There were no restrictions on CVC duration of occlusion or on the length of time since implantation of the device <p>CVC Type: non-tunnelled CVC (single, double or triple lumen), PICCs, implanted ports</p> <p>Site of CVC Placement: Not reported</p>

Moll 2006 (Continued)

Exclusion Criteria:

- Catheters used for haemodialysis or therapeutic pheresis
- CVCs inserted less than 48 hours before the detection of occlusion were excluded
- Occlusion was suspected to be due to incorrect catheter placement or other mechanical obstruction
- Pregnant or nursing
- Sustained hypertension
- Significant risk of bleeding

Disease Status:

Not reported

Interventions	<ul style="list-style-type: none">• Alfimeprase 0.3 mg/2mL• Alfimeprase 1.0 mg/2mL• Alfimeprase 3.0 mg/2mL• Alteplase 2.0 mg/2mL <p>CVC patency restoration was assessed at 5, 15, 30 and 120 minutes after treatment with one or two instillations of study drug. Treatment success was assessed by attempting to aspirate 3.0 mL of venous blood with an empty, sterile 10 mL syringe. If unsuccessful, any aspirated drug was reinstalled. If successful, flushing of the lumen with 5.0 mL of sterile saline was attempted.</p> <p>If the first administration of study drug did not restore patency of the CVC after 120 minutes, a second dose of the same study drug preparation was instilled and CVC function was assess at 5, 15, 30 and 120 minutes after second instillation.</p> <p>The total dose a study participant could receive was:</p> <ul style="list-style-type: none">• Alfimeprase 6.0 mg• Alteplase 4.0 mg	
Outcomes	<p>Efficacy Endpoints:</p> <ul style="list-style-type: none">• Rates of successful restoration of function to an occluded CVC, at 5, 15, 30 and 120 minutes, following one or two instillations of study drug <p>Safety Endpoints:</p> <ul style="list-style-type: none">• Major haemorrhagic events: stroke (intracranial haemorrhage); embolic events for up to 5 days after treatment with study drug; severe blood loss (>5 mL/kg) or blood loss requiring transfusion or causing hypotension• Non-serious adverse events recorded for 24 hours after study drug instillation• Deaths and serious adverse events recorded for up to 30 days after drug instillation	
Notes	Funding: "Study supported by Nuvelo Inc, San Carlos, CA"	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information reported on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported on allocation concealment
Blinding (performance bias and detection bias)	Unclear risk	Insufficient information reported for blinding

Moll 2006 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study appears to include all expected outcomes
Other bias	High risk	Conflict of interest reported Small sample size and possible unit of analysis issues

Ponec 2001

Methods	Design: Double-blind, placebo-controlled multi-centre trial Duration: November 1999 - June 2000 Number of Centres: n=26 Country: USA
Participants	Participants: n=150 participants enrolled in study; n=149 were randomized Age: PAA group 49.6 (19); AAP group 50.5 (19) Gender: PAA group male (n=33) / female (n=41); PPA group male (n=34) / female (n=41) Ethnicity: PAA group: White (n=51), Black (n=16), Asian/Pacific Islander (n=2), Hispanic (n=5), other (n=0) AAP group: White (n=57), Black (n=8), Asian/Pacific Islander (n=6), Hispanic (n=3), other (n=1) Eligibility Criteria: <ul style="list-style-type: none"> Clinically stable with a dysfunctional indwelling long-term CVC. Withdrawal dysfunction was defined as the inability to withdraw 3 mL of blood CVC Type: PICCs, CVCs with valves and implanted ports CVC Site: Not reported Exclusion Criteria: <ul style="list-style-type: none"> Not possible to infuse fluids at the volume necessary to infuse study drug into the CVC If the CVC had been inserted less than 48 hours before randomization Occlusion had been discovered more than 24 hours before randomization Participants younger than 2 years of age Participants who weigh less than 10kg CVCs with any evidence of mechanical or non-thrombotic occlusion Participants who have received any fibrinolytic agent within 24 hours of randomisation Haemodialysis catheters Disease Status: Not reported
Interventions	<ul style="list-style-type: none"> Alteplase 2 mg/2 mL, Alteplase 2 mg/2 mL, placebo (n=75) Placebo, Alteplase 2 mg/2 mL, Alteplase 2 mg/2 mL (n=74)

Interventions for restoring patency of occluded central venous catheter lumens (Review)

Ponec 2001 (Continued)

- Participants weighing between 10 and 30 kg were given a dose equal to 110% of the internal CVC volume

Each group had one opportunity to receive placebo and two opportunities to be treated with study drug. In one arm, the first study drug vial contained placebo and the second and third vials contained active alteplase. In the other arm, the first and second study drug vials contained active alteplase and the third contained placebo.

After the first vial of study drug was instilled and allowed to dwell for 120 minutes, function was re-assessed to determine if both withdrawal and infusion function were present. If function was successfully restored the patient exited the study.

Outcomes	Efficacy Endpoints: <ul style="list-style-type: none">• Comparison of the rates of restoration of CVC function after treatment for 2 hours with either alteplase (2 mg/2 mL) or placebo• Determine the rate of CVC function restoration after one or two treatments with alteplase Safety Endpoints: <ul style="list-style-type: none">• Rates of study drug related intracranial haemorrhages, major haemorrhage, embolic events and all drug related serious events	
Notes	Funding: Not reported although authors do disclose the existence of a potential conflict of interest.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Low risk	Subjects were randomly assigned by an interactive voice randomization service to one of two groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess the completeness of outcome data
Selective reporting (reporting bias)	Low risk	Insufficient information to assess study being free from selective reporting
Other bias	High risk	The study is neither a 'true' parallel or crossover in design Three authors, Hill, Li and McCluskey, have disclosed a conflict of interest

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Barrett 1990	Study did not fulfil inclusion criteria. Study authors investigated the efficacy of two different flushing solutions to prevent CVC occlusion.

Study	Reason for exclusion
Lawson 1982	Not a RCT - urokinase 5000 IU/mL was administered to 1690 occluded CVCs in Texas, USA. There was no comparison group reported.
Molinari 2004	Not a RCT - urokinase 5000IU was administered to children with malfunctioning CVCs at a hospital in Genoa, Italy, whilst urokinase 25,000 IU was administered to children with malfunctioning CVCs at a hospital in Turin, Italy.
Ng 2004	Not a RCT - subgroup analysis from a multi-centre study. Alteplase 2mg administered to 240 patients (adults and children). If the lumen remained blocked then a second instillation was given. There was no comparison group reported.
Owens 2002	Not a RCT- retrospective chart review investigating the efficacy of reteplase.
Study 1974	Study did not fulfil inclusion criteria. Authors investigated the efficacy of urokinase compared with streptokinase for treating pulmonary embolism.
Svoboda 1990	Not a RCT. Multi-centred open-label study investigating the efficacy of Urokinase 5000 IU for restoring patency of occluded CVCs. There was no comparison group reported.
Zeitler 1976	Study did not fulfil any of the inclusion criteria - treatment for peripheral artery disease.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Gabrail 2010](#)

Methods	A phase III randomized, double-blind, placebo-controlled trial
Participants	Participants with a dysfunctional CVC
Interventions	In treatment arm one participants received a regimen of tenecteplase (up to 2mg), then if needed a second dose of tenecteplase and a third dose of placebo. In treatment arm two participants received a regimen of placebo followed by one or two doses of tenecteplase (up to 2mg)
Outcomes	Restored patency of occluded CVCs. CVC function was assessed at 15, 30 and 120 minutes
Notes	

[Levine R](#)

Methods	A phase III, randomized, double-blind, placebo-controlled trial
Participants	Adults and paediatrics with dysfunctional CVCs from 24 centres in USA and Canada
Interventions	Tenecteplase compared with placebo
Outcomes	Percentage of patients who had restoration of CVC patency following a single administration of study drug
Notes	Recruitment Status: Completed 14 July 2010 Sponsor: Genetech

Muller 2010

Methods	Not reported
Participants	28 participants with an occluded PICC line
Interventions	Urokinase 20,000 IU over 30 minutes
Outcomes	Restored patency
Notes	

NCT00073515

Methods	A Phase II multi-centre, randomized, double-blind study
Participants	Adults participants with dysfunctional central venous access devices
Interventions	Alfimeprase compared with active control
Outcomes	Not reported
Notes	Recruitment Status: Completed Sponsor: ARCA Biopharma, Inc

DATA AND ANALYSES

Comparison 1. Urokinase compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Restored patency of CVC following one or two installations of study drug	2	287	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.47, 2.95]
1.1 Urokinase 25, 000 IU	1	35	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.85, 6.06]
1.2 Urokinase 15, 000 IU	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.88, 6.24]
1.3 Urokinase 5, 000 IU	2	215	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.35, 3.01]

Analysis 1.1. Comparison 1 Urokinase compared with placebo, Outcome 1 Restored patency of CVC following one or two installations of study drug.

ADDITIONAL TABLES

Table 1. Results for drug interventions

Thrombolytic Drug Interventions					
Study	Urokinase		Placebo		Risk Ratio
Haire 1994	Alteplase 2mg/mL		Urokinase		
			10,000 IU		
	Events	Totals	Events	Totals	M-H, Fixed, 95% CI
	25	28	13	22	1.51 [1.04 to 2.19]
Ponec 2001	Alteplase 2mg		Placebo		
	Events	Totals	Events	Totals	M-H, Fixed, 95% CI

Table 1. Results for drug interventions (Continued)

	51	75	12	74	4.19 [2.44 to 7.20]
Fink 2004	Alteplase 1 mg/1mL		Alteplase 2mg/2 mL		
	Events	Totals	Events	Totals	M-H, Fixed, 95% CI
1st installation	20	27	18	23	0.95 [0.69 to 1.29]
2nd installation	21	27	19	23	0.94 [0.71 to 1.24]
Moll 2006	Alfimeprase		Alteplase 2mg		
	Events	Totals	Events	Totals	M-H, Fixed, 95% CI
Alfimeprase 3.0 mg (restored patency of CVC following one or two installations of study drug)	6	10	3	4	0.80 [0.37 to 1.71]
Alfimeprase 1.0 mg (restored patency of CVC following one or two installations of study drug)	9	16	3	4	0.75 [0.37 to 1.53]
Alfimeprase 0.3 mg (restored patency of CVC following one or two installations of study drug)	6	16	2	5	0.94 [0.27 to 3.26]
Anticoagulant Drug Interventions					
Horne III 1997	Urokinase plus heparin		Urokinase		
	Events	Total	Events	Total	M-H, Fixed, 95%CI
Patency assessed at 1 hr	8	21	5	21	1.60 [0.63 to 4.09]
Patency assessed at 3 hrs	11	21	10	21	1.10 [0.60 to 2.02]
Patency assessed at 6hrs	13	21	12	21	1.08 [0.66 to 1.79]
Patency assessed at 12hrs	16	21	16	21	1.00 [0.71 to 1.40]

Table 2. Adverse effects

	Urokinase		Placebo		Risk Ratio	
Dietcher 2004	Events	Totals	Events	Totals	M-H, Fixed, 95% CI	
25,000 IU	4	25	0	10	3.81 [0.22 to 64.87]	Dietcher 2004 reports that one subject had two events of major severity both of which were probably not related to the study drug (subarachnoid haemorrhage status post a fall and injection site haemorrhage in the setting of thrombocytopenia requiring platelet transfusion).

Table 2. Adverse effects (Continued)

15,000 IU	2	27	0	10	1.96 [0.10 to 37.72]	epistaxis (1); metorrhagia (1)
5000 IU						
Alfimeprase		Alteplase 2mg		Risk Ratio		
Study	Events	Totals	Events	Totals	M-H, Fixed, 95% CI	
Al-fimeprase 3 mg Moll 2006	3	10	1	4	1.20 [0.17 to 8.38]	Moll 2006 describes the following adverse events that are possibly or probably related to alfimeprase 3.0 mg; pyrexia and dizziness and that are possibly or probably related to alteplase 2 mg fatigue and malaise.
Al-fimeprase 1 mg Moll 2006	4	16	1	4	1.00 [0.15 to 6.67]	Moll 2006 described the following adverse events that are possibly or probably related to alfimeprase 1.0 mg; generalized pruritus, nausea, fungaemia, and urticaria.
Al-fimeprase 0.3 mg Moll 2006	4	16	1	5	1.25 [0.18 to 8.77]	Moll 2006 described the following adverse events that are possibly or probably related to alfimeprase 0.3 mg; depressed level of consciousness and renal failure.

Table 3. Catheter-related blood stream infection

Alfimeprase		Alteplase 2mg		Risk Ratio	
Study	Events	Totals	Events	Totals	M-H, Fixed, 95% CI
Alfimeprase 1 mg Moll 2006	1	16	0	4	0.88 [0.04 to 18.47]

Table 4. Mortality

Urokinase		Placebo		Risk Ratio	
Study	Events	Totals	Events	Totals	M-H, Fixed, 95% CI
Haire 2004 Urokinase 5000 IU	0	118	1	61	0.17 [0.01 to 4.20]

APPENDICES

Appendix 1. Glossary of terms

Chest Xray (radiograph)	A type of x-ray that is commonly used to detect abnormalities of the lungs. A chest x-ray can also detect some abnormalities of the heart, aorta and bones in the thoracic area (Websters New World Medical Dictionary 2009 p.79).
Linogram	A linogram is a diagnostic procedure that enables the CVC lumen to be seen on fluroscopy imaging following an injection of contrast medium into the occluded CVC lumen (Barnacle 2007)
Ultrasound	High frequency sound waves can be bounced off the tissues by using special devices. The echoes are then converted into a picture called a sonogram. Ultrasound allows an inside view of the soft tissues and body cavities without the use of invasive techniques (Websters New World Medical Dictionary 2009 p.439)
Venography (venogram)	A diagnostic procedure that enables <i>veins</i> to be seen on an x-ray film after they have been injected with a substance opaque to x-rays. It is used to detect abnormalities or diseases of the veins, such as a narrowing or blockage of a thrombosis (BMA 2002 p. 581)

Appendix 2. Central venous catheter types and venous insertion sites

Catheter type and venous insertion sites

Tunnelled central venous catheters: an entry site incision is made near the collar bone to enable the health care professional to place the tip of the catheter into a large vein such as the subclavian, external jugular or internal jugular. The remaining catheter tubing is secured beneath the skin and brought out through an exit site on the chest. These catheters are for long-term use, months or years, if they remain functional. They enable patients with chronic health conditions to leave hospital and continue treatment regimens at home. These catheters are often referred to by brand name which include, Broviac®, Groshong® and Hickman®.

Totally implanted central venous catheters: these implanted catheters have a self-sealing injection port which is situated beneath the skin on the chest. The port is accessed with a special type of needle through the skin to enable the administration of drug therapies and fluids. The catheter tip is usually inserted into a large vein such as the subclavian, external jugular or cephalic vein. Totally implanted catheters are also used for intermittent long-term use. With the access port being completely covered by skin it facilitates the individual adult or child to lead a more 'normal' lifestyle and enables them to continue with activities such as bathing and swimming.

Peripherally Inserted Central Catheter (PICC): these catheters are usually inserted into the basilic or cephalic veins in the arm. Insertion of PICCs is less invasive in comparison to insertion of the tunnelled and implanted catheters. PICCs can be used in acute care settings for intermediate care or for treatment regimens that extend over a longer duration of time.

Non-tunnelled central venous catheters: are typically used in patients with an acute illness who require drug therapies, fluids and or / close fluid balance monitoring for a relatively short to intermediate period of time. These catheters are usually placed directly into one of the following veins, internal jugular, subclavian or femoral, then secured to the skin at the entry site.

Appendix 3. CENTRAL

#1 (central venous cathet*) or (vascular access device*) or ((broviac or hickman) near line*) or portacath* or (peripherally inserted central cathet*) or groshong or ((femoral or subclavian or jugular or long) near line*)

#2 MeSH descriptor Catheterization, Central Venous explode all trees

#3 (#1 OR #2)

#4 urokinase OR actilyse OR rt-PA OR alfineprase OR tenecteplase OR reteplase OR streptokinase OR streptase OR heparin OR warfrin OR ethanol OR sodium bicarbonate OR hydrochloric acid

#5 (N-hydrochloric NEAR acid)
 #6 ((endoluminal OR intraluminal) NEAR brush*)
 #7 snar* OR (amplatz NEAR snar*)
 #8 (guidewire NEAR exchanged)
 #9 MeSH descriptor Urokinase-Type Plasminogen Activator explode all trees
 #10 MeSH descriptor Tissue Plasminogen Activator explode all trees
 #11 MeSH descriptor Streptokinase explode all trees
 #12 MeSH descriptor Heparin explode all trees
 #13 MeSH descriptor Ethanol explode all trees
 #14 MeSH descriptor Sodium Bicarbonate explode all trees
 #15 MeSH descriptor Hydrochloric Acid explode all trees
 #16 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
 #17 (#3 AND #16)

Appendix 4. MEDLINE (OvidSP, 1950 to September 2011)

1. (central ADJ6 venous ADJ6 cathet*).mp. OR exp CATHETERIZATION/ OR exp CATHETERIZATION, CENTRAL VENOUS/ OR exp CATHETERS, INDWELLING/ OR exp CATHETERIZATION, PERIPHERAL/ OR (vascular ADJ6 access ADJ6 device*).mp. OR (peripherally ADJ6 inserted ADJ6 central ADJ6 cathet*) OR portacath*.mp. OR groshong*.mp. OR (femoral ADJ6 venous ADJ6 line*).mp. OR (femoral ADJ6 venous cathet*).mp. OR (subclavian ADJ6 line*).mp. OR (subclavian ADJ6 cathet*).mp. OR (internal ADJ6 jugular ADJ6 line*).mp. OR (internal ADJ6 jugular ADJ6 cathet*).mp. OR (long ADJ6 line*).mp.
 2. urokinase.mp. OR exp UROKINASE-TYPE PLASMINOGEN ACTIVATOR/ OR alteplase.mp. OR exp TISSUE PLASMINOGEN ACTIVATOR/ OR actilyse.mp. OR tenectapase.mp. OR alfineprase.mp. OR reteplase.mp. OR exp STREPTOKINASE/ OR streptokinase.mp. OR exp HEPARIN/ OR heparin.mp. OR calciparin.mp. OR monoparin.mp. OR multiparin.mp. OR exp WARFARIN/ OR warfarin.mp. OR marevan.mp. OR exp ETHANOL/ OR ethanol.mp. OR exp SODIUM BICARBONATE/ OR exp HYDROCHLORIC ACID/ OR (hydrochloric adj6 acid).mp. OR (endoluminal adj6 brush*).mp. OR (intraluminal adj6 brush*).mp. OR snar*.mp. OR (amplatz adj6 snar*).mp. OR (amplatz adj6 goose adj6 neck adj6 snar*).mp. OR (guidewire adj6 exchange).mp.
 3. (randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals.sh not (humans.sh and animals.sh))
 4. 1 and 2 and 3

Appendix 5. EMBASE (OvidSP, 1980 to September 2011)

1. (central ADJ6 venous ADJ6 cathet*).mp. OR exp CATHETERIZATION/ OR exp CATHETERIZATION, CENTRAL VENOUS/ OR exp CATHETERS, INDWELLING/ OR exp CATHETERIZATION, PERIPHERAL/ OR (vascular ADJ6 access ADJ6 device*).mp. OR (peripherally ADJ6 inserted ADJ6 central ADJ6 cathet*) OR portacath*.mp. OR groshong*.mp. OR (femoral ADJ6 venous ADJ6 line*).mp. OR (femoral ADJ6 venous cathet*).mp. OR (subclavian ADJ6 line*).mp. OR (subclavian ADJ6 cathet*).mp. OR (internal ADJ6 jugular ADJ6 line*).mp. OR (internal ADJ6 jugular ADJ6 cathet*).mp. OR (long ADJ6 line*).mp.
 2. urokinase.mp. OR exp UROKINASE-TYPE PLASMINOGEN ACTIVATOR/ OR alteplase.mp. OR exp TISSUE PLASMINOGEN ACTIVATOR/ OR actilyse.mp. OR tenectapase.mp. OR alfineprase.mp. OR reteplase.mp. OR exp STREPTOKINASE/ OR streptokinase.mp. OR exp HEPARIN/ OR heparin.mp. OR calciparin.mp. OR monoparin.mp. OR multiparin.mp. OR exp WARFARIN/ OR warfarin.mp. OR marevan.mp. OR exp ETHANOL/ OR ethanol.mp. OR exp SODIUM BICARBONATE/ OR exp HYDROCHLORIC ACID/ OR (hydrochloric adj6 acid).mp. OR (endoluminal adj6 brush*).mp. OR (intraluminal adj6 brush*).mp. OR snar*.mp. OR (amplatz adj6 snar*).mp. OR (amplatz adj6 goose adj6 neck adj6 snar*).mp. OR (guidewire adj6 exchange).mp.
 3. ((randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/) or ((random* or cross?over* or factorial* or placebo* or volunteer*) or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))) .ti,ab) not (animals.sh not (humans.sh and animals.sh))
 4. 1 and 2 and 3

Appendix 6. CINAHL via EBSCO host (1982 to September 2011)

S1 TX (central venous cathet*) OR (vascular access device*) OR (peripherally inserted central cathet*) OR portacath* OR groshong* OR (femoral venous line*) OR (femoral venous cathet*) OR (subclavian line*) OR (subclavian cathet*) OR (internal jugular line*) OR (internal jugular cathet*) OR (long line*)
 S2(MH "Catheterization+") OR (MH "Catheterization, Peripheral+") OR (MH "Catheterization, Central Venous+")
 S3 S1 or S2
 S4 urokinase OR alteplase OR actilyse OR tenectapase OR alfineprase OR reteplase OR streptokinase OR heparin* OR calciparin OR monoparin OR multiparin OR warfarin OR marevan OR ethanol OR (hydrochloric acid) OR (endoluminal brush*) OR (intraluminal brush*) OR snar* OR (amplatz snar*) OR (amplatz goose neck snar*) OR (guidewire exchange)
 S5(MM "Tissue Plasminogen Activator") OR (MH "Plasminogen Activators+") OR (MH "Streptokinase+") OR (MM "Heparin") OR (MM "Warfarin") OR (MH "Ethanol+") OR (MM "Sodium Bicarbonate") OR (MM "Hydrochloric Acid")
 S6 S4 or S5
 S7 S3 and S6

S8(MM "Placebos") OR (MM "Random Assignment") OR "random" OR (MM "Clinical Trials") OR (MM "Clinical Trial Registry") OR "trial"
OR (MM "Double-Blind Studies") OR (MM "Single-Blind Studies") OR (MM "Triple-Blind Studies") OR (MH "Prospective Studies+") OR (MM
"Multicenter Studies")
S9 S7 and S8

Appendix 7. Data extraction form

Study Selection, Quality Assessment & Data Extraction Sheet

First Author	Conference Proceeding/Journal etc	Year

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author (s)	Journal/Conference proceedings etc	Year
A			
B			
C			

Participant and Trial Characteristics
Age (mean, median, range etc)
Sex of participants (numbers / % etc)
Participant eligibility definition
Exclusion Criteria
Disease status / type, etc
Co-morbidity
Ethnicity
Confounding variables

(Continued)

Date/duration of study

Single centre/multi-centre

Country

How many were randomized?

Type of intervention(s)

Type of comparison(s)

Number of participants in intervention group

Number of participants who received intended treatment

Number of participants who were analysed

Median (range) length of follow-up reported

Time-points when measurements were taken during study

Time-points reported in study

Trial design

Funding Source

Key conclusions of study authors

Risk of Bias

Sequence generation

(Continued)

State method used to generate sequence allocation and reasons for grading	Evidence for Domain
Quote:	Yes (low risk of bias random)
Comment:	Unclear (uncertain risk of bias)
	No (high risk of bias alternate)

Allocation concealment	
State method used to conceal allocation sequence and reasons for grading	Evidence for Domain
Quote:	Yes (low risk of bias)
Comment:	Unclear (uncertain risk of bias)
	No (high risk of bias)

Blinding of participants, research personnel and outcome assessors	
Was knowledge of the allocated interventions adequately prevented during the study	Evidence for domain
Quote:	Yes (low risk of blinding)
Comment:	Unclear (uncertain risk of bias)
	No (high risk of bias)

Incomplete outcome data	
Were incomplete outcome data adequately addressed?	Grade
Quote:	Yes (low risk of bias)
Comment:	Unclear (uncertain risk of bias)
	No (high risk of bias)

Selective outcome reporting

Are the reports of the study free of suggestion of selective outcome reporting? Grade

Quote: Yes (low risk of bias)

Comment: Unclear (uncertain risk of bias)

No (high risk of bias)

Other potential threats to validity

Was the study free of other problems that could put it at a risk of bias? Grade

Quote: Yes (low risk of bias)

Comment: Unclear (uncertain risk of bias)

No (high risk of bias)

Data Extraction

Outcomes relevant to your review

Restoration of patency	Yes / no
------------------------	----------

Duration of patency	Yes / no
---------------------	----------

CRBSI	Yes /no
-------	---------

Adverse effects	Yes / no
-----------------	----------

Continuous Data

Outcomes	Unit of measurement	Intervention Group	Control Group	Additional information
		n	Mean (SD)	
		n	Mean (SD)	

(Continued)

Duration of patency

Dichotomous Data

Outcomes	Intervention group (n) n=number of participants not number of events	Control group (n) n=number of participants not num- ber of events	Additional informa- tion
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Restoration of patency

CRBSI

Adverse effects

Other information relevant to the results

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

References to other trials

Did this report include any references to published reports of potential eligible trials not already identified for this review?	Yes / no
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First author	Journal/conference	Year of publication
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Did this report include any references to unpublished data?

Yes / no

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review (Clare van Miert (CvM))
 Co-ordinating the review (CvM)
 Draft the protocol (CvM)
 Develop search strategy and liaise with the CARG trials Search Co-ordinator (CvM)
 Search for trials (CvM)
 Screening search results (CvM, Rebecca Hill (RH) and Leanne Jones (LJ))
 Obtain copies of trials (CvM)
 Select trials for inclusion (CvM and RH, (LJ to arbitrate))
 Appraising quality of included studies (CvM and RH)
 Extract data from trials (CvM, RH and LJ)
 Writing to authors, of studies, for additional information (CvM)
 Providing additional data about studies (CvM)
 Obtaining and screening data from unpublished studies (CvM and RH)
 Data management for the review (CvM)
 Enter data into [RevMan 5.1](#) (CvM and RH)
 RevMan statistical data (CvM and RH)
 Statistical analysis (CvM and RH)
 Interpret the data (CvM and RH)
 Writing review (CvM)
 Guarantor for the review (CvM)
 Proof reading of review before submission (CvM, RH and LJ)

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Alder Hey Childrens' NHS Foundation Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We have adapted the search strategy for use in databases using a different provider. This is due to institutional changes made in accessing electronic databases. These new strategies now include the use of filters for identification of randomized controlled trials.
- We have decided to have a separate outcome for death as opposed to this outcome being included under adverse effects.

- We have renamed mechanical interventions as surgical interventions.
- The original protocol suggested assessing methodological quality based on the criteria reported by [Juni 2001](#). The methodological quality is now being assessed by the criteria suggested by [Higgins 2011a](#) in the latest edition of the *Cochrane Handbook for Systematic Reviews of Interventions*.
- We have also incorporated the principles of the GRADE system ([Guyatt 2008](#)) in order to assess the quality of the body of evidence associated with the predefined outcomes in this review and have constructed 'Summary of Findings' tables using the Grade software.
- Due to identifying issues with the unit of analysis we have had to include strategies on how we will manage this data in the analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Catheters; Anticoagulants [*administration & dosage]; Catheterization, Central Venous [*instrumentation]; Equipment Failure; Thrombosis [complications] [*drug therapy]; Tissue Plasminogen Activator [administration & dosage]; Urokinase-Type Plasminogen Activator [administration & dosage]

MeSH check words

Adult; Child; Humans