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Infusion techniques for peripheral arterial thrombolysis (Review)

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Infusion techniques for peripheral arterial thrombolysis (Review)

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[Intervention Review]

Infusion techniques for peripheral arterial thrombolysis

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ABSTRACT

Background

Acute limb ischaemia usually is caused by a blood clot blocking an artery or a bypass graft. Severe acute ischaemia will lead to irreversible damage to muscles and nerves if blood flow is not restored in a few hours. Once irreversible damage occurs, amputation will be necessary and the condition can be life-threatening. Infusion of clot-busting drugs (thrombolysis) is a useful tool in the management of acute limb ischaemia. Fibrinolytic drugs are used to disperse blood clots (thrombi) to clear arterial occlusion and restore blood flow. Thrombolysis is less invasive than surgery. A variety of techniques are used to deliver fibrinolytic agents. This is an update of a review first published in 2004.

Objectives

To compare the effects of infusion techniques during peripheral arterial thrombolysis for treatment of patients with acute limb ischaemia.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registries to 20 October 2020. We undertook reference checking to identify additional studies.

Selection criteria

We included all randomised controlled trials (RCTs) comparing infusion techniques for fibrinolytic agents in the treatment of acute limb ischaemia.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane. We assessed the risk of bias in included trials using the Cochrane 'Risk of bias' tool. We evaluated certainty of evidence using GRADE. For dichotomous outcomes, we calculated the odds ratio (OR) with the corresponding 95% confidence interval (CI). We were not able to carry out meta-analyses due to clinical heterogeneity, so we have reported the results and performed the comparisons narratively. The main outcomes of interest were amputation-free survival or limb salvage, amputation, mortality, vessel patency, duration of thrombolysis, and complications such as cerebrovascular accident and major and minor bleeding.

Main results

Nine studies with a total of 671 participants are included in this update. Trials covered a variety of infusion techniques, dosage regimens, and adjunctive agents. We grouped trials according to types of techniques assessed (e.g. intravenous and intra-arterial delivery of the agent, 'high-' and 'low-dose' regimens of the agent, continuous infusion and 'forced infusion' of the agent, use of adjunctive antiplatelet agents). We assessed the certainty of evidence as very low to low due to the limited power of individual studies to deliver clinically relevant results, small and heterogeneous study populations, use of different inclusion criteria by each study in terms of severity and duration of

ischaemia, considerably different outcome measures between trials, and use of different fibrinolytic agents. This heterogeneity prevented pooling of data in meta-analyses.

No regimen has been shown to confer benefit in terms of amputation-free survival (at 30 days), amputation, or death. For vessel patency, complete success was more likely with intra-arterial (IA) than with intravenous (IV) infusion (odds ratio (OR) 13.22, 95% confidence interval (CI) 2.79 to 62.67; 1 study, 40 participants; low-certainty evidence); radiological failure may be more likely with IV infusion (OR 0.02, 95% CI 0.00 to 0.38; 1 study, 40 participants; low-certainty evidence). Due to the small numbers involved in each arm and design differences between arms, it is not possible to conclude whether any technique offered any advantage over another. None of the treatment strategies clearly affected complications such as cerebrovascular accident or major bleeding requiring surgery or blood transfusion. Minor bleeding complications were more frequent in systemic (intravenous) therapy compared to intra-arterial infusion (OR 0.03, 95% CI 0.00 to 0.56; 1 study, 40 participants), and in high-dose compared to low-dose therapy (OR 0.11, 95% CI 0.01 to 0.96; 1 study, 63 participants).

Limited evidence from individual trials appears to indicate that high-dose and forced-infusion regimens reduce the duration of thrombolysis. In one trial, the median duration of infusion was 4 hours (range 0.25 to 46) for the high-dose group and 20 hours (range 2 to 46) for the low-dose group. In a second trial, treatment using pulse spray was continued for a median of 120 minutes (range 40 to 310) compared with low-dose infusion for a median of 25 hours (range 2 to 60). In a third trial, the median duration of therapy was reduced with pulse spray at 195 minutes (range 90 to 1260 minutes) compared to continuous infusion at 1390 minutes (range 300 to 2400 minutes). However, none of the studies individually showed improvement in limb salvage at 30 days nor benefit for the amputation rate related to the technique of drug delivery. Similarly, no studies reported a clear difference in occurrence of cerebrovascular accident or major bleeding. Although 'high-dose' and 'forced-infusion' techniques achieved vessel patency in less time than 'low-dose' infusion, more minor bleeding complications may be associated (OR 0.11, 95% CI 0.01 to 0.96; 1 study, 72 participants; and OR 0.48, 95% CI 0.17 to 1.32; 1 study, 121 participants, respectively). Use of adjunctive platelet glycoprotein IIb/IIIa antagonists did not improve outcomes, and results were limited by inclusion of participants with non-limb-threatening ischaemia.

Authors' conclusions

There is insufficient evidence to show that any thrombolytic regimen provides a benefit over any other in terms of amputation-free survival, amputation, or 30-day mortality. The rate of CVA or major bleeding requiring surgery or blood transfusion did not clearly differ between regimens but may occur more frequently in high dose and IV regimens. This evidence was limited and of very low certainty. Minor bleeding may be more common with high-dose and IV regimens.

In this context, thrombolysis may be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa) compared with surgery. Caution is advised for patients who do not have limb-threatening ischaemia (Rutherford grade I) because of risks of major haemorrhage, cerebrovascular accident, and death from thrombolysis.

PLAIN LANGUAGE SUMMARY

Infusion techniques for peripheral arterial thrombolysis

Background

Abrupt reduction in blood flow to a limb (acute limb ischaemia) usually is caused by a blood clot (thrombus) blocking an artery or a bypass graft. Severe acute ischaemia will lead to irreversible damage to muscles and nerves if blood flow is not restored in a few hours. Once irreversible damage occurs, amputation will be necessary and the condition can be life-threatening. Infusion of clot-busting drugs (thrombolysis) can restore blood flow by dispersing the clot; this approach is less invasive than open surgery.

Is any infusion technique for delivering thrombolysis better than another?

We wanted to know if any method of delivering clot-busting drugs offered greater benefit compared to another for important outcomes such as preventing amputation and death, restoring blood flow, and reducing length of time needed to deliver drugs; and if any technique caused greater harm than another (such as stroke or bleeding)?

How did we identify and evaluate the evidence?

First, we searched the medical literature for randomised controlled trials (RCTs) - clinical studies where people are randomly put into one of two or more treatment groups. This type of study provides the most robust evidence about effects of treatment. We then compared trial results and summarised the evidence from all studies. Finally, we assessed how certain the evidence was. To do this, we considered factors such as the way studies were conducted, study size, and consistency of findings across studies. Based on our assessments, we categorised the evidence as very low, low, moderate, or high certainty.

What did we find?

We found nine RCTs with a total of 671 participants with varying severity of ischaemia who were randomised to receive thrombolysis by different infusion techniques. These studies used very different trial designs, which prevented pooling of data. Two studies compared intra-arterial and intravenous drug delivery using different thrombolytic agents. Six studies compared high- and low-dose regimens, or

continuous infusion and forced-infusion (pulse spray) regimens. Studies provided no definition of what high or low dose was, used different agents with or without initial lacing of the clot with a high dose of the agent (bolus), and delivered agents into the artery or the thrombus. One study compared use of additional antiplatelet agents with thrombolysis.

Limited evidence of very low and low certainty from individual studies may indicate that greater benefit is seen when the thrombolytic agent is delivered into the thrombus: systemic intravenous thrombolysis is less effective than intra-arterial thrombolysis. 'High-dose' and 'forced-infusion' techniques, or use of adjunctive agents such as platelet glycoprotein IIb/IIIa inhibitors, may speed up thrombolysis, but these techniques are generally more labour-intensive and seem to be associated with increased bleeding complications compared to low-dose regimens, and there is no evidence that they lead to improved outcomes (e.g. lower amputation rates). 'Low-dose continuous infusion', following initial lacing of the thrombus with a high dose of the thrombolytic agent, is the least labour-intensive technique. Thrombolysis appears to be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa), but, because of risks of bleeding, stroke, and death, thrombolysis should be used with caution in patients who do not have limb-threatening ischaemia (Rutherford grade I). Regimens that decrease the time needed to restore blood flow may permit treatment of patients with immediately threatened limbs (Rutherford grade IIb).

More research is needed to confirm these findings.

How up-to date is this review?

Evidence in this Cochrane Review is current to 20 October 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Intra-arterial delivery compared to intravenous delivery for peripheral arterial thrombolysis

Is intra-arterial (IA) delivery or intravenous (IV) delivery of a thrombolytic agent more effective for patients with peripheral arterial thrombosis?

Patient or population: patients with < 30 days' limb ischaemia^a

Setting: hospital

Intervention: IA delivery of rt-PA

Comparison: IV delivery of rt-PA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intravenous	Risk with intra-arterial				
30-Day amputation-free survival	Study population		OR 1.71 (0.40 to 7.34)	40 (1)	⊕⊕⊕⊕ VERY LOW b,c,d	There was little or no effect on 30-day amputation-free survival in the IA group (14/20) compared to the IV group (16/20)
	700 per 1000	800 per 1000 (483 to 945)				
Amputation (up to 6 months)	See comment		-	78 (2)	⊕⊕⊕⊕ LOW d,e	We were unable to pool the studies due to clinical differences (differences in study population and time point amputation assessed). There was little or no effect on amputation rates in IV and IA groups in either study
30-Day mortality	See comment		-	78 (2)	⊕⊕⊕⊕ LOW d,e	We were unable to pool the studies due to clinical differences. No deaths occurred in either group in Saroukhani 2015 , and there was no clear difference in mortality between IV and IA groups in Berridge 1991
Vessel patency - radiological success - complete (to end of treatment)	Study population		OR 13.22 (2.79 to 62.67)	40 (1)	⊕⊕⊕⊕ LOW b,d	We were unable to pool the studies due to clinical differences. Berridge 1991 reported that complete success was more likely with IA than with IV. Saroukhani 2015 reported a higher rate of angiographic improvement in the CDT (IA) group compared to the IV group, but no data were available
	300 per 1000	850 per 1000 (545 to 964)				
Duration of thrombolysis	See comment		-	78 (2)	⊕⊕⊕⊕ VERY LOW d,e,f	We were unable to draw conclusions due to the heterogeneity of methods used. See Table 1



(to end of treatment)					
CVA (up to 6 months)	See comment	-	78 (2)	⊕○○○ VERY LOW c,d,e	Berridge 1991 reported 1 CVA event in the IV group; no events were reported in the IA group. Saroukhani 2015 reported that no major complications were experienced in IA or IV groups
Major bleeding (up to 6 months)	Study population 150 per 1000 21 per 1000 (2 to 309)	OR 0.12 (0.01 to 2.53)	40 (1)	⊕○○○ VERY LOW b,c,d	Major bleeding may occur more frequently in the IV group (3/20) compared to the IA group (0/20), but the 95% CI indicates there may be no difference

***The risk in the intervention group** (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).

CDT: catheter-directed thrombolysis; **CI:** confidence interval; **CVA:** cerebrovascular accident; **IA:** intra-arterial; **IV:** intravenous; **OR:** odds ratio; **rt-PA:** recombinant tissue plasminogen activator.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aStudies differed in the acute thrombotic arterial insufficiency population included.

- [Berridge 1991](#): < 30 days' critical ischaemia of the limb.
- [Saroukhani 2015](#): < 14 days' acute lower limb ischaemia.
- See [Characteristics of included studies](#).

^bWe downgraded one step for risk of bias concerns ([Berridge 1991](#); no blinding of personnel or outcome assessors).

^cWe downgraded one step for inconsistency (wide confidence intervals).

^dWe downgraded one step for imprecision (small numbers of participants with low total event rates).

^eWe downgraded one step for risk of bias concerns ([Berridge 1991](#); no blinding of personnel or outcome assessors; [Saroukhani 2015](#); other bias concerns).

^fWe downgraded one step for inconsistency (different methods of thrombolysis).

Summary of findings 2. High-dose compared to low-dose regimens of thrombolytic agents

Is high-dose or low-dose delivery of a thrombolytic agent more effective for patients with peripheral arterial thrombosis?

Patient or population: patients with < 42 days' limb ischaemia^a

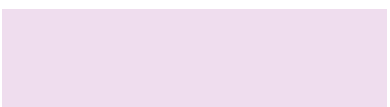
Setting: hospital

Intervention: high-dose thrombolytics

Comparison: low-dose thrombolytics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose thrombolytics	Risk with high-dose thrombolytics				
30-Day amputation-free survival	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. True salvage cannot be calculated given the inclusion of patients with viable limbs and differing severity of disease
Amputation (follow-up ranged from 30 days to over 1 year)	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in rates of amputation between any of low- or high-dose groups
30-Day mortality	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in mortality between any of low- or high-dose groups
Vessel patency (at end of treatment)	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. Studies used different ways to measure clot lysis. Individual studies showed little or no difference in patency between groups
Duration of thrombolysis (to end of treatment)	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to draw conclusions due to the heterogeneity of methods used. See Table 2
CVA (follow-up ranged from 30 days to over 1 year)	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. When reported, little or no effect on CVA events was detected in the individual studies
Major bleeding	See comment		-	302 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in major bleeding events between low- or high-dose groups

(follow-up ranged from 30 days to over 1 year)



***The risk in the intervention group** (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; **CVA:** cerebrovascular accident.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aStudies differed in the acute thrombotic arterial insufficiency population included.

- Braithwaite 1997: < 30 days' acute ischaemia of the lower limb.
- Cragg 1991: acute and chronic ischaemia.
- Plate 2006: < 30 days' acute and sub-acute lower limb ischaemia.
- Yusuf 1995: < 42 days' lower limb ischaemia.
- See [Characteristics of included studies](#).

^bWe downgraded one step due to risk of bias concerns (Braithwaite 1997; Cragg 1991; unclear or high risk of selection bias; Braithwaite 1997; Cragg 1991; Plate 2006; Yusuf 1995: no blinding of personnel or outcome assessors).

^cWe downgraded one step due to inconsistency (clinical heterogeneity between studies prevented meta-analysis).

^dWe downgraded one step due to indirectness (studies included participants with varying severity of disease).

^eWe downgraded two steps due to inconsistency (clinical heterogeneity between studies prevented meta-analysis; different thrombolysis methods and different ways to measure outcomes).

Summary of findings 3. Continuous infusion compared to forced (or pulse) infusion of thrombolytic agents

Is conventional continuous infusion or forced/pulse infusion delivery of a thrombolytic agent more effective for patients with peripheral arterial thrombosis?

Patient or population: patients with less than 42 days' lower limb ischaemia^a

Setting: hospital

Intervention: continuous infusion

Comparison: forced (or pulse) infusion

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Nº. of participants (studies)	Certainty of the evidence (GRADE)	Comments
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	Risk with forced infusion	Risk with continuous infusion				
30-Day amputation-free survival	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. True salvage cannot be calculated given the inclusion of patients with viable limbs and differing severity of disease	
Amputation (follow-up to 30 days)	See comment	-	164 (3)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in rates of amputation between continuous and forced infusion groups	
30-Day mortality	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,c,d}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in mortality between continuous and forced infusion groups	
Vessel patency (up to 30 days)	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. Individual studies showed little or no difference in patency between continuous and forced infusion groups	
Duration of thrombolysis (to end of treatment)	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to draw conclusions due to the heterogeneity of methods used. See Table 3 and Table 4	
CVA (follow-up to 30 days)	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. When reported, little or no effect on CVA events was detected in the individual studies	
Major bleeding (follow-up to 30 days)	See comment	-	304 (4)	⊕○○○ VERY LOW ^{b,e}	We were unable to pool data due to heterogeneity between studies. When reported, no clear difference in major bleeding was detected between groups in the individual studies	

***The risk in the intervention group** (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; **CVA:** cerebrovascular accident.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aStudies differed in the acute thrombotic arterial insufficiency population included.

- Braithwaite 1997: < 30 days' acute ischaemia of the lower limb.
- Comerota 2019: < 14 days' limb ischaemia.
- Cragg 1991: acute and chronic ischaemia.
- Kandarpa 1993 < 30 days' limb ischaemia.
- Plate 2006: < 30 days' acute and sub-acute lower limb ischaemia.
- Yusuf 1995: < 42 days' lower limb ischaemia.
- See [Characteristics of included studies](#).

^bWe downgraded one step due to risk of bias concerns (Kandarpa 1993; Plate 2006; Yusuf 1995: no blinding of personnel or outcome assessors).

^cWe downgraded one step due to inconsistency (clinical heterogeneity between studies prevented meta-analysis).

^dWe downgraded one step due to indirectness (studies included participants with varying severity of disease).

^eWe downgraded two steps due to inconsistency (clinical heterogeneity between studies prevented meta-analysis; different thrombolysis methods and different ways to measure outcomes).

Summary of findings 4. Thrombolysis with or without adjunctive antiplatelet agents

Is the use of adjunctive antiplatelet agents with thrombolysis more effective for patients with peripheral arterial thrombosis?

Patient or population: patients with less than 42 days' lower limb ischaemia

Setting: hospital

Intervention: IA urokinase with adjunctive abciximab

Comparison: IA urokinase with placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk without adjunctive antiplatelet agents	Risk with adjunctive antiplatelet agents				
30-Day amputation-free survival	See comment		-	70 (1)	-	30-Day survival was not reported

Amputation (follow-up to over 1 year)	See comment	-	70 (1)	-	This could not be calculated from the data provided
30-Day mortality	See comment	-	70 (1)	-	This could not be calculated from the data provided
Vessel patency (follow-up over 1 year)	Study population 770 per 1000 801 per 1000 (566 to 925)	OR 1.20 (0.39 to 3.69)	70 (1)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	The authors' definition of patency does not clearly distinguish between the presence of thrombus and any underlying stenosis There was little or no difference in patency between treatment groups
Duration of thrombolysis (follow-up to end of treatment)	See comment	-	70 (1)	⊕⊕⊕⊕ LOW ^{a,b}	The median duration of thrombolysis was 120 minutes for each group
CVA (follow-up to over 1 year)	See comment	-	70 (1)	⊕⊕⊕⊕ LOW ^{a,b}	None was reported
Major bleeding (follow-up to over 1 year)	Study population 80 per 1000 21 per 1000 (1 to 299)	OR 0.25 (0.01 to 4.9)	70 (1)	⊕⊕⊕⊕ VERY LOW ^{a,b,d}	No evidence showed a difference between groups

***The risk in the intervention group** (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; **CVA:** cerebrovascular accident; **IA:** intra-arterial; **OR:** odds ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aWe downgraded one step due to risk of bias concerns (Duda 2001; baseline differences between groups).

^bWe downgraded one step due to imprecision (one small study and low event rate).

^cWe downgraded one step due to indirectness (definition of outcome does not differentiate between thrombosis and stenosis).

^dWe downgraded one step due to inconsistency (wide confidence intervals).

BACKGROUND

Description of the condition

Acute limb ischaemia (ALI) results from an abrupt reduction in blood flow to a limb. It usually is caused by a blood clot (thrombosis) that forms in a diseased artery or a bypass graft (Norgren 2007). A less common cause is embolic occlusion, which is caused by a blood clot that is carried in the circulation until it lodges in a peripheral artery. These thrombi have usually formed in the heart before breaking off into the bloodstream. Clinical manifestations of ALI vary depending on the magnitude of blood flow reduction. For example, occlusion of a small branch vessel may be asymptomatic. A greater degree of ischaemia will result in onset of cramp-like calf pain during exercise (intermittent claudication). Acute arterial occlusion in a patient with pre-existing claudication may cause little change in symptoms due to the presence of established collateral circulation. More significant ischaemia leads to pain at rest, and ischaemic damage to nerves and muscles leads to paraesthesia, loss of sensation, and finally paralysis. Severe ischaemia leads to tissue death requiring amputation, if flow is not promptly restored (Norgren 2007).

Description of the intervention

Interventions for ALI are aimed at restoring arterial flow within the limb. A range of treatment options are available, depending on the severity of the ischaemia. Immediate surgery is recommended for immediately threatened limbs (embolectomy, thrombectomy, bypass grafting), and amputation may be required when restoring blood flow to the limbs is not possible. This review focuses on patients whose symptoms require an intervention to relieve severe symptoms or to prevent amputation, when the limb is not immediately threatened. For these patients, revascularisation using peripheral arterial thrombolysis to restore blood flow is the standard treatment (Creager 2012).

How the intervention might work

Peripheral arterial thrombolysis is the process of using fibrinolytic drugs to dissolve occluding thrombi. Thrombolysis has become established as a useful tool in the management of ALI and offers an alternative to open surgery (Darwood 2018). It is particularly useful for those cases of less than two weeks' duration (STILE 1994). Although data from randomised controlled studies are not extensive, much has been learned about indications, risks, and benefits of thrombolysis. Different thrombolytic agents have been used and are the topic of a separate review (Robertson 2013). This review focuses on infusion techniques of drug administration for thrombolysis.

Originally, peripheral arterial thrombolysis was performed via intravenous administration with relatively high doses of the drug used to achieve therapeutic levels at the site of arterial occlusion (blockage). Subsequently, delivery of low doses of the drug directly into the thrombus became more popular (Dotter 1974). This aimed to achieve higher local drug concentrations with a smaller total dose. Success rates appeared much improved and complication rates became more acceptable. In an attempt to achieve faster thrombolysis, high-dose infusions (McNamara 1984), initial high-dose bolus (Sullivan 1989), and forced-injection techniques such as 'pulse spray' were developed (Kandarpa 1988). Forced-infusion techniques use special catheters with multiple side holes to inject the fibrinolytic agent at high pressure, with the intention that the

drug will penetrate deep into the thrombus. Relatively few studies have compared these different techniques, and much debate concerning the optimal method of drug delivery continues (Kessel 2004). Platelets are an important part of the blood clotting cascade, and using adjunctive medication to prevent platelet aggregation and activation may help prevent clot propagation while speeding dissolution (Braithwaite 1995). Percutaneous mechanical devices for aspiration, rheolysis, mechanical fragmentation, and ultrasonography-assisted fibrinolysis are sometimes used independently or in addition to thrombolysis (Rodgers 2007). It is thought that these shorten the duration of therapy, but data comparing these devices are limited (Araujo 2019).

Why it is important to do this review

Patients with ALI are often elderly and may have significant comorbidities. This review presents available evidence regarding which infusion technique is more effective for initial management of ALI by restoring blood flow rapidly with minimal adverse effects.

OBJECTIVES

To compare the effects of infusion techniques during peripheral arterial thrombolysis for treatment of patients with acute limb ischaemia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in which participants were randomly allocated to receive peripheral arterial thrombolysis by different techniques. The type of thrombolytic agent used was not of interest because that is the topic of a separate Cochrane Review (Robertson 2013).

Types of participants

We included studies involving patients with limb-threatening acute limb ischaemia (ALI; Rutherford classification grade IIa or worse) treated with peripheral arterial thrombolysis to restore vessel patency following acute thromboembolic occlusion of a native peripheral artery, or a lower limb arterial bypass graft. We excluded studies including only grade I patients. We included studies involving grade I/IIa/IIb patients, provided most participants were grade II. Patients were included regardless of diabetic status, use of aspirin or anticoagulation post thrombolysis, or use of concurrent heparin.

Only studies that included patients with 'limb-threatening' ischaemia were considered (i.e. those with Rutherford classification grade IIa or worse). Patients with grade I ischaemia (viable limb) may benefit from therapy to improve the circulation but are unlikely to require amputation if left untreated. In patients with grade I ALI, there is usually no urgency to intervene unless there is a desire to salvage a thrombosed arterial bypass graft. This distinction is important, as many operators consider risks of thrombolysis to outweigh the benefits for patients with intermittent claudication and would defer treatment for a few weeks to allow the thrombus to mature and reduce the risk of embolisation (Braithwaite 1999).

Infusion techniques for peripheral arterial thrombolysis (Review)

We excluded studies of patients with occluded arteriovenous dialysis fistulae and deep vein thrombosis, as these conditions do not compromise limb blood flow.

Types of interventions

We considered the following regimens with any thrombolytic.

- Intravenous infusions.
- Intra-arterial infusions.
- Low-dose infusions.
- High-dose bolus regimens.
- Forced-infusion techniques (when the drug is administered intermittently in high-pressure pulses intended to force the agent into the thrombus, e.g. pulse spray).
- Adjunctive drugs.

Types of outcome measures

Primary outcomes

- 30-Day amputation-free survival or limb salvage (freedom from death or amputation (major or minor) at 30 days)
- Amputation
- Mortality

Secondary outcomes

- Vessel patency
- Duration of thrombolysis
- Complications (including cerebrovascular accident (CVA), minor and major haemorrhage, distal embolisation)

Search methods for identification of studies

Electronic searches

For this update, the Cochrane Vascular Information Specialist first searched the following databases for relevant trials on 15 October 2015.

- Cochrane Vascular Specialised Register.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 10), in the Cochrane Library, via the Cochrane Register of Studies Online.

See [Appendix 1](#) for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Information Specialist subsequently conducted further systematic searches of the following databases for RCTs and controlled clinical trials without language, publication year, or publication status restrictions.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS Web, searched on 20 October 2020).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, Cochrane Register of Studies Online (CRSO 20 October 2020, Issue 9).
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (searched from 1 January 2017 to 20 October 2020).
- Embase Ovid (searched from 1 January 2017 to 20 October 2020).

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ebsco (searched from 1 January 2017 to 20 October 2020).
- Allied and Complementary Medicine Database (AMED) Ovid (searched from 1 January 2017 to 20 October 2020).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. When appropriate, these strategies were combined with adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6; [Lefebvre 2011](#)). Search strategies for major databases are provided in [Appendix 1](#).

The Information Specialist searched the following trials registries on 20 October 2020.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We checked the reference lists of included studies for additional articles.

Data collection and analysis

Selection of studies

For this update, review authors assessed citations retrieved by the search strategies for reports of relevant RCTs. We assessed articles identified by the searches using Covidence software ([Covidence](#)). Initial screening was carried out by one review author, or with review author support, and non-relevant articles were removed (DK, IR, CB, or MS). Potentially relevant, full-text articles were then assessed independently by two review authors, or with review author support (DK, IR, JP, CB, or MS), according to the [Criteria for considering studies for this review](#). We listed all studies excluded after full-text assessment and reasons for their exclusion in a [Characteristics of excluded studies](#) table. We constructed a PRISMA diagram to illustrate the study selection process. We resolved disagreements by discussion.

Data extraction and management

Data were extracted independently by DK or CB, and were cross-checked by IR or JP. Any discrepancies were resolved by discussion. The following information was collected.

- Participants: age, sex distribution.
- Severity of ischaemia: ankle brachial index (ABI), European Consensus definition of critical ischaemia ([Consensus Document](#)), Fontaine classification ([Fontaine 1954](#)), Ad Hoc Committee Recommendations ([Rutherford 1986](#)), Society of Interventional Radiology Standards for Patients With Acute Limb Ischaemia ([SIR standards](#)).
- Outcome measures: amputation-free survival or limb salvage, amputation, death, vessel/graft patency, duration of thrombolysis, complications (cerebrovascular accident (CVA), minor and major haemorrhage, distal embolisation).

Assessment of risk of bias in included studies

Two review authors (two of CB, JP, DK) independently assessed methodological quality of included trials using Cochrane's 'Risk of bias' tool and discussed assessment to reach agreement. Assessment of risk of bias in included studies was undertaken in accordance with recommendations described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These comprise a description and a judgement (low risk, high risk, or unclear risk) for each domain in a risk of bias table. Each entry addresses a specific feature of the study.

- Sequence generation.
- Allocation concealment.
- Blinding.
- Incomplete outcome data.
- Selective reporting.
- Any other bias.

Measures of treatment effect

Measures of effect for dichotomous data were estimated as odds ratios (ORs) and were calculated with 95% confidence intervals (CIs). For continuous data (duration of thrombolysis), we intended to calculate mean differences (MDs) or standardised mean differences (SMDs). Trials used different angiographic endpoints (e.g. estimated clearing of thrombus, restoration of flow, patent to next branch vessel). In addition, frequency of angiographic assessment often differed greatly between control and study groups. This prevented statistical analysis of the outcome 'duration of thrombolysis'.

Unit of analysis issues

In Cragg 1991, 63 patients had 72 episodes of thrombolysis. These represented recurrent thrombosis, and data analysis for this study uses the number of episodes of thrombolysis. In the remaining studies, participants were the unit of analysis. Data from Cragg 1991 were combined only in analyses for complications.

Dealing with missing data

We intended to contact trial authors to request further information when we noted substantial missing data. As no substantial data were missing, we did not contact trial authors to make this request. We did contact these authors to request clarification over unclear and inconsistent reporting (Saroukhani 2015).

Assessment of heterogeneity

We assessed clinical heterogeneity by inspecting individual study characteristics. When possible, we also investigated heterogeneity amongst trials by visually assessing forest plots and CIs and by using the I^2 statistic (we considered $I^2 \geq 50\%$ as showing substantial heterogeneity).

Assessment of reporting biases

We intended to use funnel plots for publication bias if more than 10 trials were included in a meta-analysis (Higgins 2011); however, as insufficient trials were available, we could not do this. We carefully assessed all individual studies to look for selective reporting bias.

Data synthesis

We had planned to carry out meta-analysis using a fixed-effect model when heterogeneity was low (determined by I^2 statistic $< 50\%$), or a random-effects model when substantial heterogeneity was present (I^2 statistic $\geq 50\%$). We reported data using Review Manager 5 (Review Manager 2020). When data could not be pooled due to heterogeneity between trials, we reported and discussed results narratively.

Subgroup analysis and investigation of heterogeneity

For most comparisons, subgroup analysis was not possible because data were insufficient. Such an analysis will be carried out for future versions of this review if data are available. We were able to carry out subgroup analysis on Comerota 2019. We investigated effects on outcomes due to use of a balloon occlusion catheter and duration of the thrombolysis procedure.

Sensitivity analysis

We did not carry out sensitivity analysis, as we identified insufficient trials.

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables to present the findings of this review for the comparisons 'Intra-arterial delivery compared to intravenous delivery for peripheral arterial thrombolysis' (Summary of findings 1); 'High-dose compared to low-dose regimens of thrombolytic agents' (Summary of findings 2); 'Continuous infusion compared to forced (or pulse) infusion of thrombolytic agents' (Summary of findings 3); and 'Thrombolysis with or without adjunctive antiplatelet agents' (Summary of findings 4). We selected the most important and most clinically relevant outcomes (both desirable and undesirable) thought to be essential for decision-making for each 'Summary of findings' table. These include the following.

- 30-Day amputation-free survival or limb salvage.
- Amputation.
- 30-Day mortality.
- Vessel patency.
- Duration of thrombolysis.
- CVA.
- Major bleeding.

We used the system developed by the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) for grading the certainty of evidence as high, moderate, low, and very low, based on within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of population bias (GRADE 2004).

RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.

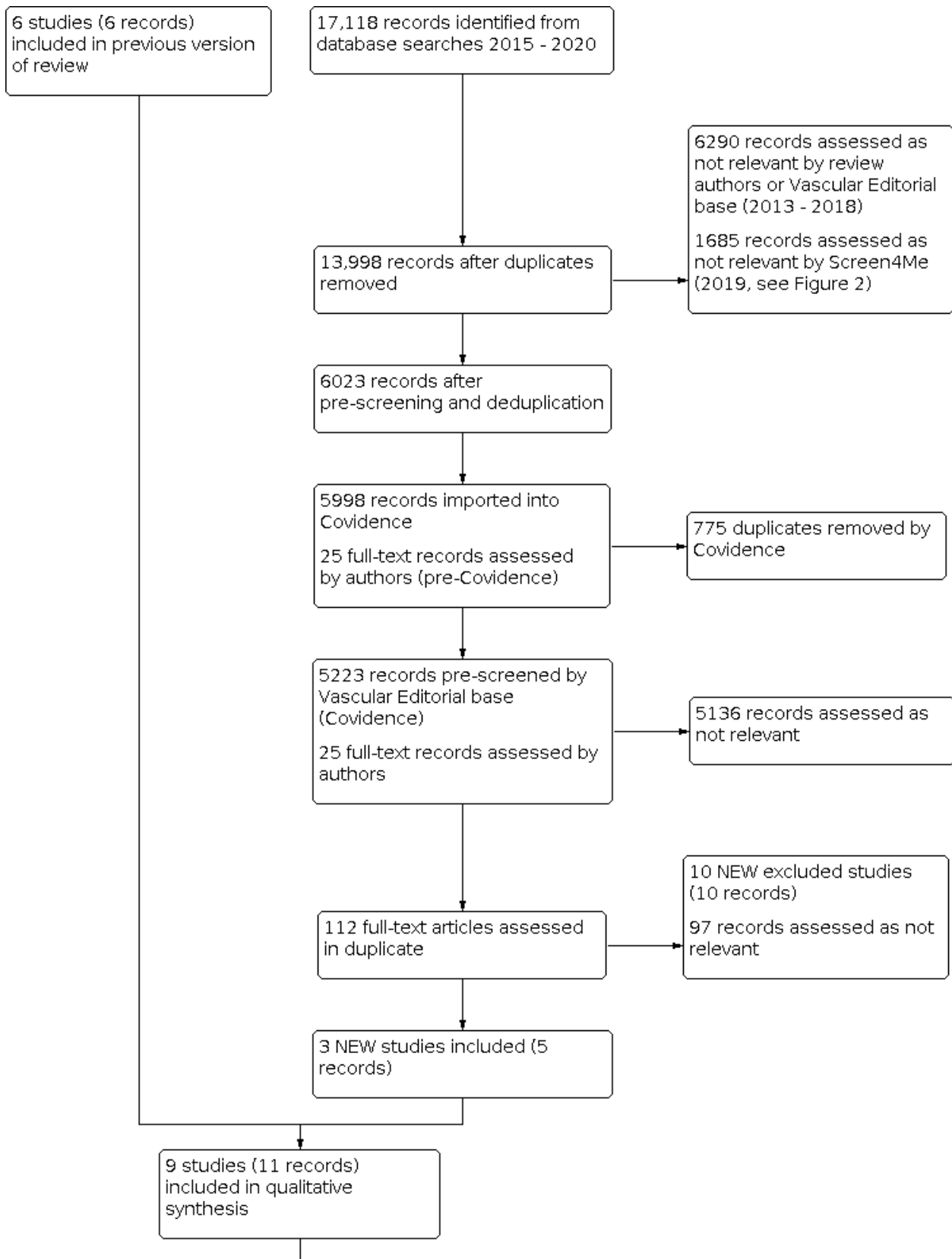
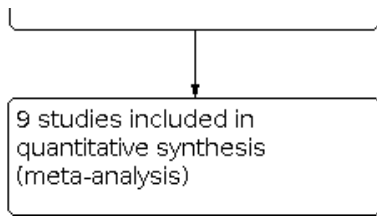


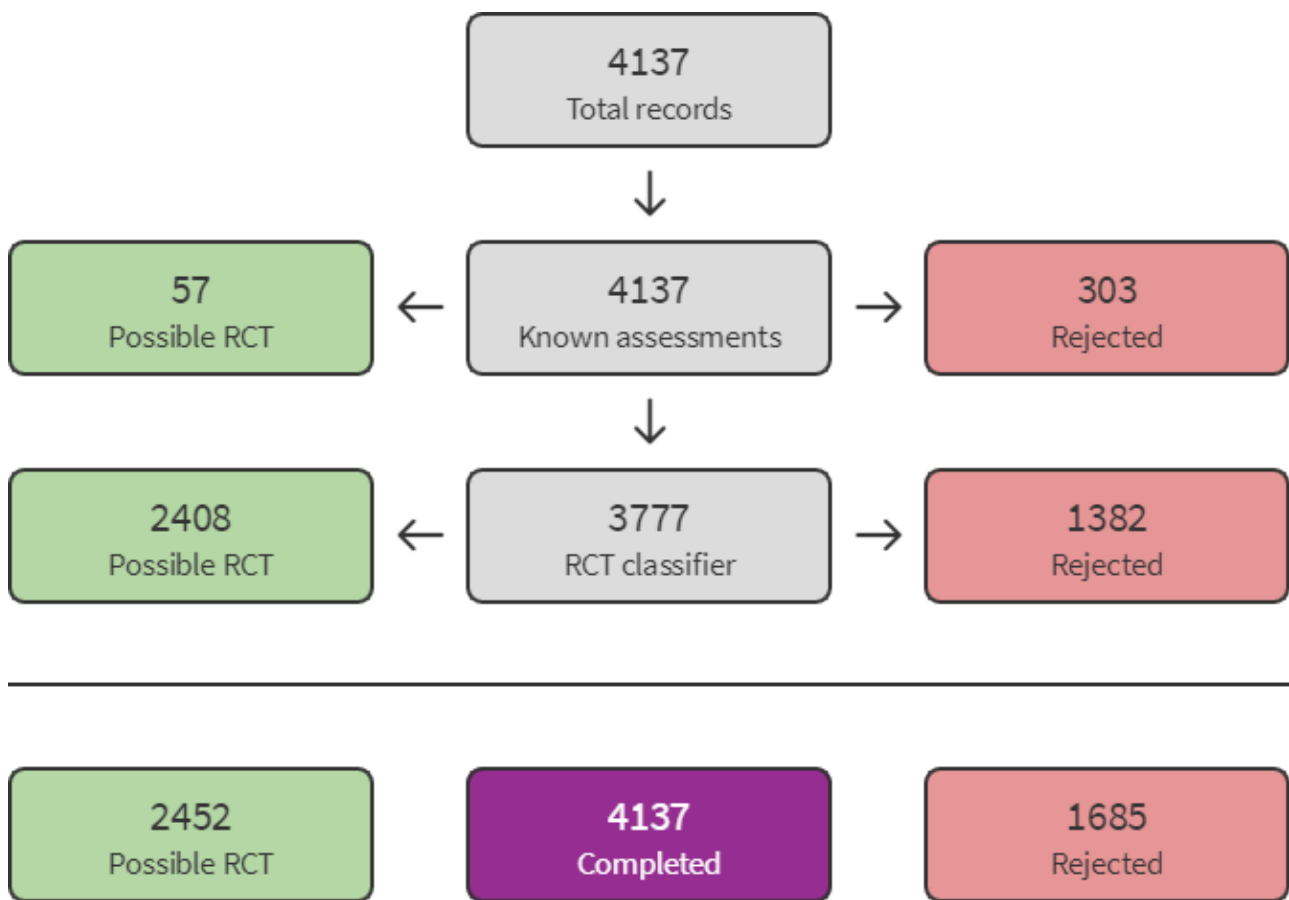
Figure 1. (Continued)



Several searches were carried out since the previous version of this review was published (Kessel 2004). For searches to 2015, results were pre-screened by the editorial base. We used Cochrane's Screen4Me workflow to help identify potential reports of RCTs in 2019. Results of the Screen4Me assessment process are shown in

Figure 2. We then assessed the remaining 2452 'possible' records identified by Screen4Me using Covidence (covidence.org). We also used Covidence to screen search results from additional top-up searches.

Figure 2. Screen4Me flow diagram.



Included studies

See the [Characteristics of included studies](#) table for further details.

We included three additional trials in this update (Comerota 2019; Plate 2006; Saroukhani 2015), making a total of nine RCTs with 671 participants that fulfilled the inclusion criteria for this review (Berridge 1991; Braithwaite 1997; Comerota 2019; Cragg 1991; Duda 2001; Kandarpa 1993; Plate 2006; Saroukhani 2015; Yusuf 1995). These trials covered a variety of thrombolytics, infusion techniques, dosage regimens, and adjunctive agents. Kandarpa

1993 and Yusuf 1995 compared the same techniques but used different thrombolytic agents.

Most of these trials were small and individually had limited power, with the smallest trial involving 25 participants (Kandarpa 1993), and the largest 174 (Comerota 2019). Plate 2006 intended to recruit 590 patients but was stopped prematurely due to low recruitment rates, with only 121 patients, and as a result was underpowered. Trials were carried out internationally, with participants recruited in Belgium, Bulgaria, Czech Republic, Germany, India, Iran, Peru,

Poland, Romania, Serbia, Slovakia, Sweden, the UK, Ukraine, and the USA. All studies, except Yusuf 1995, reported numbers of males and females, with a total of 383 men and 164 women included. The mean age of participants ranged from 54 years in Saroukhani 2015 to 72 years in Plate 2006. Comerota 2019 provided mean ages for subgroups, from which we calculated the overall mean age to be 64 years.

There were considerable differences in the clinical status of patient groups and in lesion characteristics in the included studies.

The term 'acute limb ischaemia (ALI)' is ill defined, encompassing both speed of onset and duration of symptoms. Both are likely to have an impact on prognosis. For example, consider a patient with pre-existing intermittent claudication (IC) on the basis of peripheral arterial disease (PAD) compared with a patient with normal arteries who experiences an embolus. The former may experience a sudden decrease in walking distance if the superficial femoral artery occludes due to in situ thrombosis, but the limb is likely to be viable. Conversely, if the latter experiences an embolus to the superficial femoral artery, the abrupt reduction in blood flow will not be compensated and the patient will require prompt revascularisation to avoid irreversible ischaemia requiring amputation. Thus patients with acute onset of ischaemia due to occlusion of the superficial femoral artery can have vastly different prognoses.

We have noted considerable heterogeneity among participant groups assessed within the reported trials in terms of severity and duration of ischaemia. Most of these studies included some participants with intermittent claudication (grade I ischaemia) (Rutherford 1986); only Saroukhani 2015 clearly included only participants with Rutherford grade IIa and IIb. Patients with grade I ischaemia may require treatment for symptomatic relief, but they will not have limb-threatening ischaemia (i.e. they are not at risk of amputation). The greater the proportion of participants with intermittent claudication, the greater the risk of bias if amputation rates and amputation-free survival are used as outcome measures. The same is true when outcomes for participants with chronic limb ischaemia (arbitrarily defined as > 14 days' duration) are considered; these patients have survived the immediate threat of the "acute ischaemic insult". They are effectively "stable", although those with critical ischaemia (rest pain and tissue loss) have high risks of amputation and death within one year. Both Comerota 2019 and Saroukhani 2015 used 14 days of symptoms as an inclusion criterion, with most included studies stating up to 30 days were required for inclusion (Berridge 1991; Braithwaite 1997; Kandarpa 1993; Plate 2006). Cragg 1991 included participants with acute and chronic ischaemia, Plate 2006 included participants with acute and sub-acute lower limb ischaemia, and Duda 2001 and Yusuf 1995 included participants with ischaemia of duration up to 42 days.

Differences in prognosis are associated with native arterial and bypass graft occlusion, with the latter usually more responsive to thrombolysis.

Kandarpa 1993 included mainly patients with graft occlusion (21/25, 84%), but in Yusuf 1995, patients mainly had native arterial occlusion (14/18, 78%) and the Berridge 1991 cohort comprised only those with native arteries. Berridge 1991 included only patients with critical limb ischaemia, with average occlusion length of 15 cm; in Braithwaite 1997, 20% (19/93) of patients had IC; and the other studies included some patients with non-

critical ischaemia. In the PROMPT study (Duda 2001), 40% of the treatment group were claudicants compared to only 15% in the control group. Saroukhani 2015 reported the cause of ALI to be embolism from another source in four participants and thrombosis in the remaining ones. Plate 2006 included occlusions of embolic origin and accepted in situ thromboses of native vessels and vascular grafts. Thirty-five patients had occluded grafts (30 with synthetic and five with autogenous graft material) in an aorto-iliac (8), femoropopliteal (22), or tibial (5) position (Plate 2006). Comerota 2019 accepted thrombosed bypass grafts or native arteries, provided occlusion occurred more than one month after synthetic graft or six months after autologous graft placement.

Different doses of different thrombolytic agents, various outcome measures, and different definitions of success were used in the different studies. Five studies used recombinant tissue plasminogen activator (rt-PA) (Berridge 1991; Braithwaite 1997; Plate 2006; Saroukhani 2015; Yusuf 1995), and three studies used urokinase (UK) (Cragg 1991; Duda 2001; Kandarpa 1993). One study used plasmin (Comerota 2019).

Inclusion and exclusion criteria were described in all trials, but it was not always possible to discriminate between patients with differing severity of ischaemia.

Included studies used different outcome measures. Berridge 1991; Braithwaite 1997; Comerota 2019; Cragg 1991; Kandarpa 1993; Saroukhani 2015; and Yusuf 1995 had clearly defined outcome measures. Duda 2001 used a composite endpoint of avoidance of surgical revascularisation or amputation and a secondary endpoint of rate of thrombolysis per centimetre of thrombus. Plate 2006 allocated a score of zero to five based on clinical outcome, from no additional treatment (0) to death (5).

Most studies had a follow-up period of 30 days (Braithwaite 1997; Cragg 1991; Comerota 2019; Kandarpa 1993; Plate 2006; Yusuf 1995); Berridge 1991 reported follow-up to three months, Saroukhani 2015 six months, and Duda 2001 one year.

Trials comparing intra-arterial and intravenous delivery of the agent

Berridge 1991 compared intravenous (IV) rt-PA (variable dose 1 to 10 mg/h) with intra-arterial (IA) rt-PA (0.5 mg/h) and IA streptokinase (5000 U/h) in 60 patients with critical ischaemia of the limb of less than 30 days' duration. Only the comparison of IV and IA rt-PA is considered in this review.

Saroukhani 2015 compared IV alteplase infusion (0.6 mg/kg, 20% as initial bolus) over 2 hours with IA alteplase (5-mg bolus, then 0.05 mg/kg/h every 2 hours) for 24 hours in 38 patients with grade IIa and IIb ALI, with symptoms less than 14 days and absence of distal runoff. Both regimens were repeated the day after, if improvement was seen in peripheral circulation assessment parameters.

Trials comparing high- and low-dose regimens of the thrombolytic agent

No threshold for low or high dose of a thrombolytic agent has been clearly defined. Different studies used different agents and a variety of treatment regimens.

Braithwaite 1997 compared IA continuous low-dose infusion (CIF) of rt-PA (0.5 mg/h or 1 mg/h) with IA high-dose bolus infusion (3 ×

5 mg, then, if needed, infusion at 3.5 mg/h) in 100 patients with ALI of up to 30 days' duration.

Cragg 1991 compared intra-thrombus high-dose UK (bolus of 250,000 U, followed by IA infusion of 250,000 U/h for 4 hours, then 125,000 U/h) and low-dose (bolus of 50,000 U, followed by 50,000 U/h) infusions of UK in 63 patients with a mix of acute and chronic lower limb ischaemia.

Plate 2006 compared high-dose, intra-thrombus forced periodic (pulse spray) infusion of rt-PA (0.33 mg/mL, 2 pulses of 0.13 mg (0.4 mL)/min for up to 2 hours) with low-dose infusion of rt-PA (initial intra-thrombus bolus of 0.25 mg (2.5 mL), then continuous infusion of 0.5 mg (5 mL)/h up to 48 hours plus 600 U/h of heparin) in 121 patients with "sudden onset of unilateral lower limb ischaemia within 30 days". The low dose was delivered by continuous infusion, and the high dose by forced periodic infusion (i.e. dosage and technique differed in the two study groups).

Yusuf 1995 compared IA continuous low-dose infusion (CIF) of rt-PA (0.5 mg/h) with high-dose pulse spray rt-PA (0.33 mg/mL: 0.2 mL every 15 seconds for the first 15 minutes, then every 30 seconds) in 18 patients with lower limb ischaemia of up to 42 days' duration. The low dose was delivered by continuous infusion, and the high dose by forced periodic infusion (i.e. dosage and technique differed in the two study groups).

Trials comparing continuous infusion with forced infusion or pulse spray of the agent

Kandarpa 1993 compared forced infusion (intra-thrombus bolus of UK (25,000 IU/10-cm thrombus), then intra-thrombus pulse spray of UK (10,000 U/mL)) with continuous infusion (CIF) (intra-thrombus bolus (25,000 IU/10 cm thrombus), then slow intra-thrombus UK 3000 U/mL). Overall, UK was used at equivalent dose rates, and the study population included 25 patients with lower limb ischaemia of up to 30 days' duration.

Comerota 2019 compared multiple treatment arms and three separate randomisation cohorts, with eight groups (155 patients) in total receiving IA CIF of 150 mg plasmin. Patients had Society of Vascular Surgery acute ischaemia categories I and IIa of up to 2 weeks' duration. In the first randomised cohort, of the four groups receiving plasmin, three had initial pulse spray infusion and one did not. Three groups had 5-hour infusions (10, 15, and 30 mL/h), and one group had a 2-hour infusion (35 mL/h). This cohort also included two control groups - receiving rt-PA or placebo. Of the other two cohorts, neither had initial pulse spray. Cohort 2 had two groups receiving CIF over 5 and 2 hours, at 60 and 75 mL/h,

respectively. Cohort 3 had two groups receiving CIF over 5 and 2 hours, at 30 and 35 mL/h, respectively, with both groups having an additional distal balloon occlusion catheter placed. A fourth cohort reported by the study authors, comprising a single group, was not of interest to this review, as it involved participants who were not randomised.

Plate 2006 compared high-dose, intra-thrombus forced infusion of rt-PA (0.33 mg/mL, 2 pulses of 0.13 mg (0.4 mL)/min for up to 2 hours) with low-dose continuous infusion of rt-PA (initial intra-thrombus bolus of 0.25 mg (2.5 mL), then continuous infusion of 0.5 mg (5 mL)/h until thrombolysis complete or 48 hours plus 600 U/h of heparin) in 121 patients with "sudden onset of unilateral lower limb ischaemia within 30 days". The low dose was delivered by continuous infusion, and the high dose by forced periodic infusion (i.e. dosage and technique differed in the two study groups).

Yusuf 1995 compared IA CIF of rt-PA (0.5 mg/h) with high-dose pulse spray rt-PA (0.33 mg/mL: 0.2 mL every 15 seconds for the first 15 minutes, then every 30 seconds) in 18 patients with lower limb ischaemia of up to 42 days' duration. The low dose was delivered by continuous infusion and the high dose by forced periodic infusion (i.e. dosage and technique differed in the two study groups).

Trials comparing thrombolysis with or without adjunctive antiplatelet agents

Duda 2001 compared an adjunctive antiplatelet agent (abciximab, IV bolus abciximab 0.25 mg/kg, then IV infusion of abciximab) followed by IA pulse spray UK (bolus of 25,000 U/10 cm of thrombus, then infusion of 4000 U/m for 2 hours, then 2000 IU/m for a further 2 hours if needed) with IV 0.9% saline plus initial IA pulse spray bolus of UK 25,000 U/10 cm of thrombus, then infusion of 4000 IU/m for 2 hours, then 2000 IU/m for a further 2 hours if needed.

Excluded studies

We excluded 10 additional trials from this update ([Bagan 2013](#); [Han 2009a](#); [Han 2009b](#); [Marder 2012](#); [NCT00073554](#); [NCT00115999](#); [NCT02093468](#); [Verhamme 2012](#); [Yuan 2013](#); [Zhang 2014](#)), bringing the total to 13 excluded studies ([Bagan 2013](#); [Han 2009a](#); [Han 2009b](#); [Marder 2012](#); [NCT00073554](#); [NCT00115999](#); [NCT02093468](#); [Poredos 1999](#); [Schweizer 2000](#); [Schweizer 2003](#); [Verhamme 2012](#); [Yuan 2013](#); [Zhang 2014](#)). See the [Characteristics of excluded studies](#) table for details.

Risk of bias in included studies

See [Figure 3](#) and [Figure 4](#).

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

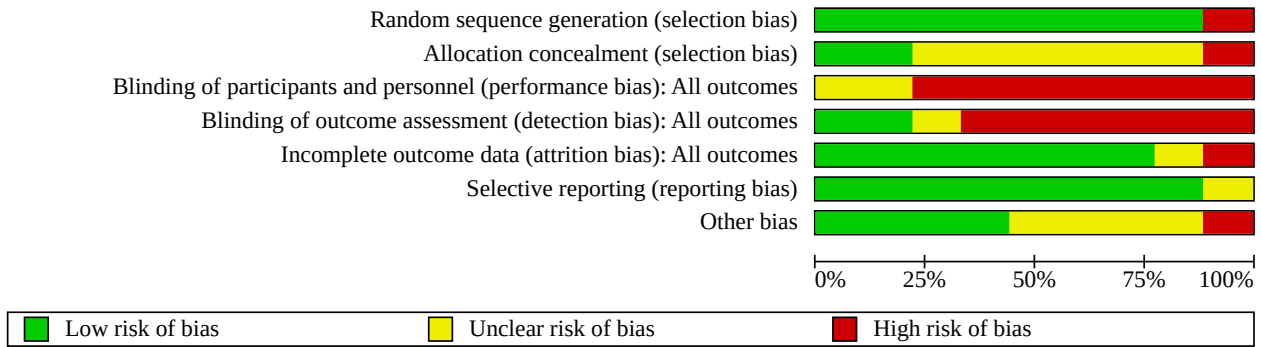


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Berridge 1991	+	?	-	-	+	+	+
Braithwaite 1997	+	?	-	-	+	+	+
Comerota 2019	+	?	?	+	-	+	?
Cragg 1991	-	-	-	-	?	?	+
Duda 2001	+	+	-	?	+	+	?
Kandarpa 1993	+	?	-	-	+	+	?
Plate 2006	+	?	-	-	+	+	?
Saroukhani 2015	+	?	?	+	+	+	-
Yusuf 1995	+	+	-	-	+	+	+

Six included studies were at unclear or high risk of selection bias (Berridge 1991; Braithwaite 1997; Comerota 2019; Cragg 1991; Kandarpa 1993; Plate 2006). Most studies were unblinded due to use of different techniques to deliver the thrombolytic agent. Trialists were not blind to outcomes, and only Comerota 2019 used independent reference laboratories to assess pre-intervention and post-intervention angiograms. All but Cragg 1991 and Comerota 2019 had low risk of bias from incomplete data reporting or selective reporting. Other potential biases included study terminating early due to lack of enrolment (Plate 2006), inconsistent reporting in the article (Kandarpa 1993; Saroukhani 2015), baseline differences (Duda 2001), and deviations from the clinical trial registry protocol (Comerota 2019).

Allocation

Two trials reported adequate methods of randomisation and allocation with appropriate safeguards (e.g. used a random number generator) and so were at low risk of bias (Duda 2001; Yusuf 1995). Four studies described the randomisation process but did not provide sufficient details on allocation so were assessed as being at unclear risk (Berridge 1991; Comerota 2019; Plate 2006; Saroukhani 2015).

Cragg 1991 used alternation to determine treatment groups and so was judged as being at high risk of bias. Braithwaite 1997 used computer-generated randomisation cards contained in consecutively numbered sealed envelopes, but it was unclear whether the envelopes were opaque, so it is unclear whether this could have introduced selection bias. In Kandarpa 1993, patients were randomised by selection of consecutively numbered sealed envelopes. As it was not clear if the envelopes were opaque, we assessed this study as being at unclear risk of selection bias.

Blinding

Given the interventions being investigated, blinding of both participants and personnel would not always be possible, although blinding of outcome assessors would have been possible. Studies that did not blind personnel or outcome assessors were deemed to have high risk of both performance and detection bias (Berridge 1991; Braithwaite 1997; Cragg 1991; Kandarpa 1993; Plate 2006; Yusuf 1995). Comerota 2019 and Saroukhani 2015 did blind outcome assessors so were judged as having unclear risk of performance bias and low risk of detection bias. Duda 2001 was assessed as having high risk of performance bias and unclear risk of detection bias, as although the angiograms were reviewed by external assessors who were blind to the allocated treatment, external assessors had participated in the treatments.

Incomplete outcome data

No significant loss to follow-up was reported in any of the studies, and there were no concerns regarding missing data. Outcome reporting within trials was complete to 30 days, except for Cragg 1991, where loss to follow-up at 30 days was unclear from the data. Comerota 2019 was judged to be at high risk of attrition bias, as a mixture of per-protocol and intention-to-treat analysis was used, and groups were analysed together, without acknowledging the initial cohorts to which they had been randomised.

Selective reporting

All outcomes were reported as planned, so there are no concerns regarding selective reporting within most included trials. Outcome

reporting within trials was complete to 30 days, except for Cragg 1991, where loss to follow-up at 30 days was unclear from the data.

Other potential sources of bias

No evidence of other potential sources of bias was identified in Berridge 1991, Braithwaite 1997, Cragg 1991, or Yusuf 1995. Some inconsistency regarding reporting of data was evident in Kandarpa 1993. Unclear risk of other bias due to differences in the baseline level of participant disease severity was reported in Duda 2001: 40% of the treatment group were claudicants compared to only 15% of the control group. In Saroukhani 2015, the mean age of the catheter-directed thrombolysis (CDT) group was 55.5 years compared to 88.5 years in the IV group (cutoff age was 75 years), which may indicate potential selection bias. We queried this with the study authors, who explained that this was due to an error in the article. Saroukhani 2015 authors also reported, "Post intervention angiography was not performed in this [IV] group", yet comparisons are reported. Study authors responded to our communication to check this and confirmed that angiography was carried out in both groups. We assessed this study as being at high risk of other potential sources of bias due to these inconsistencies. Changes to the initial protocol were reported in the clinical trial registry protocol of Comerota 2019, and it is unclear if this could represent potential risk of bias. Plate 2006 was terminated early due to enrolment issues, and it is not clear how severity was assessed (participants were described as 'acute and sub-acute lower limb ischaemia'), so we judged this study to be at unclear risk of other bias.

Effects of interventions

See: **Summary of findings 1** Intra-arterial delivery compared to intravenous delivery for peripheral arterial thrombolysis; **Summary of findings 2** High-dose compared to low-dose regimens of thrombolytic agents; **Summary of findings 3** Continuous infusion compared to forced (or pulse) infusion of thrombolytic agents; **Summary of findings 4** Thrombolysis with or without adjunctive antiplatelet agents

Clinical heterogeneity and disparate outcome measures used in reporting of the included studies limit their power and their likelihood of allowing meaningful meta-analysis. This is particularly true for vessel patency and duration of thrombolysis, which were interpreted in different ways in different studies. These factors make direct comparison difficult, but effects have been described textually for each study when possible.

In these circumstances, the most meaningful method of assessment is to compare the most clinically relevant outcome measures (i.e. limb salvage, amputation, mortality, and complications (major and minor bleeding complications and cerebrovascular accident)).

It is important to be aware that limb salvage and amputation figures can be misleading due to inclusion of patients without limb-threatening ischaemia; these patients were not at risk of amputation. Major bleeding defined as a fall in haemoglobin of more than 2 g/dL or requiring transfusion or surgery is perhaps the best defined of the outcomes.

Trials comparing intra-arterial and intravenous delivery of the agent

Berridge 1991 and Saroukhani 2015 compared these methods of delivery. See [Summary of findings 1](#) and [Table 1](#). In Berridge 1991, intravenous rt-PA was infused at four different rates, and IA rt-PA was infused via a catheter embedded in the distal thrombus at a rate of 0.5 mg/h. In Saroukhani 2015, participants received either IV rt-PA (alteplase, 0.6 mg/kg, 20% as initial bolus for 2 hours) or IA catheter delivery (CDT) of rt-PA (5-mg bolus, then 0.05 mg/kg/h every 2 hours for 24 hours).

30-Day amputation-free survival

Only Berridge 1991 reported 30-day amputation-free survival and described little or no effect on 30-day amputation-free survival between methods of delivery (14/20 (70%) IV rt-PA and 16/20 (80%) IA rt-PA; odds ratio (OR) 1.71, 95% confidence interval (CI) 0.40 to 7.34; 1 study, 40 participants; very low-certainty evidence; [Analysis 1.1](#)).

The proportion of patients with asymptomatic limbs was greatest for IA rt-PA (IV rt-PA 9/20 (45%); IA rt-PA 16/20 (80%)). Ongoing critical limb ischaemia (rest pain or tissue loss) was greatest in the IV group. In the IA group, none (0%) of the 16 surviving patients without amputation had critical limb ischaemia compared to 5 of 14 (36%) in the IV group. Study authors reported that an increase in ankle brachial index (ABI) was greater in the IA rt-PA group than in the IV rt-PA group ($P < 0.001$).

Amputation

In Berridge 1991, the major amputation rate was not different between groups at 30 days (IV rt-PA 0/20 (0%); IA rt-PA 1/20 (5%)) or at 3 months (IV rt-PA 1/20 (5%); IA rt-PA 1/20 (5%)). Saroukhani 2015 reported no clear differences between groups in rates of total amputation at 6 months (IV rt-PA 6/18 (33%); IA rt-PA 4/20 (20%)). These figures include forefoot, ankle, and below-knee amputations (IV: 1, 3, 2; IA: 0, 0, 4, respectively).

Due to clinical heterogeneity, we were unable to combine the results. Amputation rates at 3 months and 6 months indicate little or no difference in effect on amputation rates between IV and IA groups (2 studies, 78 participants; low-certainty evidence; [Analysis 1.2](#)).

Mortality

In Berridge 1991, no clear difference in death rates was noted between the two groups at 30 days (IV rt-PA 3/20 (15%) and IA rt-PA 3/20 (15%)) (OR 1.00, 95% CI 0.18 to 5.67; 1 study, 40 participants; [Analysis 1.3](#)). Saroukhani 2015 analysed all participants at 6 months, so no deaths occurred in this follow-up period (2 studies, 78 participants; low-certainty evidence; [Analysis 1.3](#)).

Vessel patency

Radiological success was reported in Berridge 1991 as complete, partial (defined as "lysis of the lesion down to the next major artery distally"), or failure. Among those treated with IA rt-PA, 17 of 20 patients had complete lysis of the thrombus, 3 of 20 patients had partial lysis of the thrombus, and 0 of 20 procedures were reported as failures. In the IV rt-PA-treated group, 6 of 20 patients had complete lysis of the thrombus, 3 of 20 patients had partial lysis, and 11 of 20 procedures were

reported as failures. Complete success was more likely with IA than with IV treatment (OR 13.22, 95% CI 2.79 to 62.67; 1 study, 40 participants), and radiological failure may be more likely with IV (OR 0.02, 95% CI 0.00 to 0.38; 1 study, 40 participants; low-certainty evidence; [Analysis 1.4](#)). Saroukhani 2015 reported a higher rate of angiographic improvement in the CDT (IA) group compared to the IV group. Study methods state that the "secondary endpoint ...was complete or near complete recanalization of the occluded artery in angiography". However only a P value is reported ($P < 0.001$); no further details or results are provided (low-certainty evidence).

Duration of thrombolysis

In Berridge 1991, the duration of thrombolysis for IA rt-PA was 35 (14 to 64) hours (median and range). The duration of thrombolysis for IV rt-PA is not reported, as rate and duration of the infusion were variable, with a maximum dose of 100 mg infused at 1, 2, 5, or 10 mg/h. In Saroukhani 2015, 80% of 0.6 mg/kg of rt-PA (alteplase) was given IV over 2 hours (after 20% bolus). The IA group received an initial 5-mg bolus dose, and the remainder was infused at 0.05 mg/kg/h every 2 hours over a 24-hour period. Both regimens were repeated the day after, if improvements in the peripheral circulation were seen. See [Table 1](#). We are unable to draw any conclusions due to the heterogeneity of the studies (very low-certainty evidence).

Complications

Berridge 1991 reported the following complications.

- Cerebrovascular accident: 1 intracranial bleed reported in the IV rt-PA group (1/20, 5%); no events reported in the IA rt-PA group (0/20, 0%) (OR 0.32, 95% CI 0.01 to 8.26; 1 study, 40 participants; very low-certainty evidence; [Analysis 1.5](#)).
- Major bleeding complications: may occur more frequently in the IV rt-PA group (3/20, 15%) compared to the IA group (0/20, 0%) but the 95% CI indicates that there may be no difference (OR 0.12, 95% CI 0.01 to 2.53; 1 study, 40 participants; very low-certainty evidence; [Analysis 1.6](#)).
- Minor bleeding complications: occurred more frequently in the IV rt-PA group (9/20, 55%) than in the IA group (0/20, 0%) (OR 0.03, 95% CI 0.00 to 0.56; [Analysis 1.7](#)).

Saroukhani 2015 defined major complications as those requiring transfusion or resulting in disability. Minor complications were described as other haemorrhage, haematoma, or hypersensitivity reactions. Saroukhani 2015 reported that no major complications were experienced in the IA or IV groups. No minor complications were detected in the IV group compared to 4 of 20 (20%) in the CDT IA group. It is not clear exactly what minor events occurred, but these may have included other (non-major) haemorrhage, haematoma, or hypersensitivity reactions.

Trials comparing high- and low-dose regimens of the thrombolytic agent

Four studies compared high- and low-dose regimens (Braithwaite 1997; Cragg 1991; Plate 2006; Yusuf 1995). It was not possible to pool data because of heterogeneity in the methods and inclusion criteria, so we have presented the study results separately below. See [Summary of findings 2](#) and [Table 2](#).

Low-dose bolus and low-dose infusion versus high-dose bolus and high-dose infusion with urokinase

In [Cragg 1991](#), 72 episodes of thrombolysis were performed in 63 patients (nine patients had two separate admissions). Thirty-four patients (47%) had native arterial occlusion, and 38 (53%) graft thrombosis. Twenty-four (71%) of the native arterial occlusions and 37 (97%) of the grafts were treated within four weeks of onset of symptoms.

30-Day amputation-free survival

Thirty-day amputation-free survival was seen in 57 of 63 (90.5%) participants. Overall one death and five amputations (6/63, 9.5%) were reported. However, it is not clear in which groups these occurred. The true rate of limb salvage cannot be calculated from the data provided, given the inclusion of patients with viable limbs. It is not known how many patients had limbs that would have been at risk of amputation if left untreated (very low-certainty evidence).

Amputation

Overall, 5 of 63 (7.9%) patients had major amputation; most of these appear to have come from the high-dose group (only one could have occurred with the low-dose regimen) (very low-certainty evidence).

Mortality

A single death occurred, but it is not clear in which group the death occurred (very low-certainty evidence).

Vessel patency

Study authors describe that the extent of thrombolysis was recorded as "none (less than 10% clot lysis), partial (10% to 90% clot lysis), or complete (antegrade flow with less than 10% residual thrombus)" ([Cragg 1991](#)). It is not clear how these proportions were estimated, but only presence or absence of "complete lysis" was reported. The proportion of patients with "complete lysis" in the high-dose group did not differ from that in the low-dose group (very low-certainty evidence). See [Table 2](#). Thrombolysis was deemed to be clinically successful if (1) among patients with acute ischaemia, the patient returned to the pre-ischaemic condition; or (2) among patients with chronic ischaemia, "it aided the performance of a subsequent revascularisation procedure". All groups had similar increases in ABI following lysis, and there was no significant difference in "clinical success".

Duration of thrombolysis

Study authors report time to achieve "complete lysis" and duration of the infusion. It must be noted that the duration of the infusion was longer, reflecting that in some cases, the infusion was continued after "complete lysis" was achieved in an attempt to lyse any residual thrombus. Time to restore antegrade flow or to achieve "complete lysis" in the high-dose group did not differ from that in the low-dose group. See [Table 2](#).

Complications

- Cerebrovascular accident: no CVA reported
- Major bleeding complications: in the high-dose group, 2 patients with a fall in haemoglobin of more than 2 g/dL, 1 haematoma (localised collection of blood, usually due to bleeding at a site where an artery has been punctured to place a catheter for diagnosis and treatment) requiring evacuation, and 1 patient

requiring transfusion for puncture site bleeding. In the low-dose group, a single patient with a drop in haemoglobin of more than 4 g/L (OR 0.46, 95% CI 0.04 to 5.29; very low-certainty evidence; [Analysis 2.6](#))

- Minor bleeding complications: haematoma and puncture site bleeding were more frequent in the high-dose group (7/35 (20%)) than in the low-dose group (1/37 (2.7%)) (OR 0.11, 95% CI 0.01 to 0.96; 1 study, 72 participants; [Analysis 2.7](#))

Low-dose infusion versus high-dose bolus and high-dose infusion with rt-PA

[Braithwaite 1997](#) reported that 100 patients had ALI of less than 30 days' duration.

30-Day amputation-free survival

Thirty-day amputation-free survival did not differ between the two groups (high dose 80%; low dose 84%). True limb salvage cannot be calculated from the data provided, given the inclusion of patients with viable limbs (very low-certainty evidence). See [Table 2](#).

Amputation

The 30-day amputation rate did not differ between the two groups (high dose 6 (12%); low dose 2 (4.5%)) (OR 0.34, 95% CI 0.07 to 1.79; 1 study, 93 participants; very low-certainty evidence; [Analysis 2.2](#)).

Mortality

The 30-day mortality rate did not differ between the two groups (high dose 8%; low dose 11%) (OR 1.44, 95% CI 0.36 to 5.75; 1 study, 93 participants; very low-certainty evidence; [Analysis 2.3](#)).

Vessel patency

Study authors defined "complete lysis" as clearance of the occluded vessel with restoration of flow to runoff and re-establishment of peripheral pulses.

"Clinically useful" lysis was defined as partial clearance of thrombus, relieving rest pain or improving ABI by 0.2; or as "partial clearance" of thrombus, enabling a procedure to be performed, when none was possible before therapy.

Complete lysis was achieved in 22 (45%) and 21 (48%) patients (OR 1.12, 95% CI 0.50 to 2.54; 1 study, 93 participants), and clinically useful lysis in 10 (20%) and 14 (32%) patients (OR 1.82, 95% CI 0.71 to 4.66; 1 study, 93 participants) in high-dose and low-dose groups, respectively. There was no difference between groups (very low-certainty evidence). See [Table 2](#) and [Analysis 2.4](#).

Duration of thrombolysis

The median duration of infusion was 4 (range 0.25 to 46) hours for the high-dose group and 20 (range 2 to 46) hours for the low-dose group ($P < 0.0001$; very low-certainty evidence). See [Table 2](#).

Complications

- Cerebrovascular accident: no events reported in the high-dose group 0/49 (0%). One incident reported in the low-dose group (1/44, 2.2%) (OR 3.41, 95% CI 0.14 to 85.99; 1 study, 93 participants; very low-certainty evidence). See [Analysis 2.5](#)
- Major bleeding complications: occurred with equal frequency in each group (high dose 6%; low dose 6.8%) (OR 1.12, 95% CI 0.21

to 5.87; 1 study, 93 participants; very low-certainty evidence). See [Analysis 2.6](#)

- Minor bleeding complications: not specified in [Braithwaite 1997](#)

Continuous infusion versus high-dose forced infusion (pulse spray) with rt-PA

Two studies compared low-dose continuous infusion (CIF) versus high-dose forced infusion (pulse spray) with rt-PA ([Plate 2006](#); [Yusuf 1995](#)). It was not possible to pool data because of heterogeneity in the methods and inclusion criteria. See [Table 2](#).

In [Plate 2006](#), 121 patients had acute onset of Rutherford grade I or II ischaemia of less than 30 days' duration.

30-Day amputation-free survival

Thirty-day amputation-free survival was reported as 49 of 58 (84%) pulse spray and 54 of 63 (86%) low-dose infusion, but true limb salvage cannot be calculated from the data provided, given inclusion of patients with viable limbs (very low-certainty evidence). See [Analysis 2.1](#).

Amputation

No difference in amputation rate was detected, with 4 of 58 (7%) in the pulse spray group and 3 of 63 (5%) in the low-dose continuous infusion group (OR 0.68, 95% CI 0.14 to 3.15; 1 study, 121 participants; very low-certainty evidence). See [Analysis 2.2](#).

Mortality

No difference in mortality was detected at 30 days, with 6 of 58 (10%) in the pulse spray group and 7 of 63 (11%) in the low-dose continuous infusion group (OR 1.08, 95% CI 0.34 to 3.43; 1 study, 121 participants; very low-certainty evidence). See [Analysis 2.3](#).

Vessel patency

The criterion for success was "adequate peripheral blood flow"; minor residual thrombus was considered acceptable. An estimate of the "degree of lysis" was assessed from angiograms obtained immediately after thrombolysis was completed. More than "75% lysis" was accomplished in 45 of 58 patients (78%) in the pulse spray high-dose group and in 41 of 61 patients (67%) in the low-dose continuous infusion group on completion of thrombolysis (OR 0.59, 95% CI 0.26 to 1.34; 1 study, 119 participants; very low-certainty evidence; [Analysis 2.4](#)). There was no difference in "incomplete lysis" immediately following completion of thrombolysis. At 30 days, there was little or no effect on "incomplete lysis" or reocclusion overall, or among patients requiring repeat thrombolysis or surgical intervention. See [Analysis 2.4](#) and [Table 2](#).

Duration of thrombolysis

Pulse spray was continued for a median of 120 (range 40 to 310) minutes. Complementary low-dose infusion was required for a median of 18 (range 1 to 50) hours in 38 of 58 (66%) patients. Low-dose continuous infusion was administered for a median of 25 (range 2 to 60) hours (very low-certainty evidence). See [Table 2](#).

Complications

- Cerebrovascular accident: 3 of 58 (5.2%) events detected in the pulse spray group compared to 1 of 63 (1.6%) in the low-dose

continuous infusion group (OR 0.30, 95% CI 0.03 to 2.93; 1 study, 121 participants; very low-certainty evidence). See [Analysis 2.5](#)

- Major bleeding complications: 4 of 58 (6.9%) complications reported in the pulse spray group compared to 8 of 63 (12.6%) in the low-dose continuous infusion group (OR 1.96, 95% CI 0.56 to 6.91; 1 study, 121 participants; very low-certainty evidence). See [Analysis 2.6](#)
- Minor bleeding complications: 12 of 58 (21%) minor bleeding complications reported in the pulse spray group compared to 7 of 63 (11%) in the low-dose continuous infusion group (OR 0.48, 95% CI 0.17 to 1.32; 1 study, 121 participants). See [Analysis 2.7](#)

In [Yusuf 1995](#), 18 patients had less than 42 days' ischaemia.

30-Day amputation-free survival

The true rate of limb salvage cannot be calculated from the data provided, given the inclusion of 2 of 9 patients in the pulse spray group and 3 of 9 patients in the continuous infusion group with viable limbs (very low-certainty evidence). See [Analysis 2.1](#).

Amputation

No clear differences in amputation rates were seen, with 2 of 9 (22%) of patients in the continuous infusion group undergoing amputation compared with 0 of 9 (0%) in the pulse spray group (OR 6.33, 95% CI 0.26 to 152.86; 1 study, 18 participants; very low-certainty evidence). See [Analysis 2.2](#).

Mortality

One death was reported in the continuous infusion group (1/9, 12%) and none in the pulse spray group (0/9, 0%) (OR 3.35, 95% CI 0.12 to 93.83; 1 study, 18 participants; very low-certainty evidence). See [Analysis 2.3](#).

Vessel patency

Radiological patency was not reported. "Success" rates were reported by study authors as not significantly different, at 88.8% in the pulse spray group and 55.5% in the continuous infusion group ($P < 0.9$), probably due to the small numbers involved ($n = 18$). Criteria for clinical success included radiological evidence of lysis with arterial recanalisation at least as far as the next major arterial collateral branch; increase in ABI greater than 0.2, indicating haemodynamic improvement; limb salvage at 30 days without surgery at the level at which lysis was performed; and no clinical evidence of rethrombosis at 30 days (very low-certainty evidence).

Duration of thrombolysis

Median duration of therapy was less with pulse spray, at 195 minutes (range 90 to 1260 minutes), compared to continuous infusion, at 1390 minutes (range 300 to 2400 minutes) ($P < 0.002$; very low-certainty evidence). See [Table 2](#).

Complications

- Cerebrovascular accident: none reported (very low-certainty evidence)
- Major bleeding complications: none in either group (very low-certainty evidence)
- Minor bleeding complications: occurred in each group but not discussed in detail

Trials comparing continuous infusion with forced or pulse spray infusion of the agent

Four studies compared continuous infusion with forced infusion (Comerota 2019; Kandarpa 1993; Plate 2006; Yusuf 1995). It was not possible to combine data because of heterogeneity in methods and inclusion criteria. See [Summary of findings 3](#) and [Table 3](#). Results for [Plate 2006](#) and [Yusuf 1995](#) have already been described above, and so are not duplicated below.

Forced-infusion (pulse spray) bolus followed by continuous infusion versus forced infusion with urokinase

In [Kandarpa 1993](#), 25 participants had less than 30 days' ischaemia. [Kandarpa 1993](#) reported that two patients in the continuous infusion group developed significant muscle swelling (compartment syndrome). "Positive clinical outcome" (i.e. improvement or resolution of ischaemic symptoms) was similar in each group (7 (59%) in the pulse spray (PS) group; 9 (69%) in the continuous infusion group).

30-Day amputation-free survival

There was no clear difference between the two groups in amputation-free survival. Limb salvage occurred in 11 of 13 (85%) patients in the continuous infusion group and in 10 of 12 (83%) in the PS group (OR 1.10, 95% CI 0.13 to 9.34; 1 study, 25 participants; very low-certainty evidence). See [Analysis 3.1](#).

Amputation

Two patients in the continuous infusion group underwent amputation (2/13; 15%) compared with no amputations in the PS group (0/12, 0%) (OR 5.43, 95% CI 0.24 to 125.59; 1 study, 25 participants; very low-certainty evidence). See [Analysis 3.2](#).

Mortality

No deaths were reported in the continuous infusion group (0/13, 0%) compared with two in the PS group (2/12, 16.6%) (OR 0.16, 95% CI 0.01 to 3.60; 1 study, 25 participants; very low-certainty evidence). See [Analysis 3.3](#).

Vessel patency

Study authors describe patency as "at least 95% thrombolysis by volume, with brisk antegrade flow" occurring within four hours. There were no clear differences in patency within four hours between the two groups (OR 0.20, 95% CI 0.02 to 2.17; 1 study, 25 participants; very low-certainty evidence; [Analysis 3.4](#)). Ten patients who underwent PS and nine who underwent continuous infusion had residual thrombi prolonging infusion. In the continuous infusion group, infusion was stopped in two participants (one due to bleeding, one due to rethrombosis following vasovagal), and one participant in each group withdrew. There were no clear differences between treatment groups in the proportions of patients achieving complete lysis within 24 hours and beyond 24 hours.

Duration of thrombolysis

There were no clear differences between treatment groups in time to complete treatment (very low-certainty evidence). See [Table 3](#).

Complications

- Cerebrovascular accident: none reported (very low-certainty evidence)

- Major bleeding complications: 3 major bleeding complications reported in the PS group (3/12, 25%) compared to 1 in the continuous infusion group (1/13, 7.7%) (OR 0.25, 95% CI 0.02 to 2.82; 1 study, 25 participants; very low-certainty evidence). See [Analysis 3.6](#)
- Minor bleeding complications: 2 minor bleeding complications reported in both the PS group (2/12, 16.6%) and the continuous infusion group (2/13, 15.3%) (OR 0.91, 95% CI 0.11 to 7.72; 1 study, 25 participants). See [Analysis 3.7](#)
- Distal embolisation: occurred in 5 patients in each group

Continuous infusion with or without additional pulse spray with or without balloon occlusion catheters

[Comerota 2019](#) compared multiple treatment arms; its primary purpose was to optimise plasmin delivery. Eight groups received CIF with different infusion times and regimens. All groups received 150 mg plasmin, four groups had CIF (no pulse), and four had CIF with additional pulse spray. Five had 5-hour infusions (10 or 15 or 30 or 60 mL/h) and three had 2-hour infusions (30 or 75 mL/h). Two used additional balloon occlusion catheters (BOCs), and six did not. Results are summarised in [Table 5](#).

30-Day amputation-free survival and amputations

Amputation survival and amputations were not specifically reported or listed as possible serious adverse events. It is unlikely any occurred during the 30 (\pm 3)-day follow-up (very low-certainty evidence).

Mortality

One death (1/140) from acute respiratory distress syndrome occurred in the CIF with pulse without BOC group, and was not considered related to treatment (very low-certainty evidence).

Vessel patency

Data for thrombolysis were reported for each subgroup. We were able to investigate the effects of CIF with or without pulse spray - 5 hours versus 2 hours and with or without additional BOC. The study included participants in analyses only if they received > 90% of the planned thrombolytic agent.

We pooled data from these groups to investigate the effects of 5-hour infusion versus 2-hour infusion, and we observed no clear effect among participants with > 50% thrombolysis (OR 1.79, 95% CI 0.83 to 3.84; 1 study, 128 participants; very low-certainty evidence; [Analysis 4.1](#)). We presented results by CIF with or without pulse to investigate whether this impacted the effects; we detected no differences when performing the test for subgroup differences ($P = 0.76$). This analysis includes data from groups that also received BOC (one in the 5-hour group and one in the 2-hour group).

We pooled data from these groups to investigate the effects of CIF with pulse versus CIF with no pulse, and we observed no clear effect among participants with > 50% thrombolysis (OR 0.67, 95% CI 0.31 to 1.42; 1 study, 128 participants; very low-certainty evidence; [Analysis 4.2](#)). We presented results by infusion time to investigate whether this impacted the effects and detected no differences when performing the test for subgroup differences ($P = 0.76$). This analysis includes data from groups that also received BOC (both in the no pulse group).

We pooled data from these groups to investigate the effects of CIF with BOC versus CIF without BOC, and we observed no clear effect among participants with > 50% thrombolysis (OR 1.09, 95% CI 0.46 to 2.58; 1 study, 128 participants; very low-certainty evidence; [Analysis 4.3](#)). Both subgroups that had BOCs were CIF - one with 5-hour infusion and one with 2-hour infusion. Subgroups without BOCs had both CIF and CIF plus pulse.

This study also provided data for participants who achieved 90% thrombolysis, revealing there may be a small increase in numbers of participants with 90% thrombolysis following 5-hour infusion compared with 2-hour infusion regimens (OR 8.17, 95% CI 1.00 to 66.60; 1 study, 131 participants; [Analysis 4.4](#)). The test for subgroup differences does not indicate any effect with or without pulse ($P = 0.95$).

There was no clear effect on 90% thrombolysis with or without the use of BOCs (OR 0.56, 95% CI 0.12 to 2.67; 1 study, 131 participants; [Analysis 4.5](#)).

Duration of thrombolysis

[Comerota 2019](#) did not report duration as an outcome but did use groups with different treatment durations. These are reported above.

Complications

- Cerebrovascular accident: no cerebral haemorrhage events reported in any of the groups included in this review (very low-certainty evidence)
- Major bleeding: data from groups within [Comerota 2019](#) pooled to investigate any effect of CIF versus additional pulse; no clear effects on numbers of major bleeding events detected (OR 0.64, 95% CI 0.11 to 3.61; 1 study, 131 participants; very low-certainty evidence; [Analysis 3.6](#)). Additional analysis carried out to investigate whether infusion times had an effect on major bleeding. No major bleeding events reported in groups relevant to this review following 2-hour infusion (0/49) compared to 7 of 96 following 5-hour infusion (OR 8.30, 95% CI 0.46 to 148.33; 1 study, 131 participants; very low-certainty evidence; [Analysis 4.6](#))
- Minor bleeding: similarly, no clear effects on numbers of minor bleeding events detected (OR 2.02; 95% CI 0.85 to 4.77; 1 study, 131 participants; [Analysis 3.7](#)). Data reported are number of participants with minor bleeding events. Some participants had more than one event, presenting by event did not change the overall effect. Additional analysis carried out to investigate whether infusion times had an effect on minor bleeding. No clear differences in minor bleeding events reported in groups relevant to this review following 2-hour infusion (7/49) and following 5-hour infusion (19/96) (OR 1.48, 95% CI 0.58 to 3.81; 1 study, 131 participants; [Analysis 4.7](#))

Individual study results reported for [Plate 2006](#) and [Yusuf 1995](#) are as reported above and within [Table 2](#) and [Table 3](#).

Trials comparing thrombolysis with or without adjunctive antiplatelet agents

Only [Duda 2001](#) compared adjunctive antiplatelet agents. See [Summary of findings 4](#) and [Table 4](#).

Forced-infusion (pulse spray) bolus followed by continuous forced infusion with urokinase, with or without platelet glycoprotein IIb/IIIa receptor antagonist

[Duda 2001](#) reported on 70 patients with less than 42 days' ischaemia.

30-Day amputation-free survival

The 30-day amputation-free survival was not reported, but 90-day amputation-free survival was reported - abciximab and UK 48 of 50 (96%); UK alone 16 of 20 (80%). Study authors reported that amputation-free survival was significantly higher at 90 days in the group receiving abciximab than in the group receiving UK alone. However, at the time of treatment, 40% of patients in the abciximab group had non-limb-threatening ischaemia compared to only 15% in the UK-alone group. True limb salvage cannot be calculated from the data provided, given inclusion of patients with viable limbs. By 30 days, 4 of 50 in the abciximab group and 3 of 20 in the UK-alone group had reached the composite endpoint of surgical revascularisation or limb amputation.

Amputation

This could not be calculated from the data provided.

Mortality

This could not be calculated from the data provided.

Vessel patency

Study authors' definition of patency does not clearly distinguish between the presence of thrombus and any underlying stenosis.

Initial patency by means of thrombolysis alone was reported in 14 of 20 from the UK-alone group and in 33 of 50 from the abciximab group (OR 1.20, 95% CI 0.39 to 3.69; 1 study, 70 participants; very low-certainty evidence; [Analysis 5.1](#)). Initial patency with thrombolysis and subsequent percutaneous intervention was reported in 20 of 20 from the UK-alone group and in 44 of 50 in the abciximab group (OR 5.99, 95% CI 0.32 to 111.44; 1 study, 70 participants; [Analysis 5.1](#)). There were no clear differences between treatment groups for either of the reported patency outcomes.

Duration of thrombolysis

The median duration of thrombolysis was 120 minutes in each group (low-certainty evidence). See [Table 4](#).

Complications

- Cerebrovascular accident: none reported (low-certainty evidence)
- Major bleeding complications: 4 of 50 (8%) in the abciximab group compared with 0 of 20 (0%) in the UK group. Analysis did not show a clear difference between groups (OR 0.25, 95% CI 0.01 to 4.90; 1 study, 70 participants; very low-certainty evidence; [Analysis 5.2](#))
- Minor bleeding complications: 9 of 50 (18%) in the abciximab group compared with 5 of 20 (25%) in the UK group. Analysis did not show a clear difference between groups (OR 1.52, 95% CI 0.44 to 5.26; 1 study, 70 participants; [Analysis 5.3](#))

DISCUSSION

Summary of main results

Nine randomised studies detailing different techniques of thrombolysis were included in this review (Berridge 1991; Braithwaite 1997; Comerota 2019; Cragg 1991; Duda 2001; Kandarpa 1993; Plate 2006; Saroukhani 2015; Yusuf 1995). The power of the individual studies to deliver clinically relevant results was limited. Study populations were small and heterogeneous, and each study used different inclusion criteria in terms of severity and duration of ischaemia. Outcome measures also differed considerably between trials. Different agents were used: studies from the UK and Sweden used recombinant tissue plasminogen activator (rt-PA) (Berridge 1991; Braithwaite 1997; Plate 2006; Yusuf 1995), while those from the USA and Germany used urokinase (Cragg 1991; Duda 2001; Kandarpa 1993). Comerota 2019, an international, multi-centre trial, used plasmin, and Saroukhani 2015, a single-centre trial, used alteplase (tissue plasminogen activator).

The combination of these factors made the included studies unsuitable for meaningful statistical comparison. For this reason, the Discussion considers, initially, the most clinically relevant outcome measures of treatment for patients with peripheral arterial ischaemia (limb salvage, amputation, mortality, and complications). Subsequently, other 'surrogate' outcome measures are discussed.

30-Day amputation free survival - limb salvage

Limb salvage can only truly be identified in Berridge 1991 and Kandarpa 1993. In Braithwaite 1997, the analysis included limb salvage rates, but their validity is questionable, as the study included many patients with intermittent claudication, which is not a limb-threatening condition. Limb salvage rates were equivalent, at about 80% for each treatment regimen, except for intravenous (IV) 'systemic therapy', for which the limb salvage rate was only 45%. In addition, Berridge 1991 reported an increase in ankle brachial index (ABI) among participants treated with intra-arterial (IA) rt-PA compared to IV rt-PA (0.57 versus 0.18; $P < 0.001$). This is in keeping with the fact that five (20%) participants in the systemic therapy group had ongoing critical ischaemia at 30 days and indicates that local IA drug delivery may be more effective than systemic IV therapy. The actual method of local delivery (pulse spray, infusion, dose rate) does not appear to affect the rate of limb salvage.

Amputation

Amputation rates varied considerably between studies (0% to 33%). However, no studies showed a clear effect on amputation rate related to the technique of drug delivery. Once again, it is noteworthy that amputation should be required only for patients with critically ischaemic limbs, and inclusion of patients with intermittent claudication makes interpretation of some of the results unclear.

Mortality

Death rates varied considerably between studies (0% to 16%). However, no studies showed a clear effect related to the technique of drug delivery. It would be worrisome if any patients with intermittent claudication were to die as a result of therapy, but

unfortunately, these patients could not be extracted from the data set.

Vessel patency

Several studies included the degree of thrombolysis and the volume of thrombus cleared. These features are difficult to quantify objectively and can be calculated only retrospectively. In addition, the concept of thrombus clearance is ambiguous, for example, 50% clearance might refer to reduction in length of the blockage by 50% with no flow within the vessel, or, alternatively, it might refer to the 'volume' of the thrombus, in which case there might be restoration of flow if the lumen was only partially occluded. Both Berridge 1991 and Yusuf 1995 included "radiological evidence of lysis with arterial recanalization at least as far as the next major arterial branch". Although this is an objective measure, it ignores the level of occlusion and does not indicate whether direct in-line runoff (continuous arterial flow to the foot) was restored. Yusuf 1995 reported that the median ABI increased following thrombolysis, from zero to 0.5 ($P < 0.02$) in the continuous group, and from zero to 0.9 ($P < 0.0001$) in the pulse spray group. Patients with an ABI of 0.9 would be expected to be free of ischaemic symptoms, and those with an ABI of 0.5 probably would have intermittent claudication. In Duda 2001, the definition of "patency" did not distinguish between remaining thrombus and underlying stenosis, and no differences were detected between the urokinase group and the abciximab group for either initial patency or patency following subsequent percutaneous interventions. The median ABI the day after intervention was 0.79 (range 0 to 1.18) in the urokinase-plus-abciximab group, and 0.79 (range 0.27 to 1.21) in the urokinase-alone group. Six trials tried to quantify the proportion of thrombus cleared (Berridge 1991; Braithwaite 1997; Comerota 2019; Cragg 1991; Kandarpa 1993; Saroukhani 2015). Three appear to have tried to calculate this from an angiogram (Comerota 2019; Kandarpa 1993; Saroukhani 2015). Broadly speaking, most study authors considered the following categories: no, partial, and complete clearance. Only removal of thrombus with restoration of brisk forward arterial flow is clinically useful. In Berridge 1991, IA infusion was associated with an increase in complete radiological success (100% versus 45%) compared with IV infusion ($P < 0.01$). Saroukhani 2015 reported a higher rate of angiographic improvement in the catheter-directed thrombolysis (CDT) (IA) group compared to the IV group ($P < 0.001$). Braithwaite 1997 reported a non-significant increase in the median number of arterial segments cleared with low-dose infusion (three segments) compared to high-dose infusion (two segments). Cragg 1991 and Kandarpa 1993 failed to show any difference in clearance with different thrombolytic regimens. Levels of thrombolysis varied between groups in Comerota 2019; no differences in numbers of participants with 50% thrombolysis were seen when continuous infusion (CIF) was compared with or without pulsing or balloon occlusion catheters, or when 5-hour infusions were compared to 2-hour infusions. Due to the small numbers involved in each arm and design differences between arms, it is not possible to conclude whether any technique offered any advantage over another.

Duration of thrombolysis

The individual trials used different angiographic endpoints (e.g. estimated clearing of thrombus, restoration of flow, patent to next branch vessel). In addition, frequency of angiographic assessment often differed greatly between control and study groups. This prevented further statistical analysis of the duration

of thrombolysis. Intuitively, it would seem that the more rapid the restoration of flow, the better, but once again, this has not been shown to affect the key outcome measures of limb salvage, amputation, and death.

Duration of thrombolysis varied considerably between studies. This might well reflect the fact that study endpoints were inconsistent. [Kandarpa 1993](#) continued thrombolysis until all thrombi had been cleared; others stopped when little thrombus remained, or when antegrade flow had been restored. In the PROMPT study, thrombus aspiration and angioplasty were performed if there was no clearing after four hours; the median duration of treatment was 120 minutes for each group ([Duda 2001](#)). The trend in these studies was for thrombolysis to be more rapid with high-dose and pulse spray regimens. [Braithwaite 1997](#) showed a significant reduction in the median duration of infusion with the high-dose regimen (median 4 hours, range 0.25 to 46 hours) compared to a median of 20 hours in the low-dose group (range 2 to 46 hours) ($P < 0.0001$). Similar low-dose rt-PA regimens at the same centre yielded different results: median 35 hours, range 14 to 64 ([Berridge 1991](#)); median 23 hours, range 5 to 40 ([Yusuf 1995](#)). This contrasted with a median duration of lytic therapy of 3.25 hours (range 1.5 to 21) in Yusuf's forced-infusion group. [Kandarpa 1993](#) failed to show any differences in mean time to recanalisation (40 minutes continuous infusion, 42 minutes forced infusion), mean time to patency (92 versus 95 minutes, respectively), or total duration of thrombolysis (28 ± 26 versus 20 ± 14 hours, respectively) with continuous infusion and pulse spray regimens. Some of the differences between results of [Kandarpa 1993](#) and [Yusuf 1995](#) may be explained by the preliminary use of forced infusion in both control and treatment groups in [Kandarpa 1993](#). [Cragg 1991](#) used another non-specific endpoint of treatment, namely, "it aided the performance of a subsequent revascularization procedure". This is also subjective and cannot be compared with absolute outcomes such as amputation and mortality. [Comerota 2019](#) had fixed infusion times, depending on the specific group; these are discussed under the outcomes of vessel patency and complications, when appropriate. Likewise, IA and IV groups in [Saroukhani 2015](#) were treated over fixed periods of time and regimens were repeated the day after, if improvements in the peripheral circulation were seen. Duration times from more recent studies seem much shorter than those from earlier studies.

Complications

Major complications

These included cerebrovascular accident and major bleeding (defined as a fall in haemoglobin > 2 g/dL, requiring transfusion or surgery). None of the treatment strategies significantly affected major complications. More incidents of major bleeding may have occurred in the systemic (IV) therapy group in [Berridge 1991](#), and in the "accelerated regimen" groups compared to the continuous treatment groups in [Cragg 1991](#), [Duda 2001](#), and [Kandarpa 1993](#), but these changes may not be meaningful and are not apparent in more recent studies. [Saroukhani 2015](#) reported that no major complications were experienced in either IA or IV groups. Major bleeding in [Comerota 2019](#) ranged from 0% to 15% incidence in different arms. Combining the data from these arms indicates that longer infusion times may result in more bleeding events, but the small numbers involved and differences in design between arms limit our confidence in this.

Minor complications

Minor bleeding complications were more frequent with systemic (IV) therapy - [Berridge 1991](#) - than with high-dose therapy - [Cragg 1991](#) - and increased with high-dose forced therapy - [Plate 2006](#). [Saroukhani 2015](#) reported no minor complications in the IV group, compared to 4 of 20 (20%) in the CDT IA group, although some inconsistency in reporting was detected. In [Comerota 2019](#), it is not possible to conclude whether any technique affected minor complications over another.

Summary

None of the different techniques that involve direct delivery of the active agent into the thrombus have been shown to be more effective in terms of restoring patency, preventing limb loss, or preventing death.

This review found evidence indicating that techniques that involve placement of catheters within the occluding thrombus are more effective for reducing ischaemia than those by which treatment is delivered IV ([Berridge 1991](#)).

The overall incidence of haemorrhagic and other major complications suggests that thrombolysis should be used with caution in patients presenting with intermittent claudication, which is in keeping with findings reported by [Braithwaite 1999](#). The findings of this review are consistent with those of the most recent European Society of Vascular Surgery (ESVS) guidelines on the management of acute limb ischaemia (ALI) ([Björck 2020](#)).

Overall completeness and applicability of evidence

This review set out to determine which is the most effective infusion technique for peripheral arterial thrombolysis and to test the hypothesis that no overall additional benefit is derived from any of the different techniques available to most patients who are suitable for peripheral arterial thrombolysis. The nine included studies cover a variety of techniques of infusion and include patients with variable duration and severity of symptoms, reflecting the spectrum of the disease. However, the power of the individual studies to deliver clinically relevant results was limited. The clinical differences between the studies that prevented pooling have resulted in our inability to clearly report the balance between benefits and complications for any of the comparisons, including high versus low dose.

It is possible that recent advances in techniques, novel thrombolytic agents (second- and third-generation thrombolytic agents), or adjunctive agents will lead to improved outcomes, but only carefully constructed and adequately powered studies will be able to demonstrate this. The development and introduction of newer endovascular technologies, such as mechanical thrombectomy or thrombo-aspiration devices, may provide alternative strategies or additional adjuncts in the armamentarium of treatment options for ALI. Again, robust comparative studies will be needed to determine whether these technologies provide equivalent or better clinical outcomes when compared to CDT. Recent ESVS guidelines suggest that the potential for more rapid revascularisation with percutaneous mechanical devices can enable non-surgical techniques to be employed in managing grade IIb ALI in selected patients, previously the preserve of open surgical treatment ([Björck 2020](#)). This potential for less invasive treatment also provides further avenues by which to treat

patients with more severe degrees of ischaemia without the need for general anaesthesia - something that has become an important consideration during the COVID-19 pandemic (Jongkind 2021).

Quality of the evidence

This review update includes nine studies with a total of 671 participants. The included studies cover a range of therapeutic strategies for delivery of the thrombolytic agent and use of adjunctive therapies that might influence the outcome. This contrasts with a 2003 systematic review of coronary artery thrombolysis, which identified 142,097 patients in 14 trials and showed clear benefit of systemic thrombolysis in terms of acute mortality and cardiac morbidity (Dundar 2003). Compared to the evidence base for coronary artery thrombolysis, the evidence base for thrombolysis in peripheral arterial ischaemia is very small and trials are underpowered to demonstrate meaningful outcomes.

Study populations were small and heterogeneous; each study used different inclusion criteria in terms of severity and duration of ischaemia. Outcome measures also differed considerably between trials. In addition, different agents were used. We have downgraded our certainty in the evidence presented here for all outcomes to low or very low.

For the comparison 'Intra-arterial delivery compared to intravenous delivery for peripheral arterial thrombolysis', we downgraded evidence for risk of bias concerns, inconsistency, and imprecision (see [Summary of findings 1](#)). For the comparison 'High-dose compared to low-dose regimens of thrombolytic agents', we downgraded evidence for risk of bias concerns, indirectness, and inconsistency (see [Summary of findings 2](#)). For the comparison 'Continuous infusion compared to forced (or pulse) infusion of thrombolytic agents', we downgraded evidence for risk of bias concerns, indirectness, and inconsistency (see [Summary of findings 3](#)). For the comparison 'Thrombolysis with or without adjunctive antiplatelet agents', we downgraded evidence for risk of bias concerns, indirectness, inconsistency, and imprecision (see [Summary of findings 4](#)).

Potential biases in the review process

It is unlikely that any relevant studies have been missed by the searches. However, there may be publication bias because negative studies might not have been reported. Limb salvage and amputation figures can also be misleading due to inclusion of patients without limb-threatening ischaemia; these patients were not at risk of amputation to begin with, and results should be interpreted with caution.

Agreements and disagreements with other studies or reviews

The conclusions of this review are in keeping with the findings in other reports. However, it should be noted that data outside randomised trials have not been systematically reviewed.

Braithwaite 1999 reported outcomes of thrombolysis in 108 patients with acute-onset claudication (Rutherford grade I) due to native artery or bypass graft occlusion. Findings were derived from the NATALI database maintained by the British Thrombolysis Study Group. Outcomes were similar to those in seen in patients with limb-threatening ischaemia (Rutherford grade II). The incidence of major haemorrhage requiring transfusion or surgery was 6

of 108 (5.5%). The 30-day mortality was 15 of 108 (14%) and 8 of 108 (10%), and the major amputation rate was 7.8%. It is likely that patients presenting with acute-onset claudication have a different prognosis from patients with stable claudication and are at greater overall risk. However, as patients with Rutherford grade I ischaemia do not have threatened limbs, Braithwaite concluded that thrombolysis should be reserved for patients who have progressed to critical ischaemia.

Earnshaw 2004 reported outcomes in 1011 patients who had 1031 episodes of thrombolysis documented in the National Audit of Thrombolysis for Acute Leg Ischaemia (NATALI) database. Reports show 140 (12.4%) deaths and 141 (12.4%) amputations. Thirty-day amputation-free survival was seen in 852 (75.2%) patients, with patient age > 80 years and diabetes associated with worse outcomes. Major haemorrhage requiring transfusion or surgery occurred during 87 episodes (7.8%) of thrombolysis; 5 of these were fatal. Minor bleeding occurred in a further 70 episodes (6.3%). Cerebrovascular accident occurred in 26 patients (2.3%).

Plate 2009 presented a multi-variate reanalysis of data from Plate 2006. Life-threatening complications (cardiac events, cerebrovascular accident (CVA), haemorrhagic events) were seen in 15 (12%) patients within 30 days of treatment; all occurred in patients aged > 70 years.

Byrne 2014 reported outcomes in 147 patients (154 limbs) with ALI treated with thrombolysis. Eighty-three limbs were treated with continuous infusion, and 71 with pharmacomechanical thrombolysis (forced infusion) ± continuous infusion. As expected, most patients (70.1%) had grade IIa ischaemia, and roughly 20% and 10% had grade IIb and grade I ischaemia, respectively. Major amputation was required in 15.8%, and 30-day mortality was 5.2%. The most common cause of death was systemic bleeding, which occurred in 5.2%. Fifty-six of the 71 (79%) limbs treated with pharmacomechanical thrombolysis required additional continuous infusion, and duration of treatment in this group was 23.6 hours, which was almost identical to the 25.5 hours reported in the continuous infusion group. Byrne 2014 concluded that equal benefit was evident in both treatment groups.

Earnshaw 2004 and Plate 2009 attempted to identify factors associated with adverse outcomes of thrombolysis. Both identified increasing age and more severe ischaemia as predictors of amputation, death, and major complications.

Several of the studies in this review include patients with intermittent claudication, as well as those with threatened limbs. No studies separated the outcomes of these patient groups. Findings in this review demonstrate a similar incidence of major haemorrhage and amputation, and, taken in conjunction with Braithwaite 1999 and Byrne 2014, suggest that thrombolysis should be used with caution in patients with intermittent claudication.

Two excluded studies highlight the limitations of small studies to give clear conclusions, in spite of the fact that the techniques used were identical (Schweizer 2000; Schweizer 2003). In the first study (Schweizer 2000), use of abciximab was reported to significantly reduce the duration of thrombolysis to a median of 75 minutes compared to 110 minutes in the control group. In the later study, Schweizer 2003, when abciximab was compared with an alternative platelet glycoprotein IIb/IIIa receptor antagonist tirofiban, the median duration of thrombolysis was 149 and 139

minutes, respectively. It would appear that thrombolysis was not as rapid in [Schweizer 2003](#), regardless of the regimen chosen.

Two studies, both reported within a single paper, compared intra-thrombus forced infusion of alteplase with intra-thrombus forced infusion of placebo ([Han 2009a](#); [Han 2009b](#)). In both studies, patients with acute-onset lower limb ischaemia Rutherford grade I and IIa within 21 days of randomisation were judged to require vascular surgical intervention if thrombolysis was unsuccessful. No clear differences in amputation, death, or complications were seen. More interesting is the fact that arterial flow restoration was improved in both groups. Almost one in five patients having only guidewire traversal of the thrombus and infusion of placebo proximal to the thrombus improved sufficiently to be judged to no longer require surgical intervention. Almost two in five patients treated with forced infusion of placebo avoided surgery; this was equivalent to findings for alteplase and suggests that benefit is conferred by forced infusion into the thrombus, regardless of whether this involves a biologically active agent.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to show that any thrombolytic regimen provides a benefit over any other in terms of amputation-free survival, amputation, or 30-day mortality. The rate of CVA or major bleeding requiring surgery or blood transfusion did not clearly differ between regimens, but may occur more frequently in high-dose and IV regimens. This evidence was limited and of very low certainty. Minor bleeding may be more common with high-dose and IV regimens.

Limited very low- and low-certainty evidence from individual trials appears to indicate that greater benefit is seen when the thrombolytic agent is delivered into the thrombus: systemic intravenous thrombolysis is less effective than intra-arterial thrombolysis. 'High-dose' and 'forced-infusion' techniques, or use of adjunctive agents such as platelet glycoprotein IIb/IIIa inhibitors, may speed up thrombolysis, but these approaches are generally more labour-intensive and seem to be associated with increased bleeding complications compared to low-dose regimens; also, no evidence suggests that this leads to improved outcomes (e.g. lower amputation rates, decreased need for adjunctive endovascular or surgical procedures). 'Low-dose continuous infusion', following initial lacing of the thrombus with a high dose of the thrombolytic agent, is the least labour-intensive technique. Thrombolysis

appears to be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa), but, because of risks of major haemorrhage, CVA, and death, thrombolysis should be used with caution in patients who do not have limb-threatening ischaemia (Rutherford grade I). Regimens that decrease the time needed to restore blood flow may permit treatment of patients with immediately threatened limbs (Rutherford grade IIb).

Implications for research

High-certainty evidence is needed to help clinicians determine the most effective technique for peripheral arterial thrombolysis. Future researchers should be aware that only very large multi-centre trials comparing different techniques of thrombolysis are likely to be sufficiently powerful to yield clinically significant results. Although the data on IV versus IA thrombolysis is limited, the publication of [Berridge 1991](#) resulted in an almost exclusive move to IA thrombolysis in the setting of acute lower limb ischaemia. Therefore, a large-scale RCT of IV versus IA thrombolysis is unlikely. Given the increasing use of endovascular technologies such as mechanical thrombectomy or thrombo-aspiration devices, robust studies are needed to determine whether these provide equivalent or better clinical outcomes when compared to CDT in the treatment of ALI.

Future trials must be carefully constructed to ensure that study populations are truly comparable. Inclusion criteria must be clearly stated, and accepted reporting standards adhered to.

Studies focusing on speed of thrombolysis should include patients with Rutherford grade IIb ischaemia or should provide clear cost/benefit analysis demonstrating a financial advantage of the accelerated treatment regimen.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Berridge 1991

Study characteristics

Methods	<p>Study design: prospective randomised, unblinded</p> <p>Exclusion post randomisation: 6 exclusions post randomisation not included in the analysis</p> <p>Losses to follow-up: none</p>
Participants	<p>Country: UK</p> <p>No. of patients: 60 (20 in each group)</p> <p>Age, years: mean 71</p> <p>Gender: 39 M; 21 F</p> <p>Inclusion criteria: critical lower limb ischaemia of < 30 days' duration</p> <p>Exclusion criteria: recent stroke, surgery, or major trauma; childbearing potential; bleeding diathesis; unable to consent; emboli < 2 days' duration; severe ischaemia with good runoff</p>
Interventions	<p>Treatment: IA infusion</p> <p>20 participants rt-PA: 0.5 mg/h (Boehringer Ingelheim, Bracknell, UK) + 250 units heparin (Unihep Leo 1000, Leo Laboratories, Bucks, UK)</p> <p>20 participants streptokinase: 5000 units/h (Streptase, Hoescht, Hounslow, UK) + 250 units heparin. The catheter was repositioned periodically during treatment</p> <p>Control: IV infusion</p> <p>20 participants IV (systemic) rt-PA: variable dose 1, 2, 5, or 10 mg/h rt-PA (max dose 100 mg)</p> <p>Therapy was continued until complete lysis was achieved, or the patient deteriorated, or no further discernible lysis occurred either clinically or radiographically after a 12-hour period</p>
Outcomes	<p>Primary: 30-day and 3-month limb salvage and death</p> <p>Secondary: ABI, duration of thrombolytic therapy, major haemorrhage, CVA</p> <p>3-month follow-up</p>
Funding	Study funded and rt-PA supplied by Boehringer Ingelheim Ltd., Bracknell. Berkshire
Declarations of interest	Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed via a random number programme on a Casio FX-361 calculator with pre-assigned 'last digits' used for each group
Allocation concealment (selection bias)	Unclear risk	No clear details on allocation were provided

Berridge 1991 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned
Other bias	Low risk	No evidence of other bias

Braithwaite 1997
Study characteristics

Methods	<p>Study design: prospective, randomised, unblinded</p> <p>Exclusion post randomisation: 7 exclusions post randomisation not included in the analysis (due to duration of ischaemia (1), patent graft hence no lysis (1), moribund patient (1), breach of infusion protocol (4))</p> <p>Losses to follow-up: none</p>
Participants	<p>Country: UK</p> <p>No. of patients: 100</p> <p>Age, years: mean 71</p> <p>Gender: 61 M; 32 F</p> <p>Inclusion criteria: acute limb ischaemia of < 30 days' duration</p> <p>Exclusion criteria: recent stroke, surgery, or major trauma; childbearing potential; bleeding diathesis</p>
Interventions	<p>Treatment: IA high-dose bolus rt-PA</p> <p>3 × 5-mg doses of tPA (1 mg/mL) were hand-injected into the thrombus at intervals of 5 to 10 minutes, with check angiography through the same catheter after the third injection. If successful lysis was not achieved after the 3 bolus doses, an infusion of 3.5 mg/h (0.1 mg/mL), through a calibrated infusion pump, was commenced for up to 4 hours. If further thrombolysis was required after another angiogram, the infusion rate was reduced to 0.5 to 1 mg/h</p> <p>Control: IA low-dose infusion rt-PA</p> <p>0.5 mg/h or 1 mg/h rt-PA (0.1 mg in 1 mL of 0.9% saline) was given via a calibrated infusion pump</p>
Outcomes	<p>Primary: duration of thrombolytic therapy</p> <p>Secondary: degree of thrombolysis, limb salvage, amputation, major haemorrhage, death, adjunctive procedures</p>

Braithwaite 1997 (Continued)

Funding	"The authors also thank members of the Thrombolysis Study Group who helped develop the protocol and supported the trial....The Thrombolysis Study Group and the National Audit of Thrombolysis for Acute Leg Ischaemia (NATALI) database were financed by Boehringer Ingelheim Ltd and a grant from the Department of Health"
Declarations of interest	Not reported
Notes	30-day follow-up. 19 patients were claudicants; the remainder (81%) had ischaemic rest pain. 39 patients had occlusion of a bypass graft

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation: computer-generated randomisation cards in consecutively numbered sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Computer-generated randomisation cards in consecutively numbered sealed envelopes, but unclear whether envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned
Other bias	Low risk	No evidence of other bias

Comerota 2019

Study characteristics

Methods	Study design: phase 2, randomised, open-label study Exclusion post randomisation: none described Losses to follow-up: 12 (described and accounted for)
Participants	Country: international (Poland, Romania, Slovakia, Belgium, Bulgaria, Czech Republic, Germany, USA, Peru, India, Serbia, Ukraine) No. of patients: 174 Age, years: mean 64 Gender: 135 M; 39 F

Comerota 2019 (Continued)

Inclusion criteria

- > 18 years of age
- Unilateral acute thrombotic limb ischaemia event due to thrombosed native artery or bypass graft with symptom onset within 2 weeks of study entry (i.e. Society for Vascular Surgery acute ischaemic categories I and IIa). Occlusions were required to be 10 cm and confirmed by arteriography

Exclusion criteria

- Ineligible for thrombolytic treatment
- Had received treatment with a full dose of plasminogen activator (e.g. streptokinase, anistreplase, alteplase, reteplase, tenecteplase, urokinase) within the prior 48 hours; treatment with a glycoprotein IIb/IIIa class of platelet inhibitor (e.g. abciximab, eptifibatide, tirofiban) within 5 days before study entry or at any time during the study; or treatment with oral anticoagulants (e.g. warfarin, acenocumarol)
- History of cardiopulmonary resuscitation in the last year
- Previous systemic or anaphylactoid allergy to contrast agent, streptokinase, or blood products (subjects allergic to shellfish or iodine were permitted)
- Active graft infection
- Occlusion occurring within 1 month of synthetic graft placement or 6 months of autologous graft placement
- Sequential composite graft with dual outflows to correct multiple occlusions
- Deemed by the investigator to be medically unable to tolerate an open vascular procedure
- Known prothrombotic state (e.g. anti-cardiolipin antibody, human immunodeficiency virus (HIV)-associated peripheral vascular disease), known contraindication to heparin, haemoglobin < 10.0 g/dL, impaired renal function or renal disease, active cancer except non-malignant tumour or basal cell carcinoma
- History of stroke or intracranial disease

Interventions

Treatment (all intra-arterial)

- 150 mg plasmin administered without initial proximal pulse; 5-hour infusion at 10 mL/h infusion rate
- 150 mg plasmin administered with initial proximal pulse; 5-hour infusion at 15 mL/h infusion rate
- 150 mg plasmin administered with initial proximal pulse; 5-hour infusion at 30 mL/h infusion rate
- 150 mg plasmin administered with initial proximal pulse; 2-hour infusion at 35 mL/h infusion rate
- 150 mg plasmin administered without pulsing; 5-hour infusion at 60 mL/h infusion rate
- 150 mg plasmin administered without pulsing; 2-hour infusion at 75 mL/h infusion rate
- 150 mg plasmin administered without pulsing; 5-hour infusion at 30 mL/h infusion rate with balloon occlusion catheter
- 150 mg plasmin administered without pulsing; 2-hour infusion at 35 mL/h infusion rate with balloon occlusion catheter
- 250 mg plasmin administered without pulsing; 5-hour infusion at 30 mL/h infusion rate with balloon occlusion catheter

Control

- PA administered for 5 hours at dose and volume according to the investigator's clinical judgement/standard practice
- PA placebo (normal saline for injection) administered for 5 hours at dose and volume according to the investigator's clinical judgement/standard practice for PA administration (this group not relevant for meta-analysis, as not an infusion technique)

Outcomes

Primary: number of participants with > 50% thrombolysis, safety of plasmin

Secondary: major and minor bleeding, death, adverse events, abnormal laboratory values (as a measure of safety and tolerability)

Funding

This study was funded by Grifols, the sponsor of this clinical trial. The sponsor (Grifols) participated in study design, data collection, analysis, interpretation, and manuscript preparation

Comerota 2019 (Continued)

Declarations of interest "Anthony J. Comerota has been paid a consulting fee for responsibility as the principal investigator and has received funding as a study site (Jobst Vascular Institute). Lazar Davidovic has received funding as a study site (University of Belgrade, Clinic for Vascular and Endovascular Surgery, Serbian Clinical Center). Richard Shlansky-Goldberg has been paid a consulting fee for responsibility as a steering committee member. Kim Hanna and Kecia L. Courtney are employees of Grifols, which is a manufacturer of plasmin. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose"

Notes 30-day follow-up. No reply to email enquiring about patient/condition classification. One study arm not randomised (M, an exploratory group to evaluate higher dose). We have not included data from this arm. The evaluable population included all subjects receiving 90% of their assigned dose of study drug and having both baseline and EOT arteriograms. Subjects receiving plasmin treatment with BOC must have had confirmed cannulation of the target vessel by post-baseline arteriography and successful BOC inflation. The safety population included all subjects receiving any dose of study drug

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	States "computer-generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	States "computer-generated randomization schedule" but no details on allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in published article. Protocol indicated that unblinded pharmacist would prepare and dispense PA or placebo for infusion. Information about dose and volume of the control group would be provided to the investigator after randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States "the central reading facility comprised three radiologists, who performed blinded, retrospective evaluations of arteriogram imaging..."
Incomplete outcome data (attrition bias) All outcomes	High risk	All withdrawals, or losses to follow-up, reported clearly. Mixture of ITT and per-protocol analysis used. Results from multiple groups combined and analysed together
Selective reporting (reporting bias)	Low risk	All pre-planned outcomes reported in the clinicaltrials.gov record
Other bias	Unclear risk	Changes made post protocol submission (extra treatment arms added)

Cragg 1991
Study characteristics

Methods	Study design: prospective, randomised, unblinded Exclusion post randomisation: 1 exclusion post randomisation not included in analysis Losses to follow-up: not described
Participants	Country: USA No. of patients: 63 (72 infusions)

Cragg 1991 (Continued)

Age, years: mean 61

Gender: 47 M; 16 F

Inclusion criteria: acute and chronic peripheral ischaemia in native arteries and bypass grafts

Exclusion criteria: unable to traverse occlusion with a guidewire, contraindication to thrombolysis including recent stroke or major surgery, bleeding diathesis

Interventions	Treatment: high-dose urokinase; intra-thrombus UK bolus 250,000 U, then IA 250,000 U/h for 4 hours, then 125,000 U/h up to 24 hours Control: low-dose urokinase; intra-thrombus UK bolus 50,000 U, then IA 50,000 U/h up to 24 hours
Outcomes	Primary: duration of thrombolytic therapy, degree of thrombolysis Secondary: angiographic appearance, clinical grade of ischaemia, clinical success
Funding	Not reported
Declarations of interest	Not reported
Notes	Upper limb treated in 2 patients; 30-day follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation: alternation
Allocation concealment (selection bias)	High risk	Allocation based on alternation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded. Participants, but not medical staff, were blinded to dose
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Immediate outcomes reported for all participants; unclear whether all participants had 30-day follow-up
Selective reporting (reporting bias)	Unclear risk	Immediate outcomes reported for all participants; unclear whether all participants had 30-day follow-up
Other bias	Low risk	No evidence of other bias

Duda 2001
Study characteristics

Methods	Study design: blinded (patients and outcome assessors), prospective, randomised
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Duda 2001 (Continued)

	<p>Exclusion post randomisation: none</p> <p>Losses to follow-up: none</p>
Participants	<p>Country: Germany</p> <p>No. of patients: 70</p> <p>Age, years: median 68</p> <p>Gender: 39 M; 31 F</p> <p>Inclusion criteria: Rutherford grade I-IIb ischaemia, native arterial and bypass grafts, occlusion for 6 weeks or less (median duration of symptoms 14 days (range 1 to 42))</p> <p>Exclusion criteria: acute ischaemia requiring immediate revascularisation; recent trauma, stroke, or surgery; childbearing potential; severe hepatic or renal dysfunction; bleeding diathesis; recent thrombolysis</p>
Interventions	<p>Treatment: urokinase plus abciximab</p> <p>IV bolus injection of abciximab 0.25 mg/kg, then IV infusion of abciximab 0.125 µg/kg/m for 12 hours (max 10 µg/m)</p> <p>Initial IA pulse spray bolus of 25,000 IU per 10 cm of thrombus urokinase, then infusion of 4000 IU/m for 2 hours, then 2000 IU/m for a further 2 hours if needed</p> <p>Control: urokinase plus placebo</p> <p>IV 0.9% saline. Initial IA pulse spray bolus of 25,000 IU per 10 cm of thrombus, then infusion of 4000 IU/m for 2 hours, then 2000 IU/m for a further 2 hours if needed</p> <p>Thrombus aspiration and angioplasty were used if there was no recanalisation at 4 hours</p>
Outcomes	<p>Primary: rate of major complications (death, major bleeding), amputation-free survival</p> <p>Secondary: angiographic patency, time to restore flow</p>
Funding	Centocor and Lilly Deutschland
Declarations of interest	Not reported
Notes	Heterogeneous population; control group had more severe ischaemia at presentation. 40% of treatment group were claudicants compared to only 15% of control group. Follow-up available to maximum of 427 days. Approximately 80% of patients had native arterial occlusion, with two-thirds due to thrombolysis and one-third due to embolism

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation: independent computer-generated randomisation; 5:2 ratio study treatment:control
Allocation concealment (selection bias)	Low risk	Study medication allocation schedule was computer-generated by the local Institute for Medical Informatics
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were blinded, but personnel were not

Duda 2001 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Post-treatment angiographic analysis was performed by readers blinded to treatment received, but readers had participated in treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up in initial 30-day period. Longer-term follow-up not relevant to this review
Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned
Other bias	Unclear risk	Differences in baseline levels of participant disease severity (40% of treatment group were claudicants compared to only 15% of control group)

Kandarpa 1993
Study characteristics

Methods	Study design: prospective, randomised, not blinded Exclusions post randomisation: none Losses to follow-up: not described
Participants	Country: USA No. of patients: 25 (25 acutely ischaemic lower limbs) Age, years: mean 63.9 Gender: 11 M; 14 F Inclusion criteria: lower extremity limb ischaemia due to native arterial or bypass graft occlusion of < 30 days' duration Exclusion criteria: unable to cross lesion with guidewire, irreversible ischaemia, internal bleeding within 3 weeks, major surgery biopsy within 10 days, liver dysfunction, uncontrolled hypertension, trauma/CPR, cardiac emboli, bacterial endocarditis, coagulopathy, recent stroke or CNS tumour or surgery, pregnancy, age < 18 years
Interventions	All participants had IV heparin (3000 to 5000 U), then intra-thrombus bolus pulse spray urokinase (25,000 IU/10 cm thrombus delivered as 5 × 0.2-mL aliquots of 25,000 units/mL solution), then either forced infusion or continuous infusion Forced infusion: intra-thrombus urokinase 10,000 IU/mL (4000 IU/min × 2 hours to 0.2 mL/30 seconds, then 2000 IU/min × 2 hours to 0.2 mL/60 seconds (Abbokinase; Abbott Laboratories, USA); for this group, both initial bolus and treatment by prototype pulse spray pump (AngioDynamics) Slow continuous infusion: intra-thrombus urokinase 3000 IU/mL (4000 IU/min × 2 hours to 80 mL/h; 2000 IU/min × 2 hours to 40 mL/h); hand-injected If further therapy was required, urokinase was infused at 1000 units/min (20 mL/h), as required
Outcomes	Primary: patency at 4 hours (defined as 95% thrombolysis by volume), duration of thrombolytic therapy Secondary: limb salvage, amputation, major bleeding, death, adjunctive procedures, duration of hospital stay, 30-day follow-up

Kandarpa 1993 (Continued)

Funding	Supported by grant from AngioDynamics, New York, USA	
Declarations of interest	Not reported	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation by 'selection of consecutively numbered sealed envelopes'
Allocation concealment (selection bias)	Unclear risk	Study authors used consecutively numbered sealed envelopes, but unclear whether envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned
Other bias	Unclear risk	Inconsistent reporting of data in study paper

Plate 2006

Study characteristics	
Methods	Study design: multi-centre, unblinded, prospective, randomised, following angiography Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Sweden No. of patients: 121 Age, years: mean 73 (52 to 89) forced infusion; 72 (47 to 97) continuous low-dose rt-PA infusion; 72 (47 to 97) all Gender: M:F 28:24 pulse spray high-dose forced-infusion rt-PA; 29:34 continuous infusion; 63:58 all Inclusion criteria: sudden-onset unilateral lower limb ischaemia of < 30 days' duration with angiographic evidence of thromboembolic occlusion distal to aortic bifurcation; possible to pass guidewire at least 5 cm into occlusion

Plate 2006 (Continued)

Exclusion criteria: major surgery < 10 days, haematuria < 10 days, gastrointestinal bleeding < 10 days, stroke < 3 months, coagulopathy, pregnancy, brain tumour, malignant hypertension, Dacron prosthesis implanted 3 months, graft infection, irreversible or profound ischaemia, contrast allergy, life expectancy < 30 days, age < 18 years, non-cooperative

Interventions	<p>Treatment: intra-thrombus, forced periodic pulse spray, high -dose infusion rt-PA 0.33 mg/mL, 2 pulses of 0.13 mg (0.4 mL)/min for up to 2 hours, equivalent to 15 mg/h for up to 2 hours or until lysis was complete. Angiography was performed at intervals of 30 minutes, with catheter repositioning as required. If lysis was considered insufficient after 2 hours, complementary low-dose infusion was initiated as below</p> <p>Control: low-dose infusion rt-PA. Initial intra-thrombus bolus of 0.25 mg (2.5 mL), then continuous infusion of 0.5 mg (5 mL)/h (0.1 mg/mL at a rate of 5 mL/h) until thrombolysis complete or 48 hours. During low-dose thrombolysis, 600 U/h of heparin continuously infused (adjusting APTT to 60 to 120 seconds). Angiography was performed at intervals of 12 hours to check on progress. After each angiogram, the catheter was repositioned to ensure it remained within the thrombus</p> <p>After thrombolysis was completed, anticoagulation with low-molecular-weight heparin was administered subcutaneously twice daily for 3 days and patients were given oral anticoagulants or antiplatelet drugs at the discretion of the treating physician</p>
Outcomes	<p>Primary endpoints within 30 days: ordinal scale: death = 5, life-threatening complication = 4, amputation = 3, surgical intervention = 2, reocclusion = 1, none = 0. If more than 1 endpoint reached, single highest endpoint score assigned</p> <p>Secondary endpoints: degree of thrombolysis, patency of occluded vessel, amputation-free survival</p>
Funding	"The study was supported by a generous grant from Stig and Ragna Gorthon's Foundation. The pulse-spray infusion pumps were bought at a greatly reduced price from Gothia Medical AB"
Declarations of interest	"There are no conflicts of interest reported"
Notes	Study terminated prematurely due to poor recruitment; only 121 patients after 3 years. Initial target was 590 patients to be adequately powered to be able to validate study assumption that 30% of control group patients would reach primary endpoint within 30 days at 20% in high-dose group. Pulse spray infusion pumps were bought at a greatly reduced price from Gothia Medical AB, but no conflicts of interest were declared (rt-PA, Actilysew, Boehringer-Ingelheim GmbH, Ingelheim, Germany). Eighteen participants (15%) had viable limbs, and 103 (85%) rest pain or tissue loss

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Randomisation concealed from all participants, but no details on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias)	Low risk	All surviving patients followed up; no loss to follow-up at 30 days

Infusion techniques for peripheral arterial thrombolysis (Review)

Plate 2006 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes reported as planned
Other bias	Unclear risk	Study terminated prematurely (see notes above). It is not clear how severity of limb ischaemia was measured, and participants are described as 'acute and sub-acute'. Rutherford classification not reported

Saroukhani 2015
Study characteristics

Methods	<p>Study design: randomised, single-blind, clinical trial</p> <p>Exclusions post randomisation: 2</p> <p>Losses to follow-up: none</p>
Participants	<p>Country: Iran</p> <p>No. of patients: 40 (2 were excluded); 38 were assigned to undergo intravenous (n = 18) or CDT (n = 20)</p> <p>Age, years: 54.13 ± 13.5 (ranging from 20 to 75)</p> <p>Gender: 23 (60.5%) men; 15 (39.5%) women</p> <p>Inclusion criteria: < 75 years of age, symptoms of < 14 days' duration, ALI grade IIa and IIb according to Rutherford classification, absence of distal runoff in angiography before the intervention</p> <p>Exclusion criteria: severe anaemia (Hb < 8 g/dL), thrombocytopenia (platelet < 80,000/la), low serum fibrinogen (fibrinogen < 100 mg/dL), severe hypertension (systolic > 160 mmHg, diastolic > 100 mmHg), trauma or surgery within previous 14 days before intervention, history of subarachnoid haemorrhage, life expectancy < 14 months, major internal bleeding < 6 months before intervention, pregnancy, lumbar puncture 2 weeks before intervention</p>
Interventions	<p>Treatment: systemic IV alteplase (Activase, Genentech, Inc., San Francisco, USA) 0.6 mg/kg (upper limit of 50 mg) of alteplase; 20% was administered as a bolus, and the remainder was given through IV infusion over a period of 2 hours. Repeat administration a day after initial dose if improvement in peripheral circulation assessment parameters</p> <p>Control: CDT and with IA alteplase (Activase, Genentech, Inc., San Francisco, USA), with infusion rate of 0.05 mg/kg/h. First, 5 mg of alteplase was administered as a bolus; the remainder was given in divided doses every 2 hours over a period of 24 hours. A similar dosage of alteplase was given a day after initial dose if improvement was seen in peripheral circulation assessment parameters</p>
Outcomes	<p>Primary: improvement in clinical status, defined as upward shift of at least 1 grade in Rutherford classification, improvement in ABI (≥ 0.1), upward shift of at least 2 scores on VAS (pain severity)</p> <p>Secondary: complete or near-complete recanalisation of occluded artery in angiography</p> <p>Patency and clinical outcomes were measured according to the Rutherford classification, ABI, and VAS. Adverse events related to the intervention including haemorrhage, haematoma, and hypersensitivity reaction were recorded</p>
Funding	Supported by Deputy Research of Mashhad University of Medical Sciences
Declarations of interest	"Conflict of interest: none declared"

Saroukhani 2015 (Continued)

Notes We contacted study authors to request clarification over inconsistencies in the published article. A response was received clarifying that angiography was carried out in both groups; mean age in the IV group was 58.55 ± 9.98 , and "4 patients (10.5%) developed minor side effects (bleeding from puncture site) in the CDT group, no major or minor effect in IV group"

6-month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned to two study groups using a computer-based random digit generator"
Allocation concealment (selection bias)	Unclear risk	Computer-based digit randomisation used but no details on allocation provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The interventionists and the patients were not blinded to the route of therapy". Blinding would not be possible given the interventions carried out. Given unclear risk judgement, as outcome assessors were blinded but potential for bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...those recording the outcome and measuring the indices were blinded to the study groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants completed the study and were analysed
Selective reporting (reporting bias)	Low risk	All pre-planned outcomes as described in the methods section are reported
Other bias	High risk	Patient baselines: mean age CDT 55.5 compared to 88.5 in IV group, and inclusion criteria listed as 75 years old or younger. Wide SDs and judged to be not significant by study authors. Study authors report that "Post intervention angiography was not performed in [IV] this group", yet comparisons are reported. Inconsistencies between text reported and data (i.e. "...no significant difference between two groups (P = 0.017)")

Yusuf 1995
Study characteristics

Methods	Study design: prospective, unblinded, randomised Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: UK No. of patients: 18 Age, years: median 71 (pulse spray), 74 (continuous infusion) Gender: M:F not described

Infusion techniques for peripheral arterial thrombolysis (Review)

Yusuf 1995 (Continued)

Inclusion criteria: lower extremity ischaemia for 1 to 42 days

Exclusion criteria: active internal bleeding, recent stroke or surgery, infected bypass graft, pregnancy, inability to provide consent, inability to traverse lesion with a guidewire, inability to withstand further ischaemia up to 24 hours, irreversible ischaemia

Interventions	<p>Treatment: intra-arterial pulse spray rt-PA at 0.33 mg/mL: bolus of 0.2 mL (0.066 mg) every 15 seconds for the first 15 minutes and every 30 seconds thereafter, equivalent to 10 mg/h. Clinical observations were taken every 15 minutes, and angiography was performed at intervals of 30 to 120 minutes. Percutaneous transluminal balloon dilatation of any underlying stenosis was performed if required. If any residual thrombus was detected at this stage, the catheter was left for slow infusion of rt-PA via the end hole at a rate of 1 mg/h</p> <p>Control: intra-arterial infusion rt-PA at 0.5 mg/h (0.05 mg/mL at a rate of 10 mL/h). Angiography was performed at intervals of 3 to 8 hours to check on progress. After each angiogram, the catheter was repositioned to ensure it remained within the thrombus</p> <p>rt-PA protocols: pulse spray forced infusion or low-dose infusion</p>
Outcomes	<p>Primary: duration of thrombolytic therapy</p> <p>Secondary: radiological evidence of thrombolysis, increase in ABI, limb salvage at 30 days, amputation, death</p>
Funding	Not reported
Declarations of interest	Not reported
Notes	30-day follow-up. Five (28%) had viable limbs, and 13 (72%) had threatened limb viability

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation using sequentially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported as planned
Other bias	Low risk	No evidence of other bias

ABI: ankle-brachial index

ALI: acute limb ischaemia
 APTT: activated partial thromboplastin time
 BOC: balloon occlusion catheter
 CDT: catheter-directed thrombolysis
 CNS: central nervous system
 CPR: cardiopulmonary resuscitation
 CVA: cerebrovascular accident
 IA: intra-arterial
 ITT: intention-to-treat
 IV: intra-venous
 PA: plasminogen activator
 rt-PA: recombinant tissue plasminogen activator
 VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bagan 2013	Not a randomised trial. Participants mainly Rutherford grade I intermittent claudication
Han 2009a	Compares intra-thrombus forced infusion of kalimeters with intra-thrombus forced infusion of placebo and peri-thrombus placebo. Does not compare infusion techniques of thrombolytics
Han 2009b	Compares intra-thrombus forced infusion of alfineprase with intra-thrombus forced infusion of placebo. Does not compare infusion techniques of thrombolytics
Marder 2012	Pilot phase 1 safety study, not a randomised trial
NCT00073554	(HA002/NAPA1) Dose-escalation study to evaluate the safety and activity of alfineprase in patients with acute peripheral arterial occlusion
NCT00115999	(HA004/NAPA2) Compares safety and efficacy of intra-thrombus forced infusion of alfineprase 0.3 mg/kg with placebo. Does not compare infusion techniques of thrombolytics
NCT02093468	<p>Study aimed to evaluate the safety and efficacy of MST-188 (CDT rt-PA) for acute lower limb ischaemia, but study was terminated early (4 participants)</p> <p>Quote: "program discontinued to pursue alternate indications"</p>
Poredos 1999	Mean duration of ischaemia > 30 days. Used Fontaine classification for chronic limb ischaemia rather than Rutherford classification for acute limb ischaemia. Severity of ischaemia not adequately classified. Method of randomisation unclear. Impossible to assess limb salvage. Only immediate post-procedure outcome; no subsequent follow-up
Schweizer 2000	Duration of ischaemia unclear. Majority of patients had intermittent claudication, not critical ischaemia. Used Fontaine classification for chronic limb ischaemia rather than Rutherford classification for acute limb ischaemia. Majority of patients classed as grade IIb/III (i.e. short distance claudication and rest pain, when it should be one or the other). Thrombosuction performed before thrombolysis. Details of administration of thrombolysis not specified. Surrogate endpoints: re-admission to hospital, re-intervention
Schweizer 2003	Duration of ischaemia unclear. Majority of patients had intermittent claudication, not critical ischaemia. Used Fontaine classification for chronic limb ischaemia rather than Rutherford classification for acute limb ischaemia. Majority of patients classed as grade IIb/III (i.e. short distance claudication and rest pain when it should be one or the other). Thrombosuction performed before thrombolysis. Details of administration of thrombolysis not specified. Surrogate endpoints: re-admission to hospital, re-intervention
Verhamme 2012	Not a randomised trial; phase 2a safety and efficacy study

Study	Reason for exclusion
Yuan 2013	Not a randomised trial; review of patients treated before and after a change in dose of thrombolytic agent. Patients mainly chronic stable disease: > 30 days' symptoms (83%), Rutherford grade I intermittent claudication (64%)
Zhang 2014	Participants randomised to receive either 10 or 20 mg of rt-PA by CDT, but then also received endovascular intervention before outcomes measured. Cannot determine effects of infusion technique

CDT: catheter-directed thrombolysis.
 rt-PA: recombinant tissue plasminogen activator.

DATA AND ANALYSES

Comparison 1. Intra-arterial delivery versus intravenous delivery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 30-Day amputation-free survival	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.40, 7.34]
1.2 Amputation	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.1 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.2 Up to 6 months	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 30-Day mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Vessel patency	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 Radiological success - complete	1	40	Odds Ratio (M-H, Fixed, 95% CI)	13.22 [2.79, 62.67]
1.4.2 Radiological success - partial	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.67]
1.4.3 Radiological failure	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.38]
1.5 Cerebrovascular accident	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
1.6 Major bleeding	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.53]
1.7 Minor bleeding	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.56]

Analysis 1.1. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 1: 30-Day amputation-free survival

Study or Subgroup	IA		IV		Weight	Odds Ratio	Odds Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berridge 1991	16	20	14	20	100.0%	1.71 [0.40 , 7.34]	
Total (95% CI)		20		20	100.0%	1.71 [0.40 , 7.34]	
Total events:	16		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.73 (P = 0.47)							
Test for subgroup differences: Not applicable							

Analysis 1.2. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 2: Amputation

Study or Subgroup	IA		IV		Weight	Odds Ratio	Odds Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.2.1 30 days							
Berridge 1991	1	20	0	20		3.15 [0.12 , 82.16]	
1.2.2 Up to 6 months							
Berridge 1991 (1)	1	20	1	20		1.00 [0.06 , 17.18]	
Saroukhani 2015 (2)	4	20	6	18		0.50 [0.11 , 2.17]	

Footnotes

- (1) 3 month data; IV rt-PA with IA rt-PA
- (2) 6 month data: IV alteplase vs IA alteplase

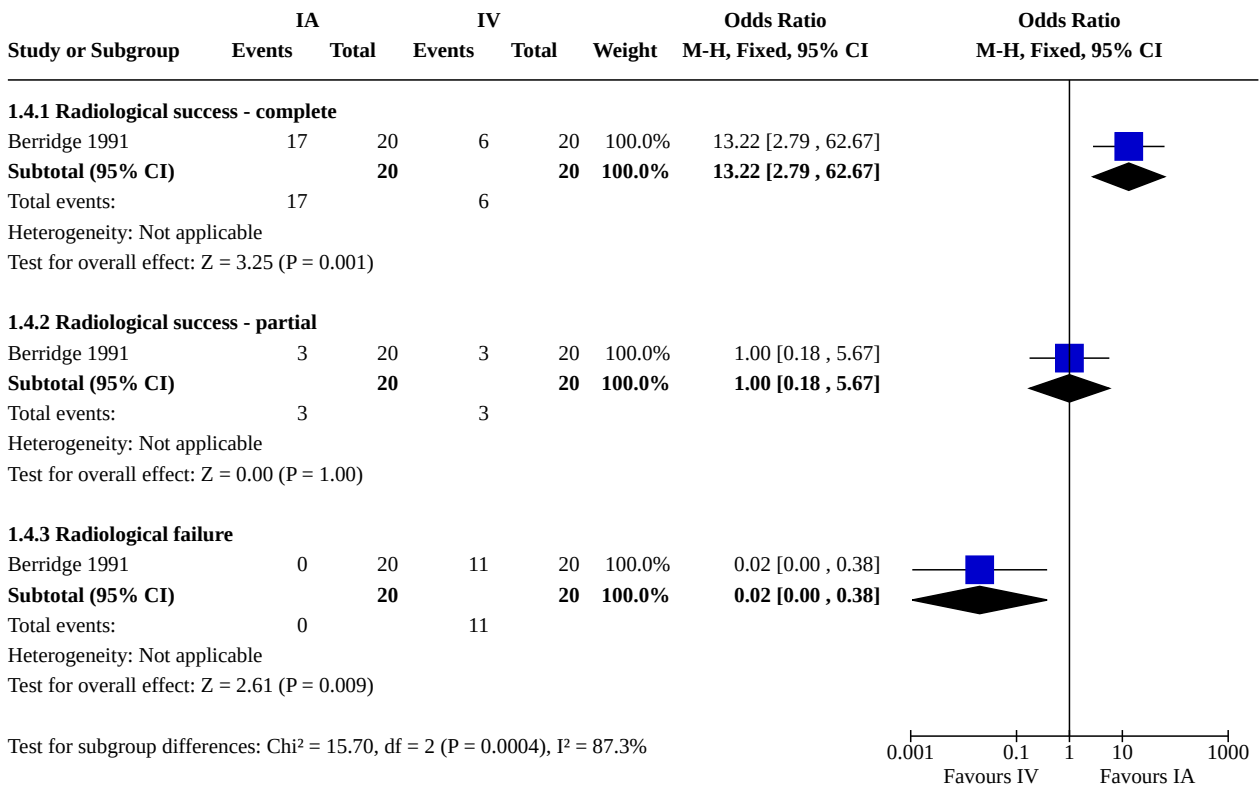
Analysis 1.3. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 3: 30-Day mortality

Study or Subgroup	IA		IV		Weight	Odds Ratio	Odds Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berridge 1991 (1)	3	20	3	20		1.00 [0.18 , 5.67]	
Saroukhani 2015 (2)	0	20	0	18		Not estimable	

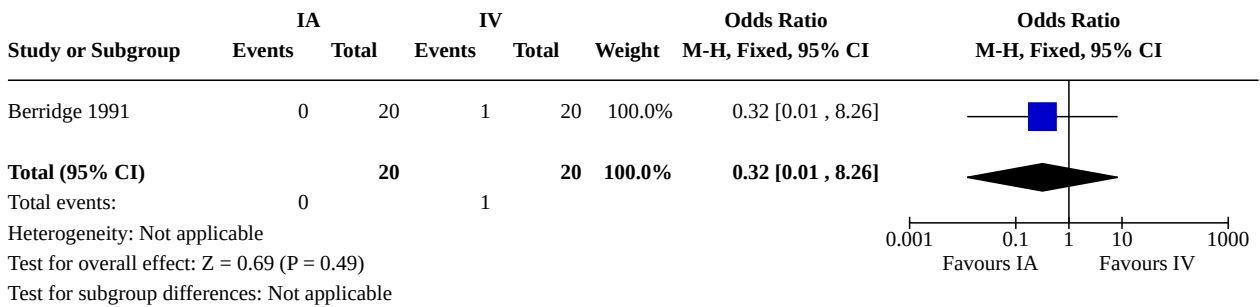
Footnotes

- (1) IV rt-PA vs IA rt-PA
- (2) IV alteplase vs IA alteplase

Analysis 1.4. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 4: Vessel patency



Analysis 1.5. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 5: Cerebrovascular accident



Analysis 1.6. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 6: Major bleeding

Study or Subgroup	IA		IV		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Berridge 1991	0	20	3	20	100.0%	0.12 [0.01 , 2.53]	
Total (95% CI)		20		20	100.0%	0.12 [0.01 , 2.53]	
Total events:	0		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1: Intra-arterial delivery versus intravenous delivery, Outcome 7: Minor bleeding

Study or Subgroup	IA		IV		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Berridge 1991	0	20	9	20	100.0%	0.03 [0.00 , 0.56]	
Total (95% CI)		20		20	100.0%	0.03 [0.00 , 0.56]	
Total events:	0		9				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable

Comparison 2. High dose versus low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 30-Day amputation-free survival	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Amputation	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3 30-Day mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4 Vessel patency	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4.1 Complete lysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4.2 Clinically useful lysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4.3 75% lysis - post thrombolysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4.4 Incomplete lysis - 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5 Cerebrovascular accident	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6 Major bleeding	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 Minor bleeding	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: High dose versus low dose, Outcome 1: 30-Day amputation-free survival

Study or Subgroup	Low dose		High dose		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Braithwaite 1997 (1)	37	44	39	49	1.36 [0.47 , 3.93]	
Plate 2006 (2)	54	63	49	58	1.10 [0.40 , 3.00]	
Yusuf 1995 (3)	6	9	9	9	0.10 [0.00 , 2.23]	

Footnotes

- (1) IA rt-PA; low dose continuous infusion vs high dose bolus
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

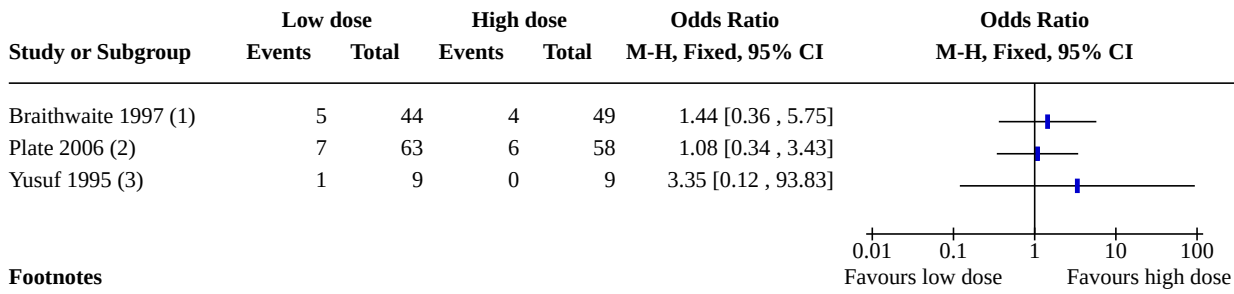
Analysis 2.2. Comparison 2: High dose versus low dose, Outcome 2: Amputation

Study or Subgroup	Low dose		High dose		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Braithwaite 1997 (1)	2	44	6	49	0.34 [0.07 , 1.79]	
Plate 2006 (2)	3	63	4	58	0.68 [0.14 , 3.15]	
Yusuf 1995 (3)	2	9	0	9	6.33 [0.26 , 152.86]	

Footnotes

- (1) IA rt-PA; low dose continuous infusion vs high dose bolus
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

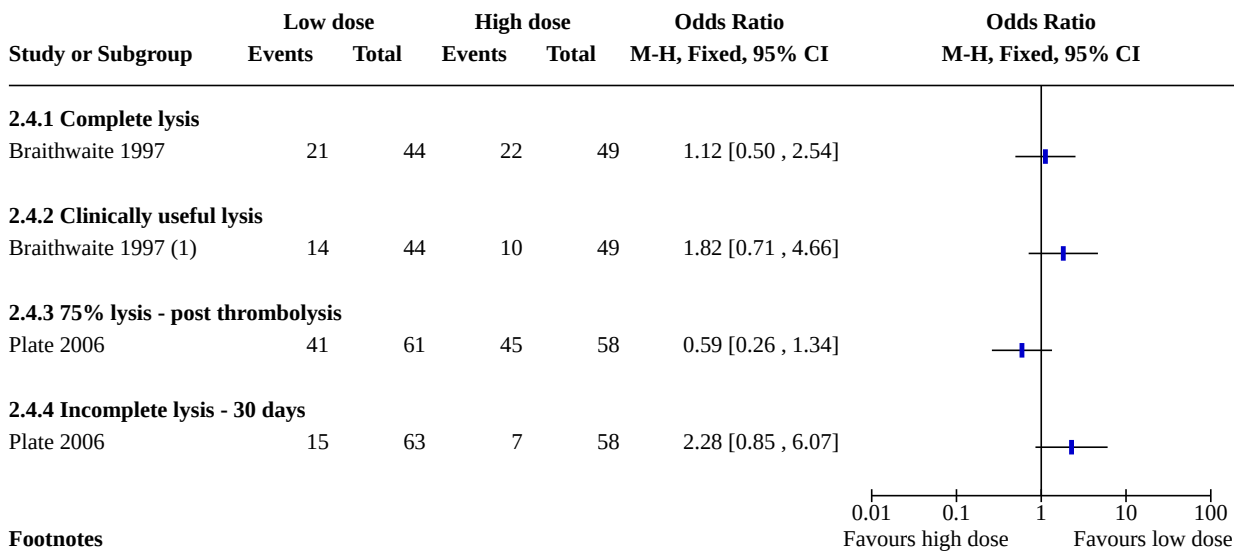
Analysis 2.3. Comparison 2: High dose versus low dose, Outcome 3: 30-Day mortality



Footnotes

- (1) IA rt-PA; low dose continuous infusion vs high dose bolus
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

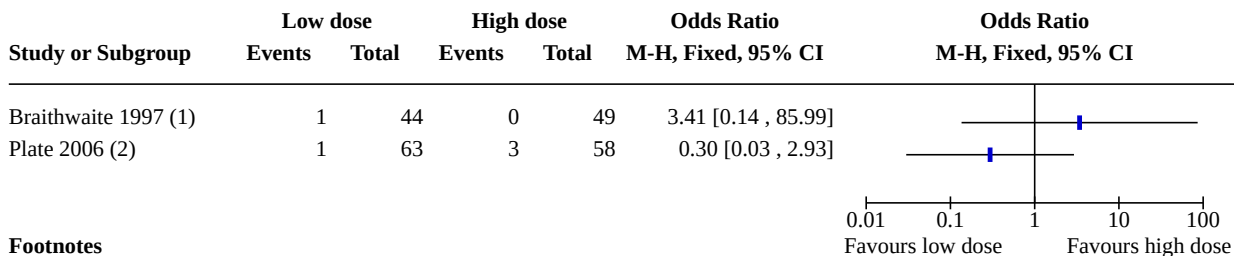
Analysis 2.4. Comparison 2: High dose versus low dose, Outcome 4: Vessel patency



Footnotes

- (1) Braithwaite reports on complete lysis

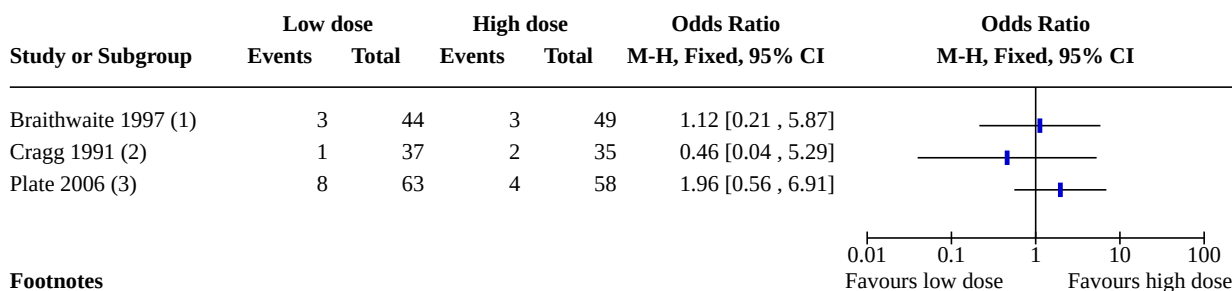
Analysis 2.5. Comparison 2: High dose versus low dose, Outcome 5: Cerebrovascular accident



Footnotes

- (1) IA rt-PA; low dose continuous infusion vs high dose bolus
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion

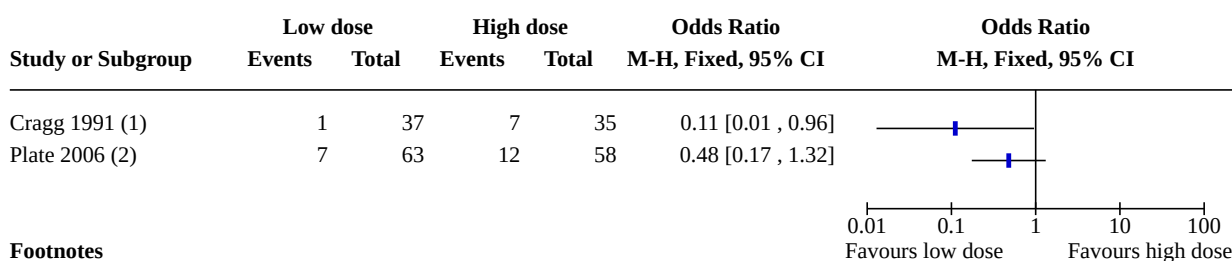
Analysis 2.6. Comparison 2: High dose versus low dose, Outcome 6: Major bleeding



Footnotes

- (1) IA rt-PA; low dose continuous infusion vs high dose bolus
- (2) UK; low dose vs high dose intra-thrombus/IA infusion
- (3) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion

Analysis 2.7. Comparison 2: High dose versus low dose, Outcome 7: Minor bleeding



Footnotes

- (1) UK; low dose vs high dose intra-thrombus/IA infusion
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion

Comparison 3. Continuous infusion versus pulse/forced infusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 30-Day amputation-free survival	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Amputation	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.3 30-Day mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.4 Vessel patency	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.4.1 90% thrombolysis (4 hours)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.4.2 90% thrombolysis (2 or 5 hours)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5 Cerebrovascular accident	1	121	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 2.93]
3.6 Major bleeding	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Minor bleeding	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 1: 30-Day amputation-free survival

Study or Subgroup	CI		Pulse		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Kandarpa 1993 (1)	11	13	10	12	1.10 [0.13 , 9.34]	
Plate 2006 (2)	54	63	49	58	1.10 [0.40 , 3.00]	
Yusuf 1995 (3)	6	9	9	9	0.10 [0.00 , 2.23]	

Footnotes

- (1) intra-thrombus UK; continuous vs pulse spray
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

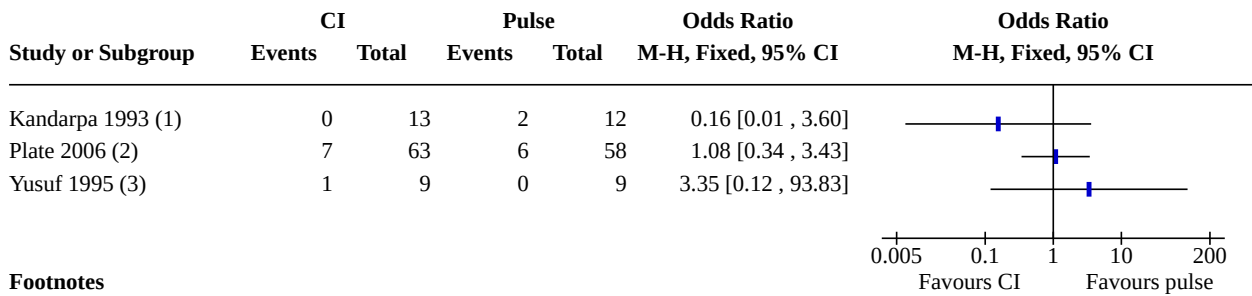
Analysis 3.2. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 2: Amputation

Study or Subgroup	CI		Pulse		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Kandarpa 1993 (1)	2	13	0	12	5.43 [0.24 , 125.59]	
Plate 2006 (2)	3	63	4	58	0.68 [0.14 , 3.15]	
Yusuf 1995 (3)	2	9	0	9	6.33 [0.26 , 152.86]	

Footnotes

- (1) intra-thrombus UK; continuous vs pulse spray
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

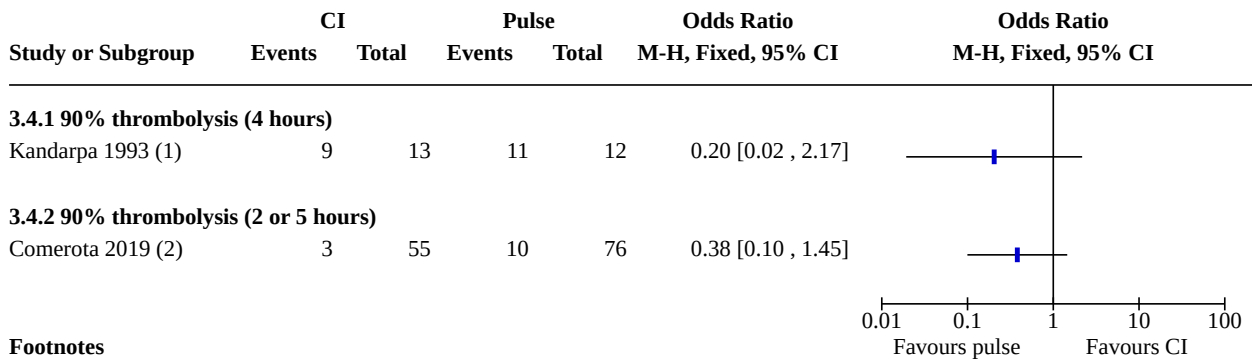
Analysis 3.3. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 3: 30-Day mortality



Footnotes

- (1) intra-thrombus UK; continuous vs pulse spray
- (2) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (3) IA rt-PA; low dose continuous infusion vs high dose pulse spray

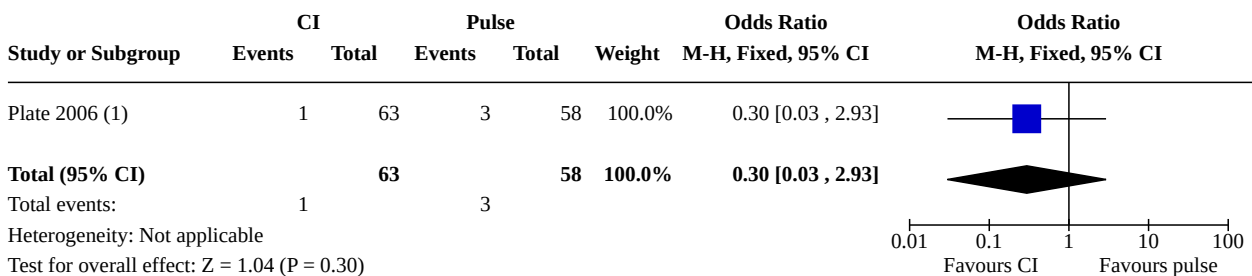
Analysis 3.4. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 4: Vessel patency



Footnotes

- (1) intra-thrombus UK; continuous vs pulse spray
- (2) IA plasmin; CI vs pulse spray (2 or 5h; w/wo BOC)

Analysis 3.5. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 5: Cerebrovascular accident

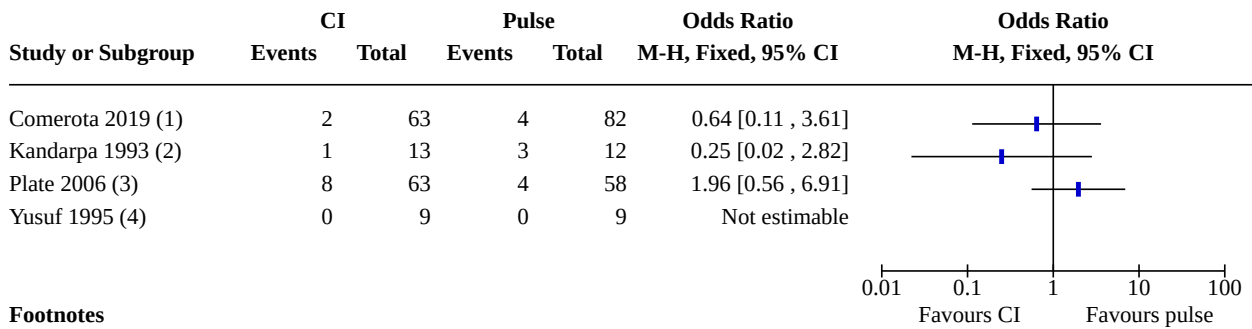


Heterogeneity: Not applicable
 Test for overall effect: Z = 1.04 (P = 0.30)
 Test for subgroup differences: Not applicable

Footnotes

- (1) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion

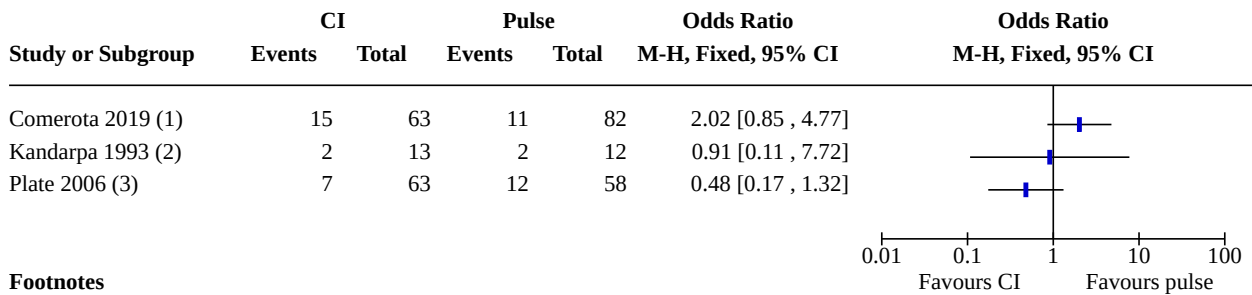
Analysis 3.6. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 6: Major bleeding



Footnotes

- (1) IA plasmin; CI vs pulse spray (2 or 5h; w/wo BOC)
- (2) intra-thrombus UK; continuous vs pulse spray
- (3) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion
- (4) IA rt-PA; low dose continuous infusion vs high dose pulse spray

Analysis 3.7. Comparison 3: Continuous infusion versus pulse/forced infusion, Outcome 7: Minor bleeding



Footnotes

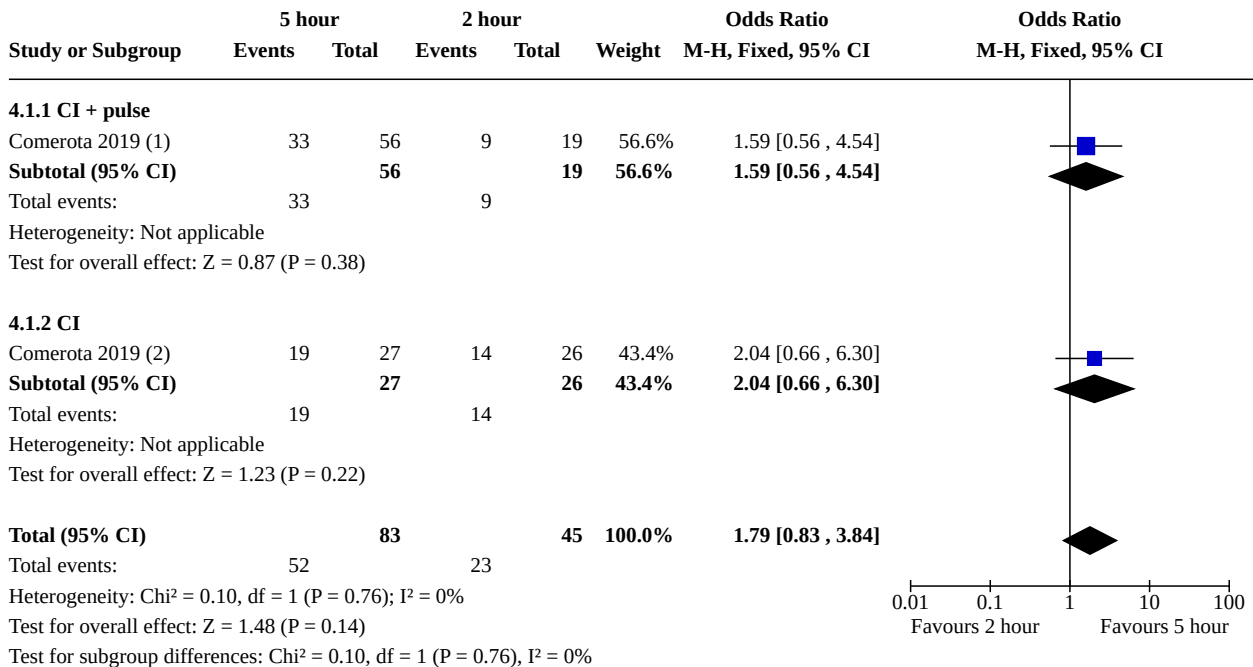
- (1) IA plasmin; CI vs pulse spray (2 or 5h; w/wo BOC)
- (2) intra-thrombus UK; continuous vs pulse spray
- (3) rt-PA; low dose IA continuous infusion vs high dose intra-thrombus forced infusion

Comparison 4. Continuous infusion with additional pulse or BOC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 50% thrombolysis: 5 hours vs 2 hours ± pulse	1	128	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.83, 3.84]
4.1.1 CI + pulse	1	75	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.56, 4.54]
4.1.2 CI	1	53	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.66, 6.30]
4.2 50% thrombolysis: CIF + pulse vs CIF	1	128	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.42]
4.2.1 5-hour infusion	1	83	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.23, 1.61]
4.2.2 2-hour infusion	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.24, 2.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 50% thrombolysis: BOC vs no BOC	1	128	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.46, 2.58]
4.3.1 5-hour infusion	1	83	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.52, 6.28]
4.3.2 2-hour infusion	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.17, 2.21]
4.4 90% thrombolysis: 5 hours vs 2 hours ± pulse	1	131	Odds Ratio (M-H, Fixed, 95% CI)	8.17 [1.00, 66.60]
4.4.1 CIF + pulse	1	76	Odds Ratio (M-H, Fixed, 95% CI)	8.62 [0.48, 154.44]
4.4.2 CIF	1	55	Odds Ratio (M-H, Fixed, 95% CI)	7.55 [0.37, 153.42]
4.5 90% thrombolysis: ± BOC	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Major bleeding: 5 hours vs 2 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7 Minor bleeding: 5 hours vs 2 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

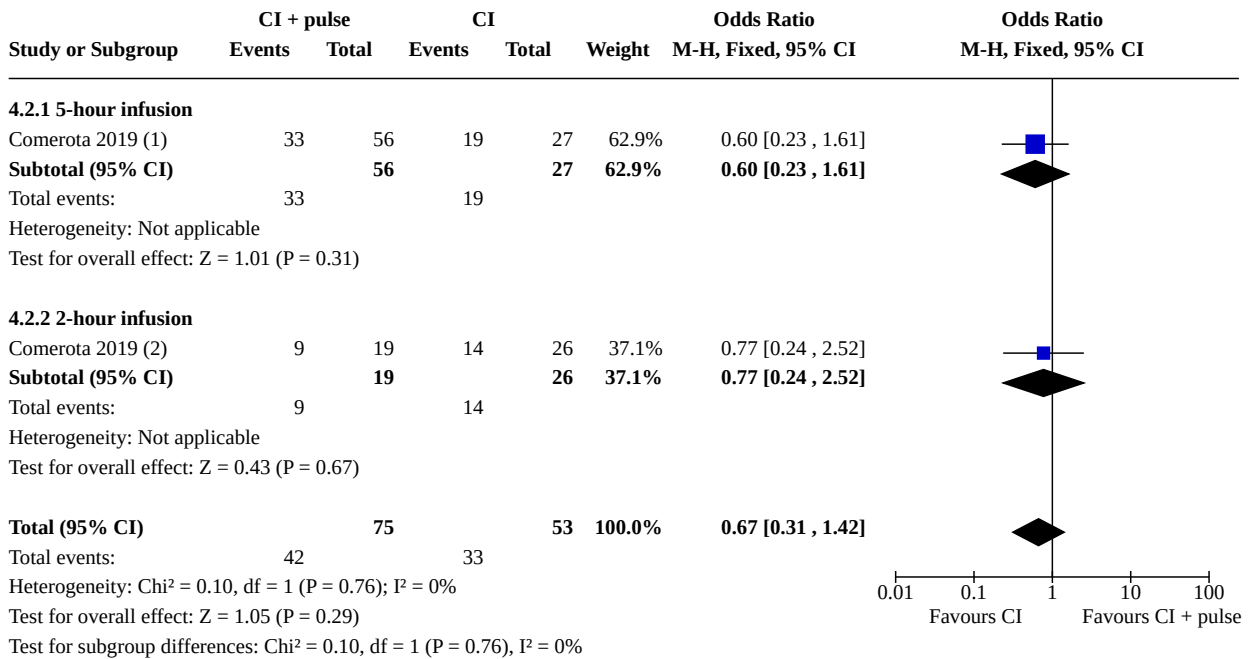
Analysis 4.1. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 1: 50% thrombolysis: 5 hours vs 2 hours ± pulse



Footnotes

- (1) IA plasmin; 5 hour vs 2 hr (CI vs pulse spray; w/wo BOC)
- (2) 2 subgroups receiving CI also had BOC (one each in 5h and 2h infusion)

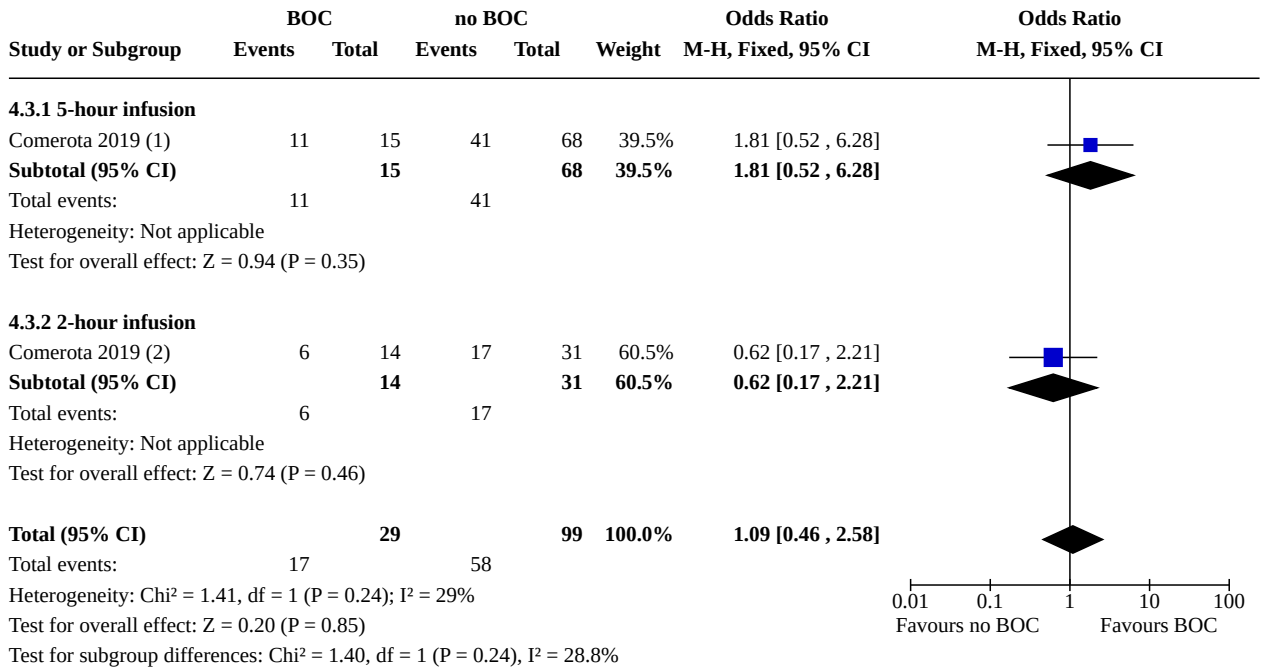
Analysis 4.2. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 2: 50% thrombolysis: CIF + pulse vs CIF



Footnotes

- (1) IA plasmin; CI vs pulse spray (2 or 5h; w/wo BOC)
- (2) 2 subgroups receiving CI also had BOC (one each in 5h and 2h infusion)

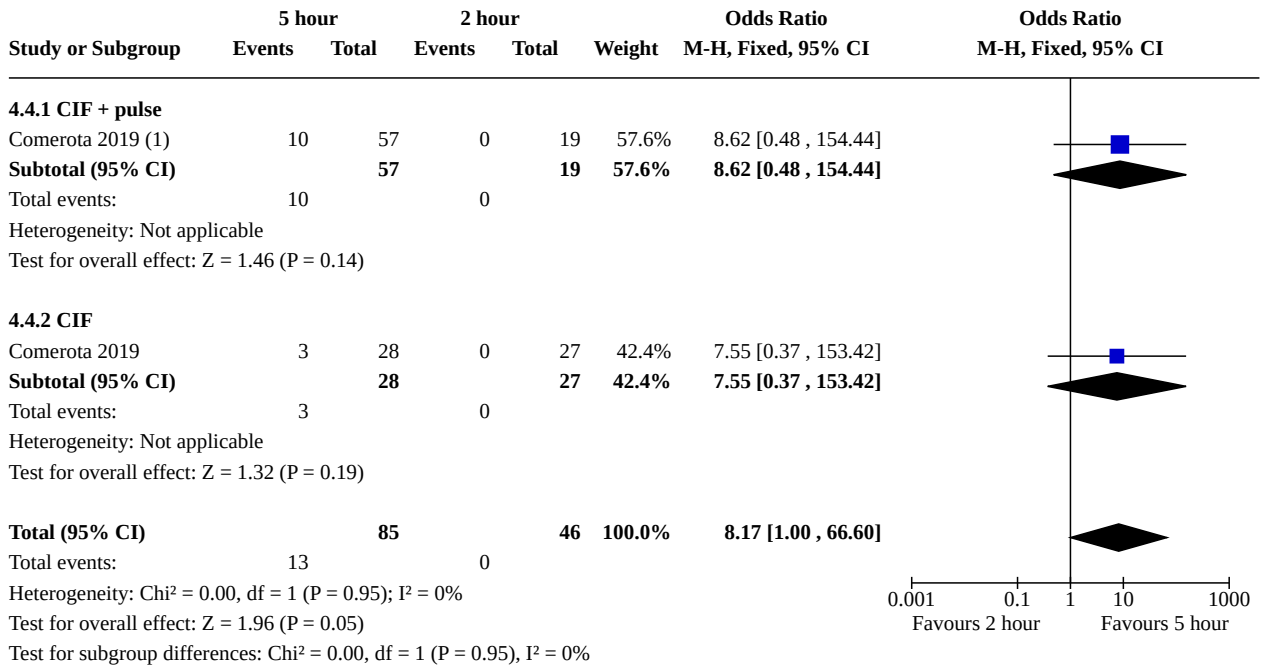
Analysis 4.3. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 3: 50% thrombolysis: BOC vs no BOC



Footnotes

- (1) IA plasmin; CI or pulse spray, 2 or 5h, w/wo BOC
- (2) Subgroups with BOC were CI, without BOC with either CI or CI plus pulse

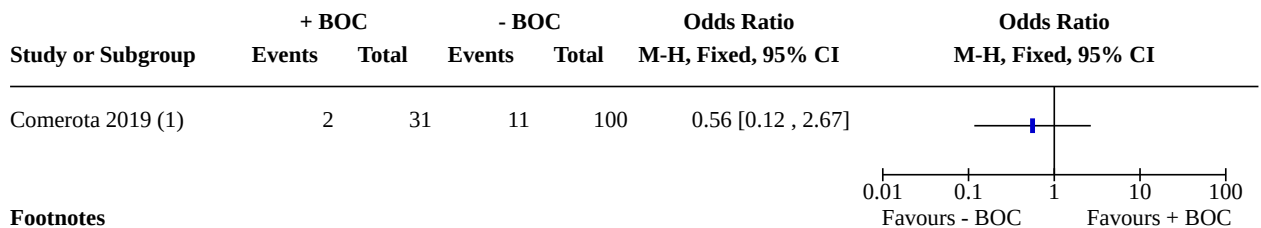
Analysis 4.4. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 4: 90% thrombolysis: 5 hours vs 2 hours ± pulse



Footnotes

(1) IA plasmin; CI or pulse spray, 2 or 5h, w/wo BOC

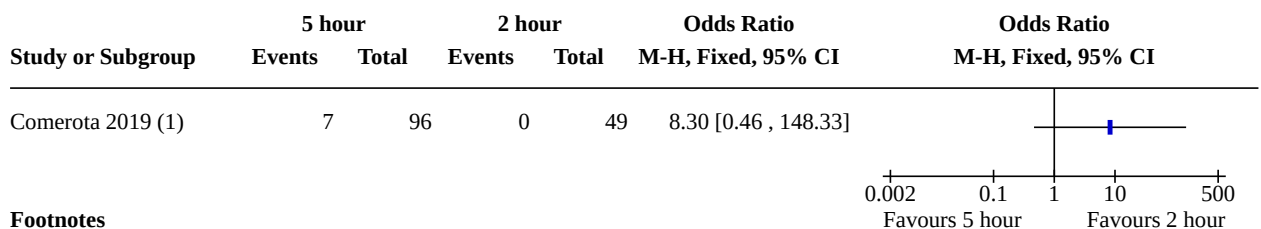
Analysis 4.5. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 5: 90% thrombolysis: ± BOC



Footnotes

(1) IA plasmin; CI or pulse spray; 2 or 5h; w/wo BOC

Analysis 4.6. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 6: Major bleeding: 5 hours vs 2 hours



Footnotes

(1) IA plasmin; CI or pulse spray, 2 or 5h; w/wo BOC

Analysis 4.7. Comparison 4: Continuous infusion with additional pulse or BOC, Outcome 7: Minor bleeding: 5 hours vs 2 hours

Study or Subgroup	5 hour		2 hour		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Comerota 2019 (1)	19	96	7	49	1.48 [0.58, 3.81]	

Footnotes

(1) IA plasmin; CI or pulse spray, 2 or 5h; w/wo BOC

Comparison 5. Urokinase with or without adjunctive antiplatelet agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Vessel patency	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1.1 Initial patency by means of thrombolysis alone	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1.2 Initial patency with thrombolysis and subsequent percutaneous intervention	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.2 Major bleeding	1	70	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 4.90]
5.3 Minor bleeding	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.44, 5.26]

Analysis 5.1. Comparison 5: Urokinase with or without adjunctive antiplatelet agents, Outcome 1: Vessel patency

Study or Subgroup	Urokinase		Adjunctive agents		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
5.1.1 Initial patency by means of thrombolysis alone						
Duda 2001 (1)	14	20	33	50	1.20 [0.39, 3.69]	
5.1.2 Initial patency with thrombolysis and subsequent percutaneous intervention						
Duda 2001 (2)	20	20	44	50	5.99 [0.32, 111.44]	

Footnotes

(1) IV saline then IA pulse spray UK vs IV abciximab then IA pulse spray UK

(2) Initial patency achieved with thrombolysis and subsequent percutaneous intervention

Analysis 5.2. Comparison 5: Urokinase with or without adjunctive antiplatelet agents, Outcome 2: Major bleeding

Study or Subgroup	Urokinase		Adjunctive agents		Weight	Odds Ratio		Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Duda 2001 (1)	0	20	4	50	100.0%	0.25 [0.01, 4.90]		
Total (95% CI)		20		50	100.0%	0.25 [0.01, 4.90]		
Total events:	0		4					
Heterogeneity: Not applicable Test for overall effect: Z = 0.91 (P = 0.36) Test for subgroup differences: Not applicable								

Footnotes

(1) IV saline then IA pulse spray UK vs IV abciximab then IA pulse spray UK

Analysis 5.3. Comparison 5: Urokinase with or without adjunctive antiplatelet agents, Outcome 3: Minor bleeding

Study or Subgroup	Urokinase		Adjunctive agents		Weight	Odds Ratio		Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Duda 2001 (1)	5	20	9	50	100.0%	1.52 [0.44, 5.26]		
Total (95% CI)		20		50	100.0%	1.52 [0.44, 5.26]		
Total events:	5		9					
Heterogeneity: Not applicable Test for overall effect: Z = 0.66 (P = 0.51) Test for subgroup differences: Not applicable								

Footnotes

(1) IV saline then IA pulse spray UK vs IV abciximab then IA pulse spray UK

ADDITIONAL TABLES

Table 1. Trials comparing intravenous and intra-arterial delivery of the agent

	Berridge 1991	Saroukhani 2015
Intervention	IV rt-PA	IV alteplase (rt-PA)
Comparison	IA rt-PA	IA (CDT) alteplase
30-Day amputation-free survival	IV rt-PA = 14/20 (70%) ^a IA rt-PA = 16/20 (80%) ^b	Not reported
Amputation	30 days IV rt-PA = 0% IA rt-PA = 1/20 (5%) 3 months IV rt-PA = 1/20 (5%)	6 months IV rt-PA = 6/18 (33%) IA rt-PA = 4/20 (20%)

Table 1. Trials comparing intravenous and intra-arterial delivery of the agent (Continued)

	IA rt-PA = 1/20 (5%)	
Mortality	IV rt-PA = 3/20 (15%) IA rt-PA = 3/20 (15%)	No deaths at 6 months
Vessel patency	Complete IV rt-PA = 6/20 (30%) IA rt-PA = 17/20 (85%) Partial (restoration of flow down to next major distal artery) IV rt-PA = 3/20 (15%) IA rt-PA = 3/20 (15%) Failure IV rt-PA = 11/20 (55%) IA rt-PA = 0/20 (0%)	Angiographic improvement reported to be higher in the IA group (P < 0.001)
Duration of thrombolysis	IV not reported IA rt-PA 35 (14 to 64) hours (median and range)	IV rt-PA infusion 2 hours IA rt-PA every 2 hours for 24-hour period Both regimens repeated day after, if improvement seen
CVA	IV rt-PA = 1/20 (5%) IA rt-PA = 0/20 (0%)	Not reported
Bleeding (major)	IV rt-PA = 3/20 (15%) IA rt-PA = 0/20 (0%)	IV rt-PA 0/18 (0%) IA rt-PA 0/20 (0%)
Bleeding (minor)	IV rt-PA = 9/20 (45%) IA rt-PA = 0/20 (0%)	Bleeding not specifically reported IV 0% minor complications IA 4/20 (20%) minor complications

CDT: catheter-directed thrombolysis.

CVA: cerebrovascular accident.

IA: intra-arterial.

IV: intravenous.

rt-PA: recombinant tissue plasminogen activator.

^a5 of 14 patients had ongoing critical ischaemia.

^bNo patients had symptomatic ischaemia.

Table 2. Trials comparing high- and low-dose regimens of the thrombolytic agent

	Braithwaite 1997	Cragg 1991	Plate 2006	Yusuf 1995
Intervention	LD infusion (rt-PA)	LD bolus and LD infusion (urokinase)	CIF (rt-PA)	CIF (rt-PA)

Table 2. Trials comparing high- and low-dose regimens of the thrombolytic agent (Continued)

Comparison	HD bolus and HD infusion (rt-PA)	HD bolus and HD infusion (urokinase)	HD forced infusion (rt-PA)	HD forced-infusion PS (rt-PA)
30-Day amputation-free survival	LD = 37/44 (84%) HD = 39/49 (80%)	Overall 1 death and 5 amputations, 6/63 (9.5%)	PS = 49/58 (84%) CIF = 54/63 (86%) ^a	CIF = 6/9 (67%) PS = 9/9 (100%)
Amputation	LD = 2/44 (4.5%) HD = 6/49 (12%)	5/63 (7.9%) Most were in the HD group	PS = 4/58 (7%) CIF = 3/63 (5%)	CIF = 2/9 (22%) PS = 0/9 (0%)
Mortality	LD = 5/44 (11%) HD = 4/49 (8%)	1, but not clear which group	PS = 6/58 (10%) CIF = 7/63 (11%)	CIF = 1/9 (12%) PS = 0/9 (0%)
Vessel patency	Complete lysis LD 21/44 (48%) HD 22/49 (45%) Clinically useful lysis LD 14/44 (32%) HD 10/49 (20%)	Complete lysis (number and time) LD - NA 12 (71) 26.0 ± 11.2 (24) LD - G 14 (80) 18.2 ± 7.9 (12) HD NA 10 (58) 20.8 ± 13.7 (12) HD - G 15 (83) 16.5 ± 11.9 (12) number (%) mean ± SD (median) hours	> 75% lysis on completion of thrombolysis (without adjunctive procedure) PS HD 45/58 (78%) CIF LD 41/61 (67%) 30-Day reocclusion PS HD 8/58 (13%) ^b CIF LD 9/63 (14%) ^b 30-Day incomplete lysis PS 7/58 (12%) CIF 15/63 (24%) 30-Day reocclusion or "incomplete lysis" requiring either repeat thrombolysis or surgery Reocclusion PS 2/58 (3%) CIF 2/63 (3%) Incomplete lysis PS 2/58 (3%) CIF 8/63 (13%)	Not reported
Duration of thrombolysis	LD 20 (2 to 46) HD 4 (0.25 to 46) Median (range) hours	LD NA 35.4 ± 14 (24) LD - G 25.3 ± 12.3 (24) HD NA 27.1 ± 15.9 (24) HD - G 22.2 ± 12 (24) mean ± SD (median) hours	CIF LD 25 (2 to 60) hours PS HD 120 (40 to 310) minutes with additional low dose in 38/58 for 18 (1 to 50) hours median (range)	CIF 1390 (300 to 2400) minutes PS 195 (90 to 1260) minutes median (range)
CVA	LD = 1/44 (2.2%)	None	PS = 3/58 (5.2%)	None

Table 2. Trials comparing high- and low-dose regimens of the thrombolytic agent (Continued)

	HD = 0/49 (0%)		CIF = 1/63 (1.6%)	
Bleeding (major)	LD = 3/44 (6.8%)	HD 2/35 (5.7%)	PS = 4/58 (6.9%)	CIF = 0/9 (0%)
	HD = 3/49 (6%)	LD 0/37 (0%)	CIF = 8/63 (12.6%)	PS = 0/9 (0%)
Bleeding (minor)	Not available	HD = 7/35 (20%)	PS = 12/58 (21%)	Not available
		LD = 1/37 (2.5%)	CIF = 7/63 (11%)	

CIF: continuous infusion.

CVA: cerebrovascular accident.

G: graft thrombosis.

HD: high dose.

LD: low dose.

NA: native arterial native occlusion.

PS: infusion pulse spray.

rt-PA: recombinant tissue plasminogen activator.

SD: standard deviation.

^a11 (19%) CIF and 7 (11%) PS patients presented with Rutherford grade I ischaemia and hence were not at risk of amputation.

^bEstimated from Figure 2 in [Plate 2006](#).

Table 3. Trials comparing continuous infusion with forced infusion of the agent

	Kandarpa 1993	Plate 2006	Yusuf 1995
Intervention	CIF (urokinase)	CIF (rt-PA)	CIF (rt-PA)
Comparison	Forced infusion - PS (urokinase)	High-dose forced infusion - PS (rt-PA)	High-dose forced infusion - PS (rt-PA)
30-Day amputation-free survival	CIF = 11/13 (85%)	PS = 49/58 (84%)	CIF = 6/9 (67%)
	PS = 10/12 (83%)	CIF = 54/63 (86%) ^a	PS = 9/9 (100%)
Amputation	CIF = 2/13 (15%)	PS = 4/58 (7%)	CIF = 2/9 (22%)
	PS = 0/12 (0%)	CIF = 3/63 (5%)	PS = 0/9 (0%)
Mortality	CIF = 0/13 (0%)	PS = 6/58 (10%)	CIF = 1/9 (12%)
	PS = 2/12 (16.6%)	CIF = 7/63 (11%)	PS = 0/9 (0%)
Vessel patency	Patency within 4 hours CIF 9/13 (70%) PS 11/12 (92%)	> 75% lysis on completion of thrombolysis (without adjunctive procedure) PS HD 45/58 (78%) CIF LD 41/61 (67%) 30-Day reocclusion or "incomplete lysis" Reocclusion PS 8/58 (13%) ^b CIF 9/63 (14%) ^b Incomplete lysis	Not reported

Table 3. Trials comparing continuous infusion with forced infusion of the agent (Continued)

		PS 7/58 (12%)	
		CIF 15/63 (24%)	
		30-Day reocclusion or "incomplete lysis" requiring either repeat thrombolysis or surgery	
		Reocclusion	
		PS 2/58 (3%)	
		CIF 2/63 (3%)	
		Incomplete lysis	
		PS 2/58 (3%)	
		CIF 8/63 (13%)	
Duration of thrombolysis	CIF 28 ± 26 hours PS 20 ± 14 hours (mean ± SD)	CIF 25 (2 to 60) hours PS 120 (40 to 310) minutes with additional LD in 38/58 18 (1 to 50) hours median (range)	CIF 1390 (300 to 2400) minutes PS 195 (90 to 1260) minutes median (range)
CVA	None	PS = 3/58 (5.2%) CIF = 1/63 (1.6%)	None
Bleeding (major)	PS = 3/12 (25%) CIF = 1/13 (7.7%) Required transfusion within 72 hours	PS = 4/58 (6.9%) CIF = 8/63 (12.6%)	CIF = 0/9 (0%) PS = 0/9 (0%)
Bleeding (minor)	PS = 2/12 (16.6%) CIF = 2/13 (15.3%)	PS = 12/58 (21%) CIF = 7/63 (11%)	Not available

CIF: continuous infusion.

CVA: cerebrovascular accident.

HD: high dose.

LD: low dose.

PS: infusion pulse spray.

rt-PA: recombinant tissue plasminogen activator.

^a11 (19%) CIF and 7 (11%) PS patients presented with Rutherford grade I ischaemia and hence were not at risk of amputation.

^bEstimated from Figure 2 in [Plate 2006](#).

Table 4. Trials comparing adjunctive antiplatelet agents

Duda 2001	
Intervention	urokinase + abciximab
Comparison	urokinase alone
Amputation-free survival ^a	urokinase + abciximab = 48/50 (96%)

Table 4. Trials comparing adjunctive antiplatelet agents *(Continued)*

	urokinase alone = 16/20 (80%)
Amputation	Not available
Mortality	Not available
Vessel patency	Initial patency by means of thrombolysis alone urokinase alone: 14/20 (70%) urokinase + abciximab: 33/50 (66%) P = 0.75 Initial patency with thrombolysis and subsequent percutaneous intervention urokinase alone: 20/20 (100%) urokinase + abciximab: 44/50 (88%) P = 0.17
Duration of thrombolysis median (range)	urokinase + abciximab = 2 (1 to 7.3) hours urokinase alone = 2 (1 to 6) hours
CVA	None
Bleeding (major)	urokinase + abciximab = 4/50 (8%) urokinase alone = 0/20 (0%)
Bleeding (minor)	urokinase + abciximab = 9/50 (18%) urokinase alone = 5/20 (25%)

^aThis is the 90-day amputation-free survival rate; 30-day amputation-free survival is not given. By 30 days, 4/50 of the abciximab group and 3/20 patients had reached the composite endpoint of surgical revascularisation or limb amputation.
 CVA: cerebrovascular accident.

Table 5. Comerota 2019 study arms and results

Group		Complications - 30 days												
ID	Plas- min dose (mg)	Infu- sion time (h)	Infu- sion rate (mL/h)	Initial bolus	No.	Am- puta- tion-free sur- vival ^a	Am- puta- tion ^a	Mortali- ty, n (N)	Patency (> 50% thromboly- sis, n (N) [%])	Major bleed- ing (%)	Minor bleed- ing (%)	Seri- ous ad- verse events (%)	Ad- verse events (%)	
pulse	A	150	5	10	N	20	-	-	1 (20)	7 (16) [44]	15	5	50	70
pulse	B	150	5	15	Y	20	-	-	0 (20)	9 (19) [47]	5	20	20	60
no pulse	G	150	5	60	N	13	-	-	0 (13)	8 (12) [67]	0	46	31	69
no pulse	H	150	2	75	N	12	-	-	0 (12)	8 (12) [67]	0	8	25	58
no pulse	jb	150	5	30	N	23	-	-	0 (21)	11 (15) [73]	10	29	33	67
no pulse	jb	150	2	35	N	19	-	-	0 (17)	6 (14) [43]	0	12	12	59
pulse	C	150	5	30	N	22	-	-	0 (22)	17 (21) [81]	5	9	27	81
pulse	D	150	2	35	N	20	-	-	0 (20)	9 (19) [47]	0	20	20	70

BOC: balloon occlusion catheter.

h: hour.

ID: group identity letter.

No.: number in the group.

^aAmputation-free survival and amputation were not mentioned.

^bThese arms also used BOC.

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
VASCULAR REGISTER IN CRSW	#1 Thrombolytic or Fibrinolytic or Plasminogen AND INREGISTER	10.10.18 – 4
		11.09.19 - 47
		20.10.20 - 27
CENTRAL	#1 MESH DESCRIPTOR Arteriosclerosis 947	10.10.18 – 1334
	#2 MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES 0	11.09.19 - 1070
	#3 MESH DESCRIPTOR Arteriosclerosis Obliterans 79	20.10.20 - 381
	#4 MESH DESCRIPTOR Atherosclerosis 1069	
	#5 MESH DESCRIPTOR Arterial Occlusive Diseases 821	
	#6 MESH DESCRIPTOR Intermittent Claudication 828	
	#7 MESH DESCRIPTOR Ischemia 1553	
	#8 MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES 2793	
	#9 (atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY 12157	
	#10 ((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or re-occlus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 10513	
	#11 (peripheral near3 dis*):TI,AB,KY 4844	
	#12 (claudic* or IC):TI,AB,KY 4116	
	#13 (isch* or CLI):TI,AB,KY 32142	
	#14 arteriopathic:TI,AB,KY 7	
	#15 dysvascular*:TI,AB,KY 23	
	#16 (leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 127	
	#17 (limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 229	
	#18 ((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 98	
	#19 ((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 98	
	#20 MESH DESCRIPTOR Iliac Artery 159	
	#21 MESH DESCRIPTOR Popliteal Artery 305	
	#22 MESH DESCRIPTOR Femoral Artery 907	

(Continued)

- #23 MESH DESCRIPTOR Tibial Arteries 38
- #24 ((femor* or iliac or popliteal or fempop* or crural or poplite* or in-frapopliteal or inguinal or femdist* or inguinal or infrainguinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 1711
- #25 ((bypass or graft) near3 (occlus* or steno* or restenos* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 1080
- #26 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 58496
- #27 MESH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES 1608
- #28 MESH DESCRIPTOR Fibrinolytic Agents 2019
- #29 MESH DESCRIPTOR Plasminogen Activators 239
- #30 (urokinase or streptokinase or streptase or tenecteplase):TI,AB,KY 2331
- #31 (reteplase or alteplase):TI,AB,KY 1037
- #32 (anistreplase or prourokinase or retavase or rapilysin):TI,AB,KY 222
- #33 (t-PA or tPA):TI,AB,KY 1661
- #34 (r-PA or rPA):TI,AB,KY 139
- #35 (lysis or thrombolysis):TI,AB,KY 4661
- #36 (plasminogen near2 activator):TI,AB,KY 4123
- #37 (clot near3 (bust* or break* or remov*)):TI,AB,KY 56
- #38 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 10661
- #39 #26 AND #38 3519
- #40 01/01/2015 TO 10/10/2018:CD 460807
- #41 #39 AND #40 1334

Clinicaltrials.gov	peripheral arterial thrombolysis OR Peripheral Vascular Diseases OR Arteriosclerosis OR Arterial Occlusive Diseases OR Ischemia Thrombolytic Therapy OR Fibrinolytic Agents OR Plasminogen Activators	10.10.18 – 253
		11.09.19 - 97
		20.10.20 - 92
WHO ICTRP Search Portal	peripheral arterial thrombolysis OR Peripheral Vascular Diseases OR Arteriosclerosis OR Arterial Occlusive Diseases OR Ischemia Thrombolytic Therapy OR Fibrinolytic Agents OR Plasminogen Activators	10.10.18 - N/A
		11.09.19 - 3
		20.10.20 - 0
MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)	1 ARTERIOSCLEROSIS/ 56464	10.10.18 - 1163
	2 exp ARTERIOLOSCLEROSIS/ 151	10.09.19 - 1058
	3 Arteriosclerosis Obliterans/ 3978	20.10.20 - 1141
	4 ATHEROSCLEROSIS/ 31632	
	5 Arterial Occlusive Diseases/ 26609	

(Continued)

- 6 Intermittent Claudication/ 7640
- 7 ISCHEMIA/ 47849
- 8 exp Peripheral Vascular Diseases/ 50459
- 9 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 173195
- 10 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 144561
- 11 (peripheral adj3 dis*).ti,ab. 38272
- 12 (claudic* or IC).ti,ab. 62586
- 13 (isch* or CLI).ti,ab. 350253
- 14 arteriopathic.ti,ab. 162
- 15 dysvascular*.ti,ab. 223
- 16 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 714
- 17 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 1836
- 18 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 1492
- 19 ((iliac or femoral or popliteal or femoro* or fempop* or crural) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 8505
- 20 exp LEG/bs [Blood Supply] 25070
- 21 Iliac Artery/ 13451
- 22 Popliteal Artery/ 9048
- 23 Femoral Artery/ 27270
- 24 Tibial Arteries/ 1512
- 25 ((femor* or iliac or popliteal or fempop* or crural or poplite* or in-frapopliteal or inguinal or femdist* or inguinal or infrainguinal or tibial) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 9813
- 26 ((bypass or graft) adj3 (occlus* or steno* or restenos* or obstruct* or lesio* or block* or obliter*)).ti,ab. 6857
- 27 or/1-26 803523
- 28 exp Thrombolytic Therapy/ 22642
- 29 Fibrinolytic Agents/ 28232
- 30 exp Plasminogen Activators/ 38431
- 31 (urokinase or streptokinase or streptase or tenecteplase).ti,ab. 20958
- 32 (reteplase or alteplase).ti,ab. 1914

(Continued)

- 33 (anistreplase or prourokinase or retavase or rapilyisin).ti,ab. 370
- 34 (t-PA or tPA).ti,ab. 26233
- 35 (r-PA or rPA).ti,ab. 4114
- 36 (lysis or thrombolysis).ti,ab. 64715
- 37 (plasminogen adj2 activator).ti,ab. 34519
- 38 (clot adj3 (bust* or break* or remov*)).ti,ab. 677
- 39 or/28-38 154230
- 40 27 and 39 26346
- 41 randomized controlled trial.pt. 469353
- 42 controlled clinical trial.pt. 92682
- 43 randomized.ab. 423387
- 44 placebo.ab. 192319
- 45 drug therapy.fs. 2052184
- 46 randomly.ab. 298375
- 47 trial.ab. 441082
- 48 groups.ab. 1839754
- 49 or/41-48 4293737
- 50 40 and 49 14832
- 51 (2017* or 2018*).ed. 1716518
- 52 50 and 51 1163

Embase	1 arteriosclerosis/ 23580	10.10.18 - 2649
	2 exp arteriolosclerosis/ 589	10.09.19 - 2412
	3 peripheral occlusive artery disease/ 31426	20.10.20 - 2300
	4 atherosclerosis/ 135258	
	5 intermittent claudication/ 8883	
	6 ischemia/ 72705	
	7 exp peripheral vascular disease/ 1609458	
	8 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 232204	
	9 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 193781	
	10 (peripheral adj3 dis*).ti,ab. 54066	
	11 (claudic* or IC).ti,ab. 63363	
	12 (isch* or CLI).ti,ab. 501942	
	13 arteriopathic.ti,ab. 181	

(Continued)

- 14 dysvascular*.ti,ab. 245
- 15 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 970
- 16 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 2672
- 17 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 2030
- 18 ((iliac or femoral or popliteal or femoro* or fempop* or crural) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 11978
- 19 iliac artery/ 13047
- 20 popliteal artery/ 7416
- 21 femoral artery/ 26899
- 22 tibial artery/ 2654
- 23 ((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainguinal or tibial) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 13840
- 24 ((bypass or graft) adj3 (occlus* or steno* or restenos* or obstruct* or lesio* or block* or obliter*).ti,ab. 8696
- 25 or/1-24 1976209
- 26 exp fibrinolytic therapy/ 22290
- 27 fibrinolytic agent/ 23713
- 28 exp plasminogen activator/ 76323
- 29 (urokinase or streptokinase or streptase or tenecteplase).ti,ab. 24654
- 30 (reteplase or alteplase).ti,ab. 3344
- 31 (anistreplase or prourokinase or retavase or rapilysin).ti,ab. 457
- 32 (t-PA or tPA).ti,ab. 33937
- 33 (r-PA or rPA).ti,ab. 5407
- 34 (lysis or thrombolysis).ti,ab. 85466
- 35 (plasminogen adj2 activator).ti,ab. 42669
- 36 (clot adj3 (bust* or break* or remov*).ti,ab. 1096
- 37 or/26-36 200879
- 38 25 and 37 79880
- 39 randomized controlled trial/ 515292
- 40 controlled clinical trial/ 458015
- 41 random\$.ti,ab. 1333198
- 42 randomization/ 79498

(Continued)

43 intermethod comparison/ 238459

44 placebo.ti,ab. 276287

45 (compare or compared or comparison).ti. 459799

46 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1796873

47 (open adj label).ti,ab. 66110

48 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 210162

49 double blind procedure/ 153442

50 parallel group\$1.ti,ab. 22211

51 (crossover or cross over).ti,ab. 94040

52 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. 288139

53 (assigned or allocated).ti,ab. 338625

54 (controlled adj7 (study or design or trial)).ti,ab. 300087

55 (volunteer or volunteers).ti,ab. 226085

56 trial.ti. 252059

57 or/39-56 4086169

58 38 and 57 19546

59 (2017* or 2018*).dc. 3017993

60 58 and 59 2649

CINAHL	S53 S51 AND S52 207	10.10.18 – 207
	S52 EM 2017 OR EM 2018 442,007	11.09.19 - 212
	S51 S37 AND S50 1,570	20.10.20 - 338
	S50 S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 347,742	
	S49 MH "Random Assignment" 39,518	
	S48 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" 33,080	
	S47 MH "Crossover Design" 11,330	
	S46 MH "Factorial Design" 924	
	S45 MH "Placebos" 8,403	
	S44 MH "Clinical Trials" 93,373	
	S43 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" 4,602	
	S42 TX crossover OR "cross-over" 14,749	
	S41 AB placebo* 28,803	

(Continued)

S40 TX random* 222,742

S39 TX trial* 254,903

S38 TX "latin square" 144

S37 S25 AND S36 4,624

S36 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
13,171

S35 TX clot n3 (bust* or break* or remov*) 180

S34 TX plasminogen n2 activator 4,708

S33 TX lysis or thrombolysis 4,673

S32 TX r-PA or rPA 307

S31 TX t-PA or tPA 1,316

S30 TX anistreplase or prourokinase or retavase or rapilysin 35

S29 TX urokinase or streptokinase or streptase or tenecteplase 1,042

S28 (MH "Plasminogen Activators+") 3,656

S27 (MH "Fibrinolytic Agents") 4,367

S26 (MH "Thrombolytic Therapy") 4,542

S25 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR
S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR
S22 OR S23 OR S24 92,329

S24 TX (bypass or graft) n3 (occlus* or steno* or restenos* or obstruct* or lesio*
or block* or obliter*) 878

S23 TX (femor* or iliac or popliteal or fempop* or crural or poplite* or in-
frapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) n3 (oc-
clus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or
block* or harden* or stiffen* or obliter*) 1,128

S22 (MH "Tibial Arteries") 147

S21 (MH "Femoral Artery") 1,201

S20 (MH "Popliteal Artery") 362

S19 (MH "Iliac Artery") 458

S18 (MH "Leg/BS") 450

S17 TX (iliac or femoral or popliteal or femoro* or fempop* or crural) n3 (oc-
clus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or
block* or harden* or stiffen* or obliter*) 964

S16 TX (lower n3 extrem*) n3 (occlus* or reocclus* or re-occlus* or steno* or
restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*) 122

S15 TX limb n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or ob-
struct* or lesio* or block* or harden* or stiffen* or obliter*) 283

S14 TX (leg n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or ob-
struct* or lesio* or block* or harden* or stiffen* or obliter*)) 130

(Continued)

S13 TX dysvascular* 173
 S12 TX arteriopathic 10
 S11 TX isch* or CLI 40,062
 S10 TX claudic* or IC 5,948
 S9 TX peripheral n3 dis* 9,366
 S8 TX ((arter* or vascular or vein* or veno* or peripher*) n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)) 12,817
 S7 TX atherosclero* or arteriosclero* or PVD or PAOD or PAD 26,677
 S6 (MH "Peripheral Vascular Diseases+") 10,544
 S5 (MH "Ischemia") 3,447
 S4 (MH "Intermittent Claudication") 846
 S3 (MH "Arterial Occlusive Diseases") 1,622
 S2 (MH "Atherosclerosis") 3,413
 S1 (MH "Arteriosclerosis") 4,818

AMED (Allied and Complementary Medicine)

1 Arteriosclerosis/ 78	10.10.18 - 0
2 exp Arteriosclerosis/ 374	10.09.19 - 1
3 Atherosclerosis/ 227	20.10.20 - 0
4 Arterial occlusive disease/ 89	
5 Intermittent claudication/ 75	
6 Ischemia/ 268	
7 exp Peripheral vascular disease/ 119	
8 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 824	
9 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 466	
10 (peripheral adj3 dis*).ti,ab. 444	
11 (claudic* or IC).ti,ab. 1034	
12 (isch* or CLI).ti,ab. 1716	
13 arteriopathic.ti,ab. 1	
14 dysvascular*.ti,ab. 58	
15 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 21	
16 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 33	
17 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 25	

(Continued)

18 ((iliac or femoral or popliteal or femoro* or fempop* or crural) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 55

19 ((femor* or iliac or popliteal or fempop* or crural or poplite* or in-frapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 110

20 ((bypass or graft) adj3 (occlus* or steno* or restenos* or obstuct* or lesio* or block* or obliter*)).ti,ab. 20

21 or/1-20 4451

22 Fibrinolytic Agents/ 7

23 (urokinase or streptokinase or streptase or tenecteplase).ti,ab. 13

24 (reteplase or alteplase).ti,ab. 2

25 (anistreplase or prourokinase or retavase or rapilysin).ti,ab. 1

26 (t-PA or tPA).ti,ab. 152

27 (r-PA or rPA).ti,ab. 13

28 (lysis or thrombolysis).ti,ab. 95

29 (plasminogen adj2 activator).ti,ab. 45

30 (clot adj3 (bust* or break* or remov*)).ti,ab. 0

31 or/22-30 286

32 21 and 31 47

33 exp CLINICAL TRIALS/ 3847

34 RANDOM ALLOCATION/ 318

35 DOUBLE BLIND METHOD/ 676

36 Clinical trial.pt. 1214

37 (clinic* adj trial*).tw. 5511

38 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. 2906

39 PLACEBOS/ 595

40 placebo*.tw. 3181

41 random*.tw. 18096

42 PROSPECTIVE STUDIES/ 1146

43 or/33-42 23190

44 32 and 43 11

45 ("2017" or "2018").yr. 5526

46 44 and 45 0

Appendix 2. CRS search strategy 2015

Search run on Fri, 9 Oct 2015

#1	MESH DESCRIPTOR Arteriosclerosis	863
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	69
#4	MESH DESCRIPTOR Atherosclerosis	493
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	695
#6	MESH DESCRIPTOR Intermittent Claudication	669
#7	MESH DESCRIPTOR Ischemia	720
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2082
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	7987
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	6756
#11	(peripheral near3 dis*):TI,AB,KY	2896
#12	(claudic* or IC):TI,AB,KY	2632
#13	(isch* or CLI):TI,AB,KY	20299
#14	arteriopathic:TI,AB,KY	7
#15	dysvascular*:TI,AB,KY	9
#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	78
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	119
#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	71
#19	((iliac or femoral or popliteal or femoro* or fempop* or crural) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	805
#20	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1062
#21	MESH DESCRIPTOR Iliac Artery	135

(Continued)

#22	MESH DESCRIPTOR Popliteal Artery	248
#23	MESH DESCRIPTOR Femoral Artery	726
#24	MESH DESCRIPTOR Tibial Arteries	30
#25	((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainguinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*))):TI,AB,KY	936
#26	((bypass or graft) near3 (occlus* or steno* or restenos* or obstruct* or lesio* or block* or obliter*))):TI,AB,KY	811
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	38306
#28	MESH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES	1449
#29	MESH DESCRIPTOR Fibrinolytic Agents	1683
#30	MESH DESCRIPTOR Plasminogen Activators EXPLODE ALL TREES	2128
#31	(urokinase or streptokinase or streptase or tenecteplase):TI,AB,KY	2031
#32	(reteplase or alteplase):TI,AB,KY	603
#33	(anistreplase or prourokinase or retavase or rapilysin):TI,AB,KY	217
#34	(t-PA or tPA):TI,AB,KY	1172
#35	(r-PA or rPA):TI,AB,KY	82
#36	(lysis or thrombolysis):TI,AB,KY	3278
#37	(plasminogen near2 activator):TI,AB,KY	3259
#38	(clot near3 (bust* or break* or remov*))):TI,AB,KY	29
#39	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	8027
#40	#27 AND #39	2338

WHAT'S NEW

Date	Event	Description
20 October 2020	New citation required but conclusions have not changed	The most recent search for this review update was performed on 20 October 2020. Three new studies were included and 10 new studies were excluded. Text was updated to reflect current Cochrane recommendations. Risk of bias for all included studies was assessed, and Summary of findings tables were added. No change was made to the conclusions

Date	Event	Description
20 October 2020	New search has been performed	The most recent search for this review update was performed on 20 October 2020. Three new studies were included and 10 new studies were excluded

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2004

Date	Event	Description
20 October 2008	Amended	Converted to new review format
14 November 2006	Amended	Edited; CDSR citations updated
20 February 2006	New search has been performed	No new trials found at last search. Review updated with minor style guide changes only
17 November 2004	Amended	Synopsis added

CONTRIBUTIONS OF AUTHORS

CB: identified possible trials and considered them for inclusion; assessed trial quality; extracted data; and wrote the review.

JP: identified possible trials and considered them for inclusion; assessed trial quality; double-checked data; and wrote the review.

DECLARATIONS OF INTEREST

CB: none known. As CB is based within Cochrane Vascular, editorial tasks for this review update were carried out by other members of the Cochrane Vascular editorial team.

JP: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

The Cochrane Vascular editorial base is supported by the Chief Scientist Office

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants have been clarified by more details on intended types of participants. Some outcomes were rephrased for clarification.

NOTES

This is the second of three reviews concerning different aspects of thrombolysis, all of which were originally covered in the generic protocol "Surgery versus thrombolysis for acute limb ischaemia", unique ID 031499080512564323.

The first review is "Surgery versus thrombolysis for initial management of acute limb ischaemia" ([Berridge 2013](#)). The third review is "Fibrinolytic agents for peripheral arterial occlusion" ([Robertson 2013](#)).

INDEX TERMS**Medical Subject Headings (MeSH)**

Fibrinolytic Agents [*administration & dosage]; Infusions, Intra-Arterial [methods]; Infusions, Intravenous [methods]; Ischemia [*drug therapy]; Leg [*blood supply]; Peripheral Vascular Diseases [drug therapy]; Randomized Controlled Trials as Topic; Thrombolytic Therapy [*methods]

MeSH check words

Humans