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A systematic review and meta-analysis of endovascular and surgical revascularization techniques in acute limb ischemia

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ABSTRACT

Background: The initial treatment of patients with acute limb ischemia (ALI) remains undefined. The aim of this article was to compare the safety and effectiveness of catheter-driven thrombolysis (CDT) with surgical revascularization and evaluate the various fibrinolytic agents, endovascular, and pharmacochemical approaches that aim for thrombectomy.

Methods: PubMed, Embase, and the Cochrane Library were searched for studies on the management of ALI by means of surgical or endovascular recanalization, returning 520 studies. All randomized, controlled trials, nonrandomized prospective, and retrospective studies were included comparing treatment of ALI.

Results: Twenty-five studies, investigating a total of 4689 patients, were included for meta-analysis spread across nine different comparisons. No differences were found in limb salvage between thrombectomy and thrombolysis. More major vascular events were seen in the thrombolysis group (6.5% compared with 4.4% in the surgically treated group; odds ratio [OR], 0.33; 95% confidence interval [CI], 0.13-0.87; $P = .02$; $I^2 = 20\%$). Comparable limb salvage was found for high- and low-dose recombinant tissue plasminogen activator (r-tPA). No significant differences were found in major vascular event between low r-tPA (14%) and high r-tPA (10.5%; $P = .13$). The 30-day limb salvage rate was 79.7% for r-tPA treatment and 60.4% for streptokinase (OR, 3.14; 95% CI, 1.26-7.85; $P = .01$; $I^2 = 0\%$). AngioJet showed more limb salvage at 6 months compared with r-tPa (OR, 2.21; 95% CI, 1.17-4.18; $P = .01$; $I^2 = 0\%$).

Conclusions: Both CDT and surgery have comparable limb salvage rates in patients with ALI; however, CDT is associated with a higher risk of hemorrhagic complications. No conclusions can be drawn regarding the risk of hemorrhagic complications regarding thrombolytic therapy by means of r-tPA, streptokinase, or urokinase. Insufficient data are available to conclude the preference of using a hybrid approach, ultrasound-accelerated CDT, heated r-tPA. or novel endovascular (rheolytical) thrombectomy systems. Future trials regarding ALI need to be constructed carefully, ensuring comparable study groups, and should follow standardized practices of outcome reporting. (J Vasc Surg 2020;71:654-68.)

Keywords: Arterial occlusive diseases therapy; Lower extremity blood supply; Thrombolysis; Thrombectomy; Mechanical thrombolysis

Acute limb ischemia (ALI) occurs when there is a sudden halt of blood flow to the arm or leg, mostly owing to thrombosis or emboli. When left untreated, it can threaten the viability of the limb, followed by infection, necrosis, limb loss and ultimately, death. The incidence of acute limb occlusion is approximately 1.5 per 10,000 persons per year.[1]

The therapeutic approach depends on the severity and duration of symptoms associated with limb ischemia at presentation.[2] For those with acute, viable, or marginally threatened extremities, treatment is aimed at restoring in-line blood flow to the foot through at least one patent artery.[1] Traditionally, this goal was accomplished surgically with a thromboembolectomy catheter; however, since the introduction of catheter-driven thrombolysis (CDT), a shift took place toward this less invasive form of therapy.[3] With CDT, thrombolytic agents, such as recombinant tissue plasminogen activator (r-tPA), urokinase and streptokinase, are continuously delivered to the site of arterial thrombosis through a catheter that is positioned within the occluded vessel to dissolve the thrombosis and achieve revascularization.

New endovascular therapies have been developed within the past decade that aim at percutaneous, catheter-based thrombus extraction. The techniques vary and are primarily aimed at mechanical disruption of the thrombus with or without additional aspiration. Owing to the rapid introduction of these new interventions, research on the efficacy is lacking.

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The objective of this meta-analysis was to compare the safety and effectiveness of CDT with surgical revascularization in the initial management of ALI, and to evaluate the various fibrinolytic agents, endovascular, and pharmacochemical approaches that aim for thrombectomy.

METHODS

Search strategy. The literature search was conducted in accordance with the PRISMA 2009 guidelines. The Cochrane, Embase, and PubMed databases were searched for studies on the management of ALI by surgical means or by endovascular recanalization (last searched April 2018). All surgical, thrombolytic, and endovascular thrombectomy strategies were considered. The full search strategy is shown in Appendix 1 (online only). Additional studies were identified by reviewing reference lists of studies found in the reviewed articles.

Study selection. Randomized controlled trials, nonrandomized prospective trials, and retrospective trials were included in which participants were allocated both randomly or nonrandomly to a method of thrombolysis or surgical thrombectomy as initial treatment for ALI. Patients with thromboembolic occlusions of either a native peripheral artery or a vascular graft were included. A study was excluded if the trial had insufficient data regarding primary or secondary outcomes, had less than a total of 15 patients, or was published in any language other than English. All articles that remained after exclusion based on title or abstract were screened to determine the study objective and outcomes compared (Fig 1). This enabled us to group all articles that led the selection of comparisons made in the meta-analysis.

Outcome measures. The primary outcome was limb salvage after 30 days, meaning the avoidance of above-knee or below-knee amputation of the lower limb. Secondary outcomes were major vascular events (MVE), defined as the occurrence of major hemorrhage needing blood transfusion or surgical or endovascular intervention, and hemorrhagic stroke.[4] In the case a study provided no limb salvage data, limb salvage numbers were calculated with the use of amputation data. In a few cases, outcome data needed to be visually approximated from a Kaplan-Meier plot. For most studies, the time frame for reporting MVE was not specified. Low-dose r-tPA was defined to be 0.1 to 1.0 mg/h and anything above this threshold was considered high dose.[5]

Data collection and analysis. The selection of trials for inclusion in this review was carried out independently by two authors (E.B.V. and R.B.). One author (E.B.V.) performed the electronic searches and identified all possible trials and sent these to the second author for consideration. Discrepancies were resolved by discussion.

Data extraction and management. Data were collected using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org) and Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Data collected from the included studies contained primary and secondary outcomes, inclusion and exclusion criteria, group sizes, and demographic differences between groups.

Assessment of risk of bias. Both random and nonrandom trials were assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[6] All studies were reviewed independently by two authors (E.B.V. and E.D.H.). Any discrepancies were resolved through discussion until consensus was achieved.

The quality of the included studies was critically appraised differently for random or nonrandom trials. Randomized trials were graded on methodologic quality by the use of the Grading of Recommendations Assessment, Development, and Evaluation process (GRADE).[7] A GRADE quality score was calculated by adding or detracting points from a base score based on seven different aspect of methodologic quality. The methodologic quality of nonrandomized trials was evaluated with the use of the Methodological Index for Nonrandomized studies (MINOR).[8]

Both GRADE and MINOR were fully evaluated by one author (E.B.V.). After the quality scores were established for the included articles, all authors discussed the results to create a definitive list of trials. Studies scoring less than 3 on the GRADE scale or less than 11 on the MINOR score were deemed to be of insufficient quality and were excluded from further analysis. Additionally, studies with no control or comparative group were excluded.

Measures of treatment effect. Meta-analysis was performed by calculating the odds ratio (OR) with 95% confidence intervals (CI) by using the Mantel-Haenszel random effect analysis method. No pooling of studies was performed.

RESULTS

The search returned 520 studies. After screening of titles and abstracts, 130 studies remained, of which 75 were excluded during full-text assessment based on the inclusion and exclusion criteria. Of the remaining 55 studies, 30 were excluded owing to insufficient quality (<3 on the GRADE or <11 on the MINORS scale) or lacked

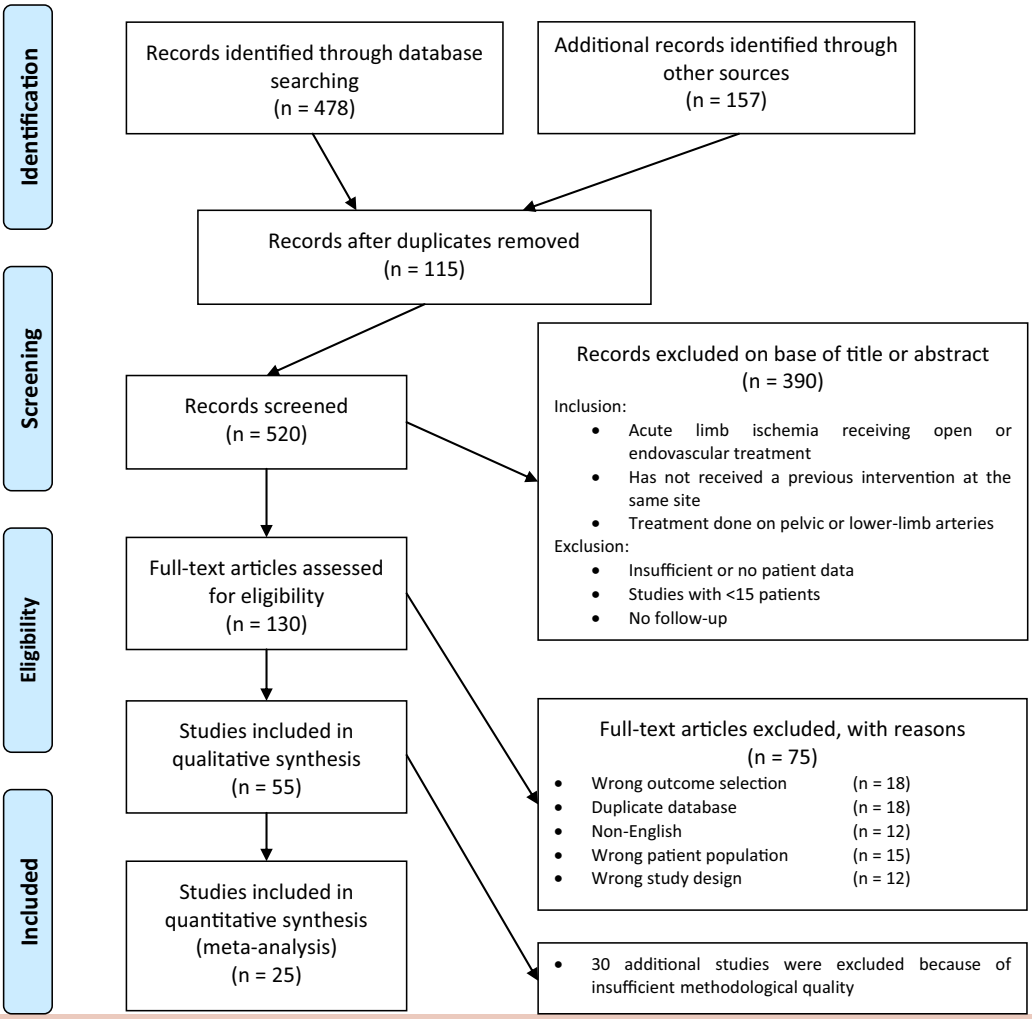

Fig 1. PRISMA flow diagram.

a control group. The review process is outlined in Fig 1. Bias and methodologic quality scores of all studies are shown in Appendix 2 (online only).

Twenty-five studies were eligible for meta-analysis, in which a total of 4689 patients were evaluated. Twelve studies were randomized, controlled trials, 3 were nonrandomized prospective studies, and 10 were retrospective studies. The 25 studies compared nine different treatment types; 10 studies compared surgery to CDT, 4 compared high-dose with low-dose r-tPA, 3 r-tPA with streptokinase, 3 r-tPA with urokinase, 3 AngioJet Peripheral Thrombectomy System (Boston Scientific, Marlborough, Mass) to r-tPA, and 2 compared ultrasound with nonultrasound-guided thrombolysis. The comparisons of Rotarex Mechanical Thrombectomy System (Straub Medical AG, Wangs, Switzerland) with r-tPA, intravenous (IV) with intra-arterial (IA) r-tPA and heated with unheated r-tPA had one study each. No eligible studies for the treatment of ALI were found for the Trellis, Hydrolyser, Oasis, Clot Buster, Arrow Trerotola, or Indigo devices.

Surgery versus CDT. Ten studies made a comparison between surgical thrombectomy and CDT. All were of sufficient quality and eligible for meta-analyses. Five were randomized controlled trials,[9-13] four retrospective,[14-17] and one nonrandomized prospective study[18] (Table I). The 30-day limb salvage data were reported by all studies. The 6-month limb salvage rate was reported by eight studies and the 1-year rate by seven studies. No significant differences regarding limb salvage were found (Fig 2, *A* and *C*). Rates of adverse events are shown in Fig 2, *D* MVE occurred significantly more often in CDT (n = 35) compared with surgery (n = 15; OR, 3.03; 95% CI, 0.13-0.87; $P = .02$; $I^2 = 20\%$).

Table I. Characteristics of included studies: Surgery versus catheter-driven thrombolysis (*CDT*)

Study	Methods	Participants	Interventions	Outcomes
Nilsson 1992	Design: RCT Lost to follow-up: 1	N = 20 Inclusion criteria: Onset of symptoms >24 hours and <14 days. Exclusion criteria: Systolic BP >200 mm Hg, recent stroke, history of GI bleed, bleeding diastasis. Group differences: No significant differences between the groups.	I. Surgery (n = 9) II. Thrombolysis (n = 11)	MVE, limb salvage 30 days
Ouriel 1994[a]	Design: RCT Lost to follow-up: Not stated	N = 114 Inclusion criteria: Onset of symptoms <7 days. Exclusion criteria: Recent major surgery, active peptic ulcer disease, history of cerebrovascular accident. Group differences: No significant differences between the groups.	I. Surgical revascularization (n = 57) II. Thrombolysis with urokinase (n = 57)	MVE, limb salvage 30 days, 6 months, and 1 year
Ouriel 1996	Design: RCT Lost to follow-up: Not stated	N = 213 Inclusion criteria: Onset of symptoms <14 days. Exclusion criteria: Systolic BP > 180, diastolic BP > 110 mm Hg, recent stroke, recent major hemorrhage. Group differences: No significant differences between the groups.	I. Surgery (n = 58) II. Thrombolysis with urokinase at 2000 IU/min (n = 48), or 4000 IU/min (n = 52), or 6000 IU/min (n = 55)	MVE, limb salvage 30 days, 6 months, and 1 year
Ouriel 1998[b]	Study design: RCT Lost to follow-up: 33	N=548 Inclusion criteria: Onset of symptoms <14 days. Exclusion criteria: Pregnancy Group differences: The thrombolysis group had significantly higher proportion of men, hepatic and renal insufficiency, and rest pain at presentation.	I. Surgery (n = 272) II. Thrombolysis with urokinase (n = 272)	MVE, limb salvage 6 months and 1 year
STILE 1994[b]	Design: RCT Lost to follow-up: 4	N = 394 Inclusion criteria: Onset of symptoms <6 months. Exclusion criteria: Active internal bleeding, recent TIA, intracranial or spinal surgery or trauma, systolic BP >180 mm Hg, diastolic BP >110 mm Hg. Group differences: No significant differences between the groups.	I. Surgery (n = 144) II. Thrombolysis r-tPA or urokinase (n = 249)	MVE, limb salvage 6 months
Hoch 1994[b]	Design: Retrospective analysis Lost to follow-up: none	N=48 Inclusion criteria: Onset of symptoms <14 days. Exclusion criteria: Recent CVA, GI hemorrhage, intra-abdominal surgery, or neurosurgery. Group differences: No significant differences between the groups.	I. Surgery (n = 29) II. Low-dose urokinase (n = 8) III. High-dose urokinase (n = 11)	MVE, limb salvage 30 days
Taha 2015[b]	Design: Retrospective analysis Lost to follow-up: 0	N = 443 Inclusion criteria: ALI owing to embolism or thrombosis of a native artery, bypass graft, or previous stent. Exclusion criteria: Blue toe syndrome and acute ischemia secondary to trauma or dissection.	I. Endovascular repair (n = 147) with standard CDT techniques or AngioJet with or without r-tPA II. r-tPA (n = 296)	MVE, limb salvage 30 days and 1 year.

(Continued on next page)

Table I. Continued.

Study	Methods	Participants	Interventions	Outcomes
		Group differences: ER patients were younger and more likely to be smokers, have a history of coronary bypass grafting and chronic renal insufficiency. OR patients were more likely to have atrial fibrillation or rhabdomyolysis.		
Seeger 1987[c]	Design: Retrospective analysis Lost to follow-up: 1	N = 24 Inclusion criteria: Not reported. Exclusion criteria: Presentation with neurologic or motor deficits in the ischemic lower extremity underwent catheter thrombectomy. Group differences: The streptokinase group had a significant higher number of symptom presence before treatment.	I. streptokinase (n = 16) II. Thrombectomy (n = 18)	MVE, limb salvage 30 days and 6 months.
deDonato 2014	Design: Retrospective analysis Lost to follow-up: 27	N = 322 Inclusion criteria: Onset of symptoms <14 days. Exclusion criteria: Not reported. Group differences: Higher incidence of atrial fibrillation or arrhythmia in the hybrid group.	I. Surgical (n = 112) II. Hybrid procedures (n = 210)	MVE, limb salvage 30 days, 6 months, and 1 year.
Earnshaw 1989[b]	Design: Prospective analysis Lost to follow-up: 28	N = 177 Inclusion criteria: None reported. Exclusion criteria: None reported. Group differences: Not reported.	I. Thrombectomy (n = 38) II. Streptokinase or r-tPA (n = 64)	MVE, limb salvage 30 days.

ALI, Acute limb ischemia; *BP*, blood pressure; *CVA*, cerebrovascular accident; *ER*, emergency room; *GI*, gastrointestinal; *MVE*, major vascular event; *OR*, operating room; *RCT*, randomized, controlled trial; *r-tPA*, recombinant tissue plasminogen activator; *TIA*, transient ischemic attack.
[a]Combined death/amputation rate used to calculate limb salvage.
[b]Amputation data used to calculate limb salvage.
[c]Limb salvage for 30 days defined as immediate result; 6 months limb salvage is defined as long-term limb salvage greater than 6 months.

Low-dose versus high-dose r-tPA. Fourteen studies made a comparison between high- and low-dose r-tPA.[19-32] Of these studies, two prospective randomized controlled trials,[5,22] one prospective nonrandomized,[23] and one retrospective study[24] were eligible for meta-analysis (Table II). Ten studies were excluded because they were of insufficient quality.[19-21,25-32]

The 30-day limb salvage results were reported by all studies (Fig 3, *A*). One study performed a comparison of limb salvage at 6 months.[22] None of the studies reported 1-year limb salvage. Meta-analysis revealed no significant differences regarding limb salvage at 30 days. No significant differences in MVE were found between the low and high r-tPA groups (Fig 3, *B*).

Streptokinase versus r-tPA. Four studies compared the use of streptokinase with r-tPA.[18,24,33,34] Of these studies, one randomized controlled trial,[33] one prospective nonrandomized,[24] and one retrospective study were eligible for meta-analysis (Table III).[18] The 30-day follow-up found a significant difference in limb salvage favoring r-tPA (Fig 4): a total of 51 limbs were salvaged in the r-tPA group compared with 29 in the streptokinase group (OR, 3.14; 95% CI, 1.26-7.85; $P = .01$; $I^2 = 0\%$). None of the studies reported 6-month or 1-year limb salvage. Only one study properly reported MVE and found no significant differences.[33]

Urokinase versus r-tPA. Five studies were found comparing the use of urokinase to r-tPA, of which two randomized controlled trials[32,35] and one retrospective study are included (Table IV).[36] Two studies were of insufficient quality and were excluded.[37,38] No significant differences in 6-month limb salvage between the two groups were found (OR, 1.38; 95% CI, 0.28-1.86; $P = .50$, Fig 5).[32,39] None of the studies reported limb salvage data at 30 days or 1 year. No data regarding MVE were reported.

Heated versus unheated r-tPA. One prospective study compared the difference between heated versus unheated r-tPA (Table V).[29] No statistical difference in

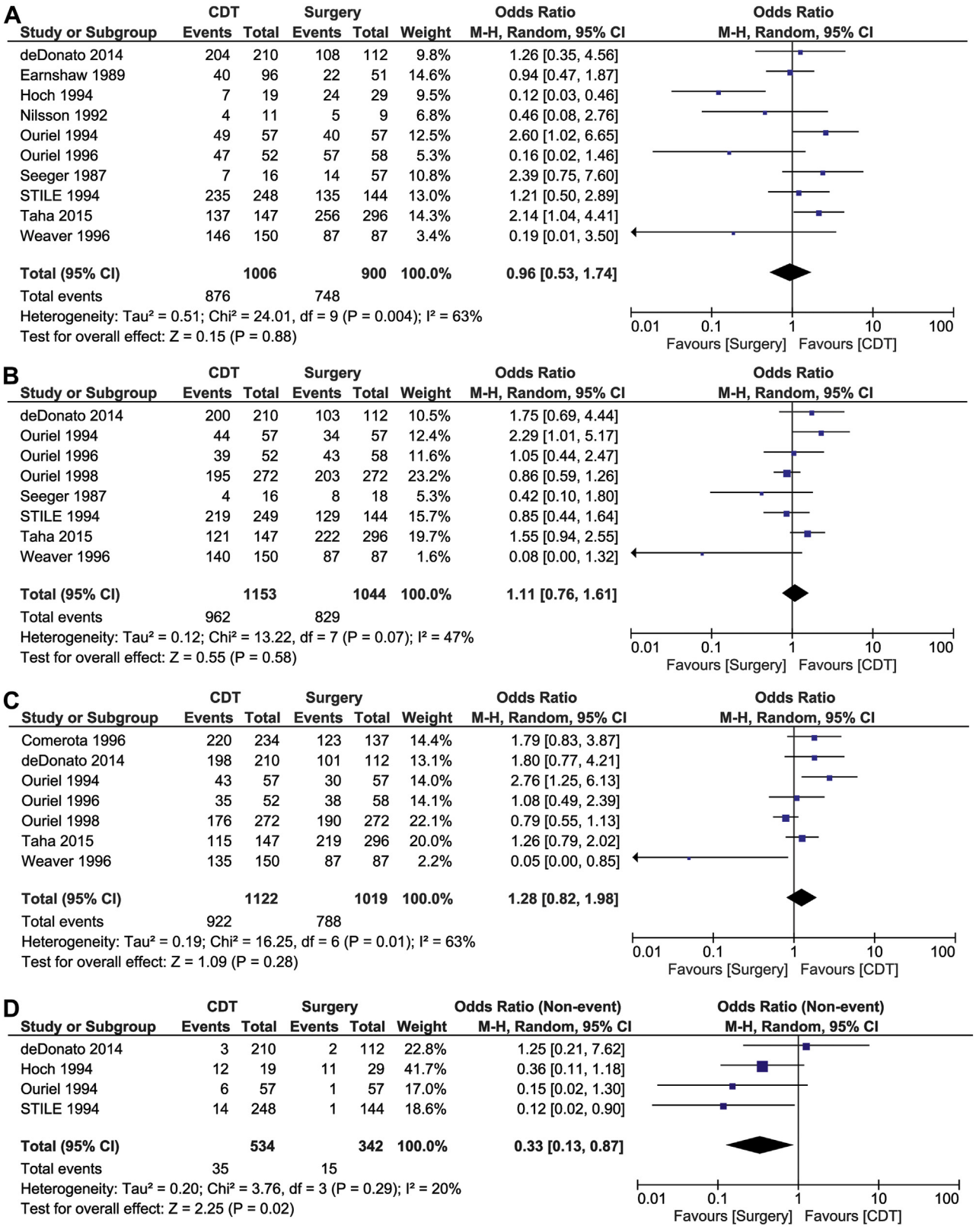

Fig 2. A, Surgery versus catheter-driven thrombolysis (*CDT*), limb salvage at 30 days. **B,** Surgery versus CDT, limb salvage at 6 months. **C,** Surgery versus CDT, limb salvage at 1 year. **D,** Surgery versus catheter-driven thrombolysis (CDT), major vascular events (MVE). *CI,* Confidence interval.

Table II. Characteristics of included studies: recombinant tissue plasminogen activator (*r-tPA*) high dose versus r-tPA low dose

Study	Methods	Participants	Interventions	Outcomes
Braithwaite 1997[a]	Design: RCT Lost to follow-up: 0	N = 100 Inclusion criteria: Onset of symptoms <30 days. Exclusion criteria: Recent history of stroke, bleeding diathesis, pregnancy. Group differences: Median age of the high-dose group was less than that of the low-dose group.	I. High-dose r-tPA (n = 49) II. Low dose r-tPA (n = 44)	MVE, limb salvage 30 days
Earnshaw 1988	Design: Retrospective analysis Lost to follow-up: 0	N = 23 Inclusion criteria: Onset of symptoms <30 days. Exclusion criteria: No patient was excluded from the study. Group differences: Not reported.	I. High-dose r-tPA (n = 12) II. Low dose r-tPA (n = 11)	MVE, limb salvage 30 days
Grip 2014	Design: Prospective analysis Lost to follow-up: 0	N = 644 Inclusion criteria: Not reported. Exclusion criteria: Not reported. Group differences: No significant differences between the groups.	I. High-dose r-tPA (n = 318) II. Low dose r-tPA (n = 431)	MVE, limb salvage 30 days
Plate 2006[a]	Study design: RCT Lost to follow-up: 0	N = 121 Inclusion criteria: Onset of symptoms <30 days. Exclusion criteria: Recent stroke, major surgery, hematuria, and gastrointestinal bleeding. Group differences: There were fewer proximal and more distal occlusions in group 1 than in group 2.	I. High-dose r-tPA (n = 58) II. Low-dose r-tPA (n = 63)	MVE, limb salvage 30 days and 1 year

MVE, Major vascular event; *RCT*, randomized, controlled trial.
[a]Amputation data used to calculate limb salvage.

the amount of salvaged limbs at 30 days was found between the groups. A statistically significant decrease in total r-tPA was noted in the heated group (24.28 mg vs 27.9 mg in the unheated group; $P = .05$) as well as shorter time to lysis (2 hours 42 minutes vs 6 hours 12 minutes with unheated r-tPA; $P = .001$). No data regarding MVE were reported.

Ultrasound versus nonultrasound r-tPA. Two studies compared the effectiveness of applying r-tPA concurrent with ultrasound waves,[30,35,40] including one randomized controlled trial[40] and one retrospective study (Table VI).[35] Because each outcome was represented by only one study, no meta-analysis could be performed. No differences for limb salvage were found at 30 days, 6 months, or 1 year.[35,40] One study reported significantly faster thrombolysis in ultrasound (17.7 ± 2.0 hours) than in the nonultrasound group (29.5 ± 3.2 hours) and fewer units of urokinase needed ($1.8 \pm 1.0 \times 10^6$ in the ultrasound group vs $2.8 \pm 1.6 \times 10^6$ in the nonultrasound group).[40]

IV versus IA r-tPA. One study compared the application of r-tPA IV with IA (Table VII).[41] This randomized controlled trial included 38 patients and reported no significant differences between the groups for 6-month limb salvage (IV = 89%, IA = 80%; $P = .096$), visual analog scale score ($P = .316$), or ankle-brachial index ($P = .360$). No meta-analysis could be performed. Significant greater angiographic improvement was seen in the IA group ($P < .001$).

AngioJetPeripheral thrombectomy system versus r-tPA. Five studies compared the use of the Angiojet system with r-tPA. Of these studies, three were included for meta-analysis (Table VIII).[42-44] These three studies all used r-tPA: Byrne et al[42] used generic r-tPA from Genentech, Hanover et al[43] used reteplase, and Leung et al[44] 2015 used actiplase. Two studies were excluded because they were of insufficient quality.[15,45]

Meta-analysis shows favoring of limb salvage with Angiojet at the 30-day, 6-month, and 1-year follow-ups (Fig 6, *A-C*). Statistical significance was only found at

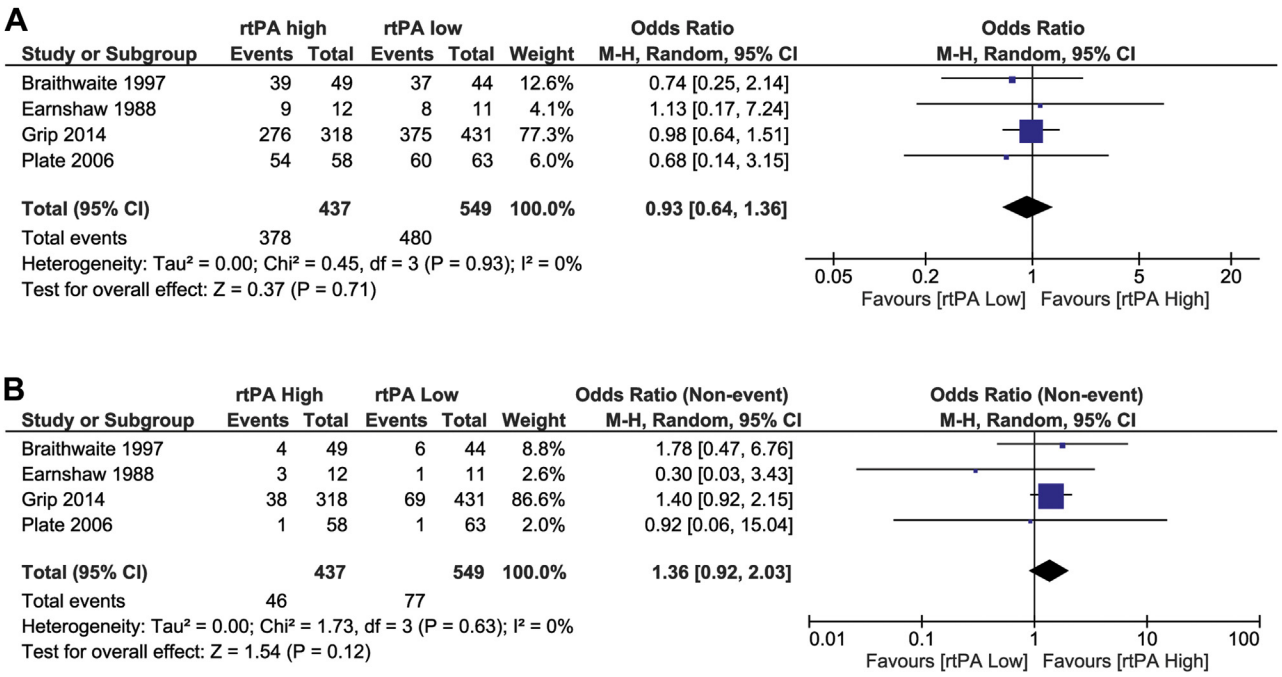

Fig 3. A, Recombinant tissue plasminogen activator (*r-tPA*) high-dose versus r-tPA low dose, limb salvage at 30 days. **B,** r-tPA high-dose versus r-tPA low dose, major vascular events (MVE). *CI,* Confidence interval.

Table III. Characteristics of included studies: Recombinant tissue plasminogen activator (*r-tPA*) versus streptokinase

Study	Methods	Participants	Interventions	Outcomes
Berridge 1989	Design: Retrospective analysis Lost to follow-up: 0	N = 44 Inclusion criteria: None reported. Exclusion criteria: None reported. Group differences: Age for r-tPA group was significantly higher than the streptokinase group.	I. streptokinase (n = 23) II. r-tPA (n = 21)	MVE, limb salvage 30 days
Berridge 1991[a]	Design: RCT Lost to follow-up: 6	N = 60 Inclusion criteria: None reported. Exclusion criteria: Recent major trauma, surgery, or cerebrovascular accident. Group differences: No significant differences between the groups.	I. streptokinase (n = 20) II. IA r-tPA (n = 20)	MVE, limb salvage 30 days
Earnshaw 1988	Design: Retrospective analysis Lost to follow-up: 0	N = 23 Inclusion criteria: Onset of symptoms <30 days. Exclusion criteria: High risk of bleeding complications, stroke in the previous 2 months. Group differences: Not reported.	I. r-tPA (n = 17) II. streptokinase (n = 5)	MVE, limb salvage 30 days

IA, Intra-arterial; *MVE,* major vascular event; *RCT,* randomized, controlled trial.
[a]Amputation data used to calculate limb salvage.

the 6-month follow-up (OR, 2.21; 95% CI, 1.17 to 4.18; $P = .01$; $I^2 = 0\%$). Only one study reported MVE, which reported no significant differences between the two groups.[42]

Rotarex mechanical thrombectomy system versus r-tPA. Two studies compared the use of Rotarex with traditional thrombolytic interventions[27,46]; one retrospective study was found to be of sufficient quality (Table IX).[27]

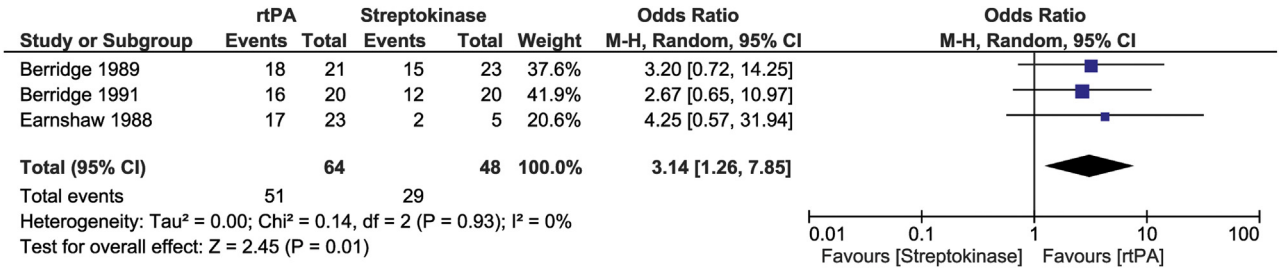

Fig 4. Recombinant tissue plasminogen activator (*r-tPA*) versus streptokinase, limb salvage at 30 days. *CI,* Confidence interval.

Table IV. Characteristics of included studies: Recombinant tissue plasminogen activator (*r-tPA*) versus urokinase

Study	Methods	Participants	Interventions	Outcomes
Schweizer 1996[a]	Study design: RCT Lost to follow-up: 18	N = 102 Inclusion criteria: Not reported. Exclusion criteria: Not reported. Group differences: No significant differences between the groups.	I. r-tPA (n = 60) II. Urokinase (n = 60)	MVE, limb salvage 6 months
Mahler 2001	Study design: RCT Lost to follow-up: 0	N = 234 Inclusion criteria: Thrombotic occlusions measuring between 5 and 40 cm. Exclusion criteria: Active bleeding disorders, recent surgical interventions, head injury or cerebrovascular events, uncontrolled hypertension. Group differences: No significant differences between the groups.	I. r-tPA (n = 124) II. Urokinase (n = 110)	MVE, limb salvage 6 months
Shortell 2001	Design: Retrospective analysis Lost to follow-up: 0	N = 60 Inclusion criteria: None reported. Exclusion criteria: History of major hemorrhage, pregnancy, bleeding diathesis, recent surgery or trauma. Group differences: No significant differences between the groups.	I. r-tPA (n = 37) II. Urokinase (n = 36)	MVE, limb salvage 30 days

MVE, Major vascular event; *RCT,* randomized, controlled trial.
[a]Amputation data used to calculate limb salvage.

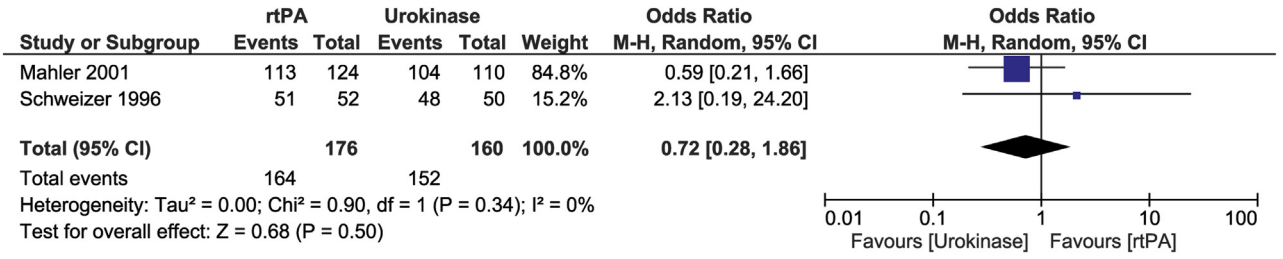

Fig 5. Recombinant tissue plasminogen activator (*r-tPA*) versus urokinase, limb salvage at 6 months. *CI,* Confidence interval.

No meta-analysis was performed. The included study reported no significant differences regarding limb salvage. Patients treated with Rotarex had a significant lower chance of enduring MVE (3.4%) compared with r-tPA (14%; $P = .01$) and critically ill patients had a lesser duration of hospital stay (1.4 ± 0.9 days com6pared with r-tPA 4.6 ± 3 days). Primary vascularization success with the Rotarex device was found to be 98%.

Table V. Characteristics of included studies: Recombinant tissue plasminogen activator (*r-tPA*) heated versus r-tPA unheated

Study	Methods	Participants	Interventions	Outcomes
Tsetis 2013	Design: Prospective analysis Lost to follow-up: 0	N = 34 Inclusion criteria: Onset of symptoms <30 days. Exclusion criteria: Occlusion peripheral bypass grafts. Group differences: No significant differences between the groups.	I. r-tPA unheated (n = 18) II. r-tPA heated (n = 16)	MVE, limb salvage 30 days

MVE, Major vascular event.

Table VI. Characteristics of included studies: Ultrasound versus nonultrasound thrombolysis

Study	Methods	Participants	Interventions	Outcomes
Schernthaner 2014[a]	Design: Retrospective Lost to follow-up: 26	N = 102 Inclusion criteria All adult patients were included. Exclusion criteria: None reported. Group differences: No significant differences between the groups.	I. Ultrasound accelerated thrombolysis (n = 75) II. Nonultrasound thrombolysis (n = 27)	MVE, limb salvage 30 days
Schrijver 2015[b]	Design: RCT Lost to follow-up: 0	N = 60 Inclusion criteria: Onset of symptoms <49 days. Exclusion criteria: Recent ischemic stroke, cerebral bleeding, or surgery. Severe hypertension (>110 mm Hg diastolic, >200 mm Hg systolic blood pressure). Group differences: No significant differences between the groups.	I. CDT urokinase (n = 32) II. Ultrasound accelerated urokinase (n = 28)	MVE, limb salvage 30 days

CDT, Catheter-driven thrombolysis; *MVE,* major vascular event; *RCT,* randomized, controlled trial.
[a]Event-free survival rate used to calculate limb salvage. Event-free survival rate was solely determined by patency loss of the target vessel.
[b]Amputation data used to calculate limb salvage.

Table VII. Characteristics of included studies: Intravenous (*IV*) alteplase versus catheter-driven thrombolysis (CDT) alteplase

Study	Methods	Participants	Interventions	Outcomes
Saroukhani 2015	Design: RCT Lost to follow-up: 0	N = 44 Inclusion criteria: Onset of symptoms <14 days. Exclusion criteria: Severe hypertension (systolic>160 mm Hg, diastolic>100 mm Hg), recent trauma or surgery, history of subarachnoid hemorrhage. Group differences: No significant differences between the groups.	I. IV alteplase (n = 18) II. Catheter-directed alteplase (n = 20)	MVE, limb salvage 30 days

MVE, Major vascular event; *RCT,* randomized, controlled trial.

DISCUSSION

This meta-analysis includes data from 25 studies that investigated current surgical and endovascular treatment strategies in a total of 4689 patients with ALI. Overall, direct comparison between trials was challenging owing to heterogeneous outcome reporting and adoption of different inclusion criteria. This was evident in the limited amount of randomized, controlled trials that were eligible for meta-analysis. Although the prospective and retrospective studies added to this meta-analysis showed the same trends of composed results as the randomized controlled trials, still no conclusions could be drawn.

Several fibrinolytic agents are used in treating ALI; however, no conclusions can be drawn regarding the occurrence of MVE in our meta-analysis. In a previous

Table VIII. Characteristics of included studies: AngioJet versus recombinant tissue plasminogen activator (*r-tPA*)

Study	Methods	Participants	Interventions	Outcomes
Byrne 2014[a]	Design: Retrospective Lost to follow-up: 0	N = 154 Inclusion criteria: None reported. Exclusion criteria: None reported. Group differences: No significant differences between the groups.	I. AngioJet with or without r-tPA (n = 71) II. r-tPA (n = 83)	MVE, limb salvage 30 days and 1 year
Hanover 2015	Design: RCT Lost to follow-up: 6	N = 81 Inclusion criteria: None reported. Exclusion criteria: Thrombus unresponsive to thrombolytic, clinical deterioration during intervention, or complications of thrombolytic. Group differences: No report has been made on group differences.	I. AngioJet with reteplase (n = 50) II. Reteplase only (n = 31)	MVE, limb salvage 30 days, 6 months, and 1 year
Leung 2015[a,b]	Design: Prospective, not randomized Lost to follow-up: not reported	N = 283 Inclusion criteria: None reported. Exclusion criteria: None reported. Group differences: No significant differences between the groups.	VII. AngioJet only (n = 86) VIII. AngioJet with activase or retavase (n = 86)	MVE, limb salvage 30 days and 1 year

MVE, Major vascular event; *RCT,* randomized, controlled trial.
[a]Amputation data used to calculate limb salvage.
[b]No MVE data available: this study used freedom of bleeding, which was not analogous to our definition of MVE.

systematic review of r-tPA, Ouriel et al[47] suggested that urokinase may be associated with a lower incidence of complications compared with r-tPA. This difference may be explained because studies were excluded that lacked clear timeframes for outcome data or contained a single cohort, which Ouriel et al[47] included by the use of pooling cohorts. Second, this meta-analysis aggregated studies with occlusions in both native vessel and bypass graft, which might influence the risk of MVE,[47] but not of limb salvage rates.[48]

The increased major bleeding events seen with both r-tPA and urokinase compared with traditional thrombectomy give way for studies exploring novel methods to shorten the total exposure time of r-tPA. It is claimed that this can be done by means of heating or acceleration with ultrasound.[29] Currently, there is limited evidence supporting the use of these methods. The quality of the studies is generally poor and most studies are single armed. Although one study detailing the application of heated to unheated r-tPA found no differences between the groups in 30-day limb salvage, a significant decrease in lysis duration and total doses of administered r-tPA was found. Similarly, a study using ultrasound to deliver r-tPA showed a significant shorter time to lysis as well as a marginally better limb salvage outcome for the group treated with ultrasound.[40] Another study reported less MVE for the nonultrasound group.[35] These findings are in accordance with a previous review done on methods of administrating r-tPA.[49]

Newer fibrinolytic agents like the modified r-tPA tenecteplase have shown promising results with decreasing the MVE in ischemic stroke research, but lack large center trials regarding ALI.[50] Small trials evaluating tenecteplase with patients suffering from ALI show similar success and complication rates compared with r-tPA.[45,51] Large center trials are needed before conclusions can be made regarding the use of tenecteplase in ALI.

Studies regarding rheolytical apparatus and innovative catheters such as the AngioJet and Rotarex present advantages compared with classical CDT, but these studies are small, use a single cohort, and are often sponsored by a device manufacturer.[52-56] Patients treated with Angiojet were found to have better limb salvage at 6 months, with no significant differences shown at 30 days or 1 year compared with r-tPA. Additionally, a shorter procedure time without a greater chance of the need for a secondary intervention was stated, but this did not significantly improve the limb salvage rates.[42,44] A single cohort study for the Rotarex device found a higher 30-day limb salvage and less MVE compared with r-tPA.[46] This study reported specific complications in using the Rotarex device. First, owing to the large vessel diameter of the common iliac artery found not all thrombi could be removed from the vessel, which led to a significant number of stents being placed to avoid distal thrombus migration. Second, stents were also placed owing to perforations caused by the Rotarex device in smaller, distal arteries. It seems that the Rotarex device might be

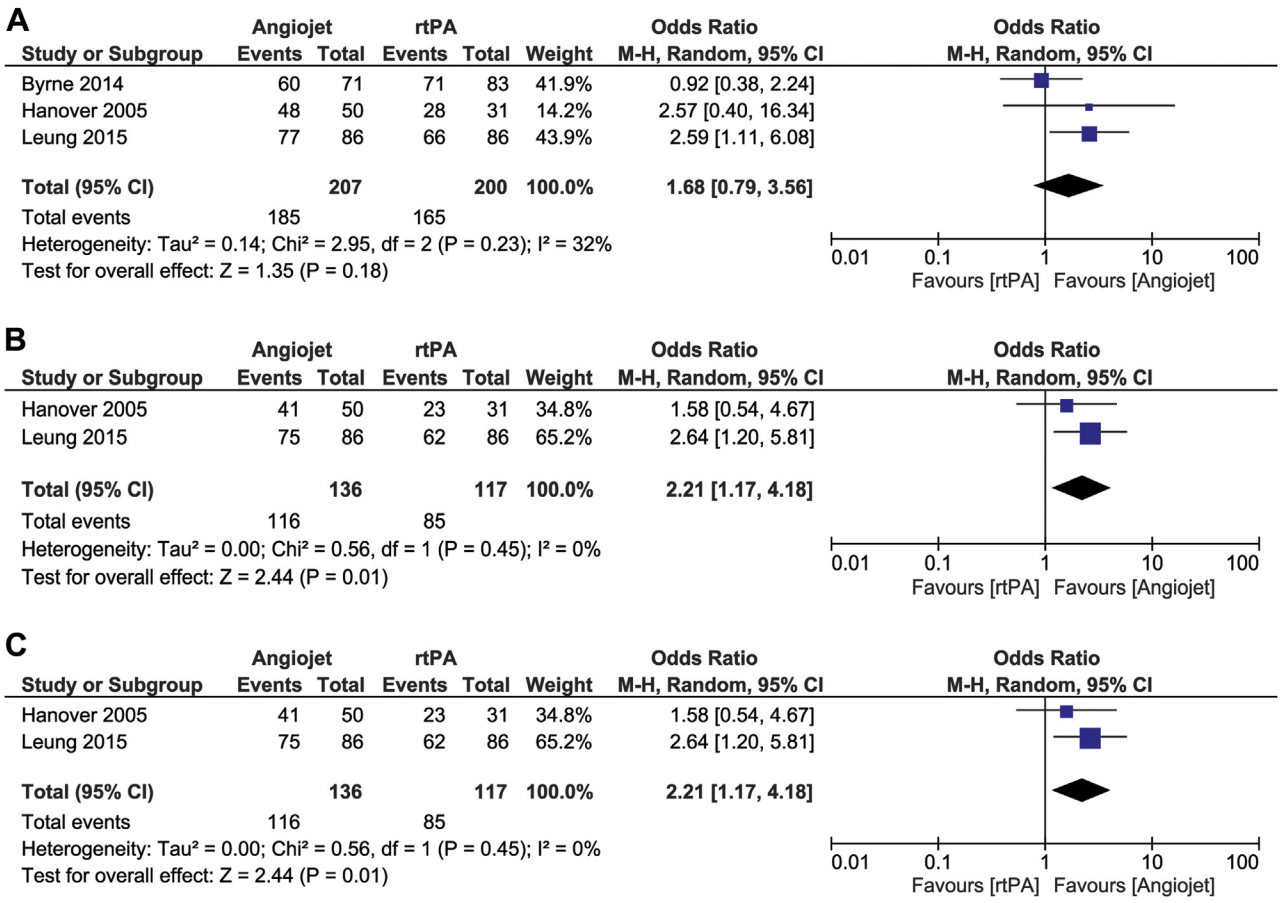

Fig 6. A, AngioJet versus recombinant tissue plasminogen activator (*r-tPA*), limb salvage at 30 days. **B,** AngioJet versus r-tPA, limb salvage at 6 months. **C,** AngioJet versus r-tPA, limb salvage at 1 year. *CI,* Confidence interval.

Table IX. Characteristics of included studies: Rotarex versus recombinant tissue plasminogen activator (*r-tPA*)

Study	Methods	Participants	Interventions	Outcomes
Kronlage 2018[a,b]	Design: Retrospective Lost to follow-up: 0	N = 202 Inclusion criteria: None reported. Exclusion criteria: None reported. Group differences: No significant differences between the groups.	I. Rotarex (n = 146) II. r-tPA (n = 28)	MVE, limb salvage 30 days

MVE, Major vascular event.
[a]Amputation data used to calculate limb salvage.
[b]Considered were the noncritical ill amputation data as reported over the groups. These data needed to be extrapolated from a Kaplan-Meier graph.

applicable in patients with thrombi in the superficial femoral and popliteal artery that fit the diameter of the device, but shows insufficient thrombi removal in larger vessels and high rate of perforations in smaller vessels. The performed meta-analysis does not support the recommendation of primary or adjuvant percutaneous mechanic thrombectomy by means of the AngioJet or the Rotarex devices for treatment ALI at present.

A major limiting factor of the current analysis is a lack of randomized controlled trials that could be included. The inclusion of both nonrandomized trials and retrospective studies may have introduced potential biases, such as confounding by indication and reporting bias. Care was taken to take risk of bias into account and evaluate the strength of evidence; however, the meta-analysis was not able to sufficiently assess many novel techniques, such as the AngioJet. Furthermore, the heterogeneity of presented outcome data limited the ability to aggregate all eligible studies. Limb salvage rates and MVE were found to be the most uniform reported outcome. Nonetheless, many studies only reported 30-day limb salvage, with some

only reporting 1-year limb salvage. Because these studies failed to adhere to consensus protocol of outcome reporting, they could not be included in the meta-analysis. Because several studies used different definitions of limb salvage, uncertainty exists regarding true numbers of limb salvage. This meta-analysis did not look at the severity of ALI at time of inclusion. This factor might lead to inappropriate outcome comparisons owing to, for example, patients with severe disease receiving one kind of intervention more often compared with healthier patients. Additionally, all outcome data were combined for native vessel and bypass occlusions because the studies did not separately report or found no significant differences between vessel types for limb salvages rates and MVE.[47,48] Within the studies comparing endovascular thrombectomy strategies, the overall methodologic quality of the included studies was poor and often only one study correctly displayed limb salvage data; examples are the studies found on the Rotarex device and vascular complications with the Angiojet.

CONCLUSIONS

CDT and surgery have comparable limb salvage rates; however, MVE are more frequent in the thrombolysis group. No conclusions can be drawn regarding MVE in thrombolytic therapy by means of r-tPA, streptokinase, or urokinase. Insufficient data are available to conclude the preference of using a hybrid approach, ultrasound-accelerated CDT, heated r-tPA, or novel endovascular (rheolytical) thrombectomy systems. Future trials regarding ALI need to be carefully constructed ensuring comparable study groups and should follow standardized practices of outcome reporting and treatment guidelines.[57]

AUTHOR CONTRIBUTIONS

Conception and design: EV, CZ, RB
Analysis and interpretation: EV, MV, EDH, RB
Data collection: EV, MV, MK, RB
Writing the article: EV, RB
Critical revision of the article: EV, MV, CZ, EDH, MK, RB
Final approval of the article: EV, MV, CZ, EDH, MK, RB
Statistical analysis: EV, MV, RB
Obtained funding: Not applicable
Overall responsibility: RB

REFERENCES

1. Creager M, Kaufman J, Conte M. Clinical practice. Acute limb ischemia. N Engl J Med 2012;366:2198-206.
2. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e686-725.
3. Berridge DC, Kessel DO, Robertson I. Surgery versus thrombolysis for initial management of acute limb ischaemia. Cochrane Database Syst Rev 2013;(6):CD002784.
4. Thrombolysis in the management of lower limb peripheral arterial occlusion–a consensus document. J Vasc Interv Radiol 2003;14(Suppl):S337-49.
5. Braithwaite B, Buckenham T, Galland R, Heather B, Earnshaw J. Prospective randomized trial of high-dose bolus versus low-dose tissue plasminogen activator infusion in the management of acute limb ischaemia. Thrombolysis Study Group. Br J Surg 1997;84:646-50.
6. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
7. Dijkers M. Introducing GRADE: a systematic approach to rating evidence in systematic reviews and to guideline development, Center on Knowledge Translation for Disability and Rehabilitation Research, KT Update 2013, (1)5.
8. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712-6.
9. Falkowski A, Poncyljusz W, Samad R, Mokrzyński S. Safety and efficacy of ultra-high-dose, short-term thrombolysis with rt-PA for acute lower limb ischemia. Eur J Vasc Endovasc Surg 2013;46:118-23.
10. Kuhn JP, Hoene A, Miertsch M, Traeger T, Langner S, Hosten N, et al. Intraarterial recombinant tissue plasminogen activator thrombolysis of acute and semiacute lower limb arterial occlusion: quality assurance, complication management, and 12-month follow-up reinterventions. AJR Am J Roentgenol 2011;196:1189-93.
11. Braithwaite B, Tomlinson M, Walker S, Davies B, Buckenham T, Earnshaw J. Peripheral thrombolysis for acute-onset claudication. Thrombolysis Study Group. Br J Surg 1999;86:800-4.
12. Plate G, Jansson I, Forssell C, Weber P, Oredsson S. Thrombolysis for acute lower limb ischaemia–a prospective, randomised, multicentre study comparing two strategies. Eur J Vasc Endovasc Surg 2006;31:651-60.
13. Grip O, Kuoppala M, Acosta S, Wanhainen A, Åkeson J, Björck M. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. Br J Surg 2014;101:1105-12.
14. Earnshaw J, Westby J, Gregson R, Makin G, Hopkinson B. Local thrombolytic therapy of acute peripheral arterial ischaemia with tissue plasminogen activator: a dose-ranging study. Br J Surg 1988;75:1196-200.
15. Flis V, Kobilica N, Bergauer A, Mrdza B, Milotic F, Stirn B. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) in acute lower limb ischaemia. J Int Med Res 2011;39:1107-12.
16. Koraen L, Kuoppala M, Acosta S, Wahlgren C. Thrombolysis for lower extremity bypass graft occlusion. J Vasc Surg 2011;54:1339-44.
17. Kronlage M, Print I, Vogel B, Blessing E, Müller O, Katus H, et al. A comparative study on endovascular treatment of (sub)acute critical limb ischemia: mechanical thrombectomy vs thrombolysis. Drug Des Devel Ther 2017;11:1233-41.
18. Lukasiewicz A, Lichota W, Thews M. Outcomes of accelerated catheter-directed thrombolysis in patients with acute arterial thrombosis. Vasc Med 2016;21:453-8.
19. Tsetis DK, Katsamouris AN, Giannoukas AD, Hatzidakis AA, Kostas T, Chamalakis K, et al. Potential benefits from heating the high-dose rtPA boluses used in catheter-directed

thrombolysis for acute/subacute lower limb ischemia. J Endovasc Ther 2003;10:739-44.
20. Wissgott C, Richter A, Kamusella P, Steinkamp H. Treatment of critical limb ischemia using ultrasound-enhanced thrombolysis (PARES Trial): final results. J Endovasc Ther 2007;14:438-43.
21. Wongwanit C, Hahtapornsawan S, Chinsakchai K, Sermsathanasawadi N, Hongku K, Ruangsetakit C, et al. Catheter-directed thrombolysis for acute limb ischemia caused by native artery occlusion: an experience of a university hospital. J Med Assoc Thail 2013;96:661-8.
22. Mahler F, Schneider E, Hess H. Recombinant tissue plasminogen activator versus urokinase for local thrombolysis of femoropopliteal occlusions: a prospective, randomized multicenter trial. J Endovasc Ther 2001;8:638-47.
23. Nilsson L, Albrechtsson U, Jonung T, Ribbe E, Thorvinger B, Thörne J, et al. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomised controlled study. Eur J Vasc Surg 1992;6:189-93.
24. Ouriel K, Shortell C, DeWeese J, Green R, Francis C, Azodo M, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. J Vasc Surg 1994;19:1021-30.
25. Ouriel K, Veith F, Sasahara A, Whittemore A, Roon A, Braithwaite B, et al. Thrombolysis or peripheral arterial surgery: phase I results. J Vasc Surg 1996;23:64-75.
26. Ouriel K, Veith F, Sasahara A. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. N Engl J Med 1998;338:1105-11.
27. STILE. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg 1994;220:251-8.
28. Hoch JR, Tullis MJ, Acher CW, Heisey DM, Crummy AB, McDermott JC, et al. Thrombolysis versus surgery as the initial management for native artery occlusion: efficacy, safety, and cost. Surgery 1994;116:647-9.
29. Taha A, Byrne R, Avgerinos E, Marone L, Makaroun M, Chaer R. Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia. J Vasc Surg 2015;61:147-54.
30. Seeger J, Flynn T, Quintessenza J. Intra-arterial streptokinase in the treatment of acute arterial thrombosis. Surg Gynecol Obstet 1987;164:303-7.
31. de Donato G, Setacci F, Sirignano P, Galzerano G, Massaroni R, Setacci C. The combination of surgical embolectomy and endovascular techniques may improve outcomes of patients with acute lower limb ischemia. J Vasc Surg 2014;59:729-36.
32. Berridge D, Earnshaw J, Westby J, Makin G, Hopkinson B. Fibrinolytic profiles in local low-dose thrombolysis with streptokinase and recombinant tissue plasminogen activator. Thromb Haemost 1989;61:275-8.
33. Berridge D, Gregson R, Hopkinson B, Makin G. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. Br J Surg 1991;78:988-95.
34. Earnshaw J, Gregson R, Makin G, Hopkinson B. Acute peripheral arterial ischemia: a prospective evaluation of differential management with surgery or thrombolysis. Ann Vasc Surg 1989;3:374-9.
35. Schernthaner M, Samuels S, Biegler P, Benenati J, Uthoff H. Ultrasound-accelerated versus standard catheter-directed thrombolysis in 102 patients with acute and subacute limb ischemia. J Vasc Interv Radiol 2014;25:1149-56. quiz 1157.
36. Shortell CK, Queiroz R, Johansson M, Waldman D, Illig KA, Ouriel K, et al. Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion. J Vasc Surg 2001;34:854-9.
37. Oguni T, Korogi Y, Makita O, Yoshizumi K, Shinzato J, Takahashi M. Intraarterial catheter thrombolytic therapy for acute peripheral arterial occlusions. Radiat Med 1999;17:295-304.
38. Suggs WD, Cynamon J, Martin B, Sanchez LA, Wahl SI, Aronoff B, et al. When is urokinase treatment an effective sole or adjunctive treatment for acute limb ischemia secondary to native artery occlusion? Am J Surg 1999;178:103-6.
39. Schweizer J, Altmann E, Stösslein F, Florek H, Kaulen R. Comparison of tissue plasminogen activator and urokinase in the local infiltration thrombolysis of peripheral arterial occlusions. Eur J Radiol 1996;22:129-32.
40. Schrijver A, van Leersum M, Fioole B, Reijnen M, Hoksbergen A, Vahl A, et al. Dutch randomized trial comparing standard catheter-directed thrombolysis and ultrasound-accelerated thrombolysis for arterial thromboembolic infrainguinal disease (DUET). J Endovasc Ther 2015;22:87-95.
41. Saroukhani A, Ravari H, Rad M. Effects of intravenous and catheter directed thrombolytic therapy with recombinant tissue plasminogen activator (Alteplase) in non-traumatic acute limb ischemia; a randomized double-blind clinical trial. Bull Emerg Trauma 2015;3:86-92.
42. Byrne R, Taha A, Avgerinos E, Marone L, Makaroun M, Chaer R. Contemporary outcomes of endovascular interventions for acute limb ischemia. J Vasc Surg 2014;59:988-95.
43. Hanover T, Kalbaugh C, Gray B, Langan E 3rd, Taylor S, Androes M, et al. Safety and efficacy of reteplase for the treatment of acute arterial occlusion: complexity of underlying lesion predicts outcome. Ann Vasc Surg 2005;19:817-22.
44. Leung D, Blitz L, Nelson T, Amin A, Soukas P, Nanjundappa A, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: results from the PEARL registry. J Endovasc Ther 2015;22:546-57.
45. Allie DE, Hebert CJ, Lirtzman MD, Wyatt CH, Keller VA, Khan MH, et al. Continuous tenecteplase infusion combined with peri/postprocedural platelet glycoprotein IIb/IIIa inhibition in peripheral arterial thrombolysis: initial safety and feasibility experience. J Endovasc Ther 2004;11:427-35.
46. Zeller T, Frank U, Burgelin K, Muller C, Flugel P, Horn B, et al. Early experience with a rotational thrombectomy device for treatment of acute and subacute infra-aortic arterial occlusions. J Endovasc Ther 2003;10:322-31.
47. Ouriel K, Kandarpa K. Safety of thrombolytic therapy with urokinase or recombinant tissue plasminogen activator for peripheral arterial occlusion: a comprehensive compilation of published work. J Endovasc Ther 2004;11:436-46.
48. Breukink S, Vrouenraets B, Davies G, Voorwinde A, van Dorp T, Butzelaar R. Thrombolysis as initial treatment of peripheral native artery and bypass graft occlusions in a general community hospital. Ann Vasc Surg 2004;18:314-20.
49. Kessel D, Berridge D, Robertson I. Infusion techniques for peripheral arterial thrombolysis. Cochrane Database Syst Rev 2004:CD000985.

50. Campbell B, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med 2018;378:1573-82.
51. Hull JE, Hull MK, Urso JA, Park HA. Tenecteplase in acute lower-leg ischemia: efficacy, dose, and adverse events. J Vasc Interv Radiol 2006;17:629-36.
52. Ansel G, Botti C Jr, Silver M. Treatment of acute limb ischemia with a percutaneous mechanical thrombectomy-based endovascular approach: 5-year limb salvage and survival results from a single center series. Catheter Cardiovasc Interv 2008;72:325-30.
53. Kasirajan K, Gray B, Beavers F, Clair D, Greenberg R, Mascha E, et al. Rheolytic thrombectomy in the management of acute and subacute limb-threatening ischemia. J Vasc Interv Radiol 2001;12:413-21.
54. Papillion P, Sprouse R, Allen K, Greer M, Lesar C, Erdos L, et al. Percutaneous mechanical thrombectomy of acute lower extremity ischemia. Vasc Dis Manag 2008;5:135-8.
55. Silva J, Ramee S, Collins T, Jenkins J, Lansky A, Ansel G, et al. Rheolytic thrombectomy in the treatment of acute limb-threatening ischemia: immediate results and six-month follow-up of the multicenter AngioJet registry. Possis Peripheral AngioJet Study AngioJet Investigators. Cathet Cardiovasc Diagn 1998;45:386-93.
56. Sarac T, Hilleman D, Arko F, Zarins C, Ouriel K. Clinical and economic evaluation of the trellis thrombectomy device for arterial occlusions: preliminary analysis. J Vasc Surg 2004;39:556-9.
57. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1986;4:80-94.

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APPENDIX 1 (online only).

SEARCH STRATEGY

Pubmed electronic search. ("Ischemia"[Mesh] OR ischemia[tiab] OR ischaemia[tiab]) AND (Limb* [tiab] OR leg*[tiab] OR lower extremit*[tiab] OR peripheral arterial[tiab]) AND (Acute [tiab] OR Subacute [tiab]) AND (("Fibrinolytic Agents"[Mesh] OR Fibrolytic agents [tiab] OR "thrombolytic therapy"[Mesh] OR thrombolytic therap*[tiab] OR Thrombolysis[tiab] OR lysis*[tiab] OR lytic*[tiab] OR thrombolytic therap*[tiab] OR fibrinolytic therap*[tiab]) OR ("Thrombectomy"[Mesh] OR thrombectom* [tiab] OR "mechanical thrombolysis"[Mesh] OR mechanical*[tiab] OR pharmaco-mechanical thrombolysis [tiab] OR endovascular[tiab]))

Embase electronic search. ('Ischemia'/exp OR ischemia:ab,ti OR ischaemia:ab,ti) AND (Limb*:ab,ti OR leg*:ab,ti OR lower extremit*:ab,ti OR peripheral arterial:ab,ti) AND ('fibrinolytic agent'/exp OR 'fibrinolytic agents':ab,ti OR Thrombolysis:ab,ti OR lysis*:ab,ti OR lytic*:ab,ti OR 'thrombolytic therap*':ab,ti OR 'fibrinolytic therap*':ab,ti) AND ('thrombectomy'/exp OR thrombectom*:ab,ti OR 'pharmaco-mechanical thrombolysis':ab,ti)

Cochrane registry of trials search. 'Acute limb ischemia'

Appendix 2 (online only). Study appraisal of included and excluded studies

Study	Bias[a]							Quality[b]
	SG	AS	BPP	BOA	IOD	SOR	OB	
Allie 2004	High	High	High	High	Low	Low	Low	MINOR = 19
Ansel 2002	High	High	High	Low	Low	Low	Low	MINOR = 11
Ansel 2008	High	High	High	High	Low	Low	Low	MINOR = 12
Berridge 1989	High	Unclear	High	High	Low	Low	Low	MINOR = 18
Berridge 1991	Low	Low	high	high	Low	Low	Low	GRADE = 4
Braithwaite 1997	Low	Low	Low	Low	Low	Low	Low	GRADE =3
Braithwaite 1999	High	High	High	Low	Low	Low	Low	MINOR = 8
Breukink 2004	High	Unclear	Low	Unclear	Low	Low	Low	MINOR = 11
Byrne 2014	High	Unclear	Low	High	Low	Low	Low	MINOR = 16
Canova 2001	High	Unclear	Unclear	High	Low	Low	Low	MINOR = 7
Chen 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	MINOR = 10
Comerota 1996	Unclear	Low	Unclear	Unclear	Low	Low	Low	GRADE = 3
deDonato 2014	High	High	Unclear	Unclear	Low	Low	Low	MINOR = 21
Earnshaw 1988	High	High	High	High	Low	Low	Low	MINOR = 15
Earnshaw 1989	High	High	Unclear	Unclear	Low	Low	Low	MINOR = 16
Earnshaw 2004	High	High	High	High	Low	Low	Low	MINOR = 12
Falkowski 2013	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 13
Flis 2011	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 14
Grip 2014	High	High	Unclear	Unclear	Low	Low	Low	MINOR = 20
Hanover 2005	High	High	High	Unclear	Low	Low	Low	MINOR = 17
Hoch 1994	High	High	High	Unclear	Low	Low	Low	MINOR = 17
Kasirajan 2001	High	High	High	High	Low	Low	Low	MINOR = 8
Koraen 2011	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 8
Kronlage 2017	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 18
Kuhn 2011	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 14
Kuoppola 2008	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	MINOR = 16
Leung 2015	Unclear	Unclear	High	High	Low	Low	Low	GRADE = 2
Lukasiewicz 2016	Unclear	High	Unclear	Unclear	Low	Low	Low	MINOR = 13
Mahler 2001	Low	Low	High	High	Low	Low	Low	GRADE = 3
Nehler 2003	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 11
Nillson 1992	Low	Low	Low	Unclear	Low	Low	Low	GRADE = 4
Oguni 1999	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 9
Ouriel 1994	High	Low	Unclear	Unclear	Low	Low	Low	GRADE = 4
Ouriel 1996	Low	Low	Unclear	Unclear	Low	Low	Low	GRADE = 4
Ouriel 1998	Low	Unclear	Unclear	Unclear	Low	Low	Low	GRADE = 4
Papillion 2008	High	High	Unclear	Unclear	Low	Low	Low	MINOR = 10
Pemberton 1999	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 11
Plate 2006	High	Low	Low	Low	Low	Low	Low	GRADE = 4
Ramasundara 2001	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 10
Saroukhani 2015	Low	Low	High	Low	Low	Low	Low	GRADE = 4
Schernthaner 2014	High	High	Low	Low	Low	Low	Low	MINOR = 17
Schrijver 2015	Low	Low	High	High	Low	Low	Low	GRADE = 4
Schrijver 2016	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 20
Schweizer 1996	Low	Low	Low	High	Low	Low	Low	GRADE = 4
Seeger 1987	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 16
Shortell 2001	High	Low	Unclear	Unclear	Low	Low	Low	MINOR = 19
Silva 1998	Unclear	Unclear	High	High	Low	Low	Low	MINOR = 12

Appendix 2 (online only). Continued.

Study	Bias[a]							Quality[b]
	SG	AS	BPP	BOA	IOD	SOR	OB	
STILE 1994	Low	Low	Unclear	Low	Low	Low	Low	GRADE = 4
Suggs 1999	High	High	Unclear	Unclear	Low	Low	Low	MINOR = 10
Taha 2015	High	High	High	High	Low	Low	Low	MINOR = 21
Troisi 2016	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	MINOR = 12
Tsetis 2013	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	MINOR = 19
Wissgott 2007	High	high	Unclear	Unclear	Low	Low	Low	MINOR = 11
Wongwanit 2013	High	High	High	High	Low	Low	Low	MINOR = 12
Zeller 2003	High	High	High	High	Low	Low	Low	MINOR = 17

AC, Allocation concealment; *BPP*, blinding of participants and personnel; *BOA*, blinding of outcome assessment; *GRADE*, Grading of Recommendations Assessment, Development, and Evaluation; *MINOR*, Methodological Index for Nonrandomized studies; *IOD*, incomplete outcome data; *OB*, other bias; *SG*, random sequence generation; *SOR*, selective outcome reporting.
[a]Bias realized by consensus with 2 authors.
[b]GRADE score presented with randomized, controlled studies; MINOR score shown with nonrandomized studies.