

SYSTEMATIC REVIEW

Catheter Directed Thrombolysis Protocols for Peripheral Arterial Occlusions: a Systematic Review

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WHAT THIS PAPER ADDS

Current thrombolysis protocols for peripheral arterial occlusions are based on evidence from randomised controlled trials performed >20 years ago. To this day, there is no consensus on the optimum fibrinolytic agent or dose regimens to use. Numerous devices and techniques, such as mechanical thrombectomy and ultrasound assisted thrombolysis, have been proposed and investigated to improve the results of thrombolysis. Major bleeding complications remain a substantial clinical problem of thrombolytic therapy. The present systematic review of the literature provides an update of all reported patient cohorts with peripheral arterial occlusions treated by catheter directed thrombolysis.

Objective: Catheter directed thrombolysis (CDT) for peripheral arterial occlusions is a well established alternative to thrombo-embolectomy in patients with (sub)acute limb ischaemia. However, protocols are heterogeneous and need optimisation to improve results and lower bleeding risks. The objective was to review the results and outcomes of different CDT protocols for patients with peripheral arterial occlusions.

Data sources: Electronic information sources (MEDLINE, Embase, Cochrane) and reference lists were searched to identify studies reporting results of CDT of peripheral arterial occlusions.

Methods: Two independent observers performed study selection, quality assessment and data extraction. Primary outcomes were treatment duration, success rates, and bleeding complications. Secondary outcomes were mortality and amputation rates.

Results: One hundred and six studies were included: 19 randomised controlled trials (RCTs), 38 prospective studies, 48 retrospective studies, and one mixed cohort study. The studies comprised a total number of 10,643 cases of which 9877 received CDT for lower extremity arterial occlusion, with a mean treatment duration of 21.4 h (95% confidence interval [CI] 21.0–21.8), an angiographic patency of 75% (95% CI 74.6–75.1), and freedom from amputation rate of 91% (95% CI 90.3–90.7). Pooled results showed a thrombolysis duration with high dose protocols of 21.9 h (95% CI 21.4–22.5) and 32.7 h with low dose protocols, with bleeding rates of 16.7% (95% CI 16.3–17.1) and 13.4% (95% CI 12.8–14.0), respectively. Weighted mean results for all RCTs and prospective cohorts of >100 cases analysed separately, showed comparable results to all observational cohorts pooled. Bleeding complications occurred in 18% (95% CI 17.8–18.3) of patients and remain an important risk of CDT.

Conclusion: CDT is an effective treatment for peripheral arterial occlusions, the main concern is bleeding complications. Although no formal meta-analysis could be performed, the pooled results suggest that lower doses of fibrinolytics lead to similar success rates at a cost of longer treatment duration but with less bleeding. There is large variation in treatment protocols and the available literature suffers from absence of reporting standards and high heterogeneity.

Keywords: Acute occlusive disease, CDT, Catheter directed thrombolysis, PAOD, Peripheral arterial occlusions

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INTRODUCTION

Since its introduction as an alternative treatment to open balloon thrombo-embolectomy in the 1990s, thrombolytic treatment for acute arterial occlusive disease has matured in

multiple directions. Urokinase and (recombinant) tissue plasminogen activator (rtPA) are the most effective agents, but neither of these have been shown to be superior in terms of efficacy and bleeding complications.¹ Currently, catheter directed thrombolysis (CDT) is still accompanied by treatment failure with the need for surgery and/or limb loss and risk of major bleeding in a significant number of patients. A considerable literature on a wide variety of thrombolytic agents is available, but few randomised controlled clinical trials have been conducted, and the techniques and regimens are heterogeneous. The most selective, direct, in-thrombus approach yields the highest efficacy and is accompanied by fewer bleeding complications vs. non-selective, systemically administered alternatives.² However, choice of dose regimen, as well as the use of adjunctive mechanical devices, vary and the optimum protocol is debatable to this day.

The aim of the present study was to present a systematic review of the literature and review the results and reported outcomes of different CDT protocols for patients with peripheral arterial occlusions.

METHODS

Statement of design and registration

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed.^{3,4} The aims of the study, eligibility criteria, and outcomes were predefined in a protocol registered in the PROSPERO International prospective register of systematic reviews (2016:CRD42016039242). Ethical approval was not required.

Study eligibility

Included were studies reporting results of the thrombolytic treatment of patients with lower limb native arterial and bypass graft occlusions using different fibrinolytic agents (among UK and [r]tPA) and devices (ultrasound assisted thrombolysis, other device assisted thrombolysis) in published in Dutch and English.

Excluded were patients with venous thrombosis, upper limb occlusions, mesenteric thrombosis, occlusion of arteriovenous fistula, and patients treated with systemic thrombolysis, thrombolysis with streptokinase, and treatment with mechanical thrombectomy devices as sole therapy. Review articles, technical descriptions, case reports, and small patient series ($n < 20$ receiving CDT) were excluded.

Population, intervention, comparison, and outcome

Patients with peripheral arterial occlusions undergoing CDT intervention were included. Different dose regimens, fibrinolytics, and techniques were compared focusing on the outcomes of interest, which were treatment duration, angiographic success rate, clinical success rate, bleeding complications, mortality, and amputation rates.

Search strategy

A search was conducted in the MEDLINE, Cochrane, and Embase databases. The search query was based on relevant

medical subject heading (MeSH) terms (Humans, Infusions, Intra-Arterial, Arterial Occlusive Diseases, Peripheral Arterial Disease, Thrombolytic Therapy) combined with additional relevant terms (CDT, acute limb ischaemia, limb ischaemia, arterial occlusion). The exact search queries for the different databases can be found in [Appendix S1](#) (see Supplementary Material). The references of included studies and other important publications were hand searched for additional reports. The search was repeated on 17 June 2018 to include recently published articles. If studies were eligible but the minimum outcome data were missing, the authors were contacted for additional sources.

Data collection and analysis

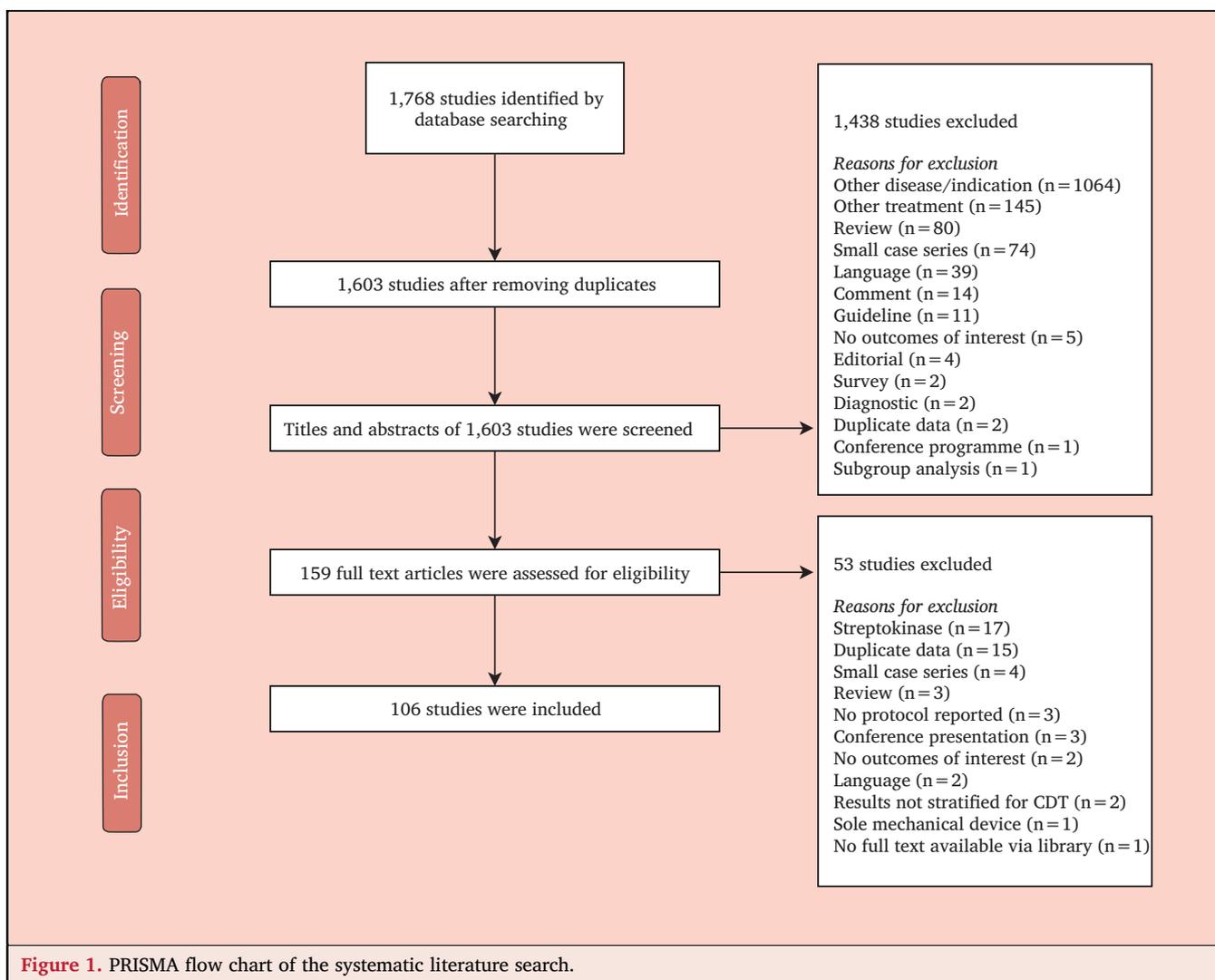
After removal of duplicates, all abstracts and titles of articles located in the search strategy were independently screened by two authors (H.E., V.J.), with any discrepancies resolved by discussion. Subsequently, the selected full citations were reviewed by the same two authors to see if they met the eligibility criteria. To avoid the inclusion of duplicate publications the data and authors of studies were examined for similarities. Studies were excluded if only abstracts of studies were available after library inquiries.

A predefined standardised data extraction form was used to extract data (by H.E.) from the included studies for assessment of study quality and evidence synthesis based on the Cochrane and PRISMA guidelines for systematic reviews,^{3,5} and entered into a Google Spreadsheets Database with audit trail option. Extracted information included study characteristics, patients and indications, treatments characteristics, outcomes with definitions, and times of measurement and information for assessment of the risk of bias and specification of missing data. Two authors (V.J., K.Y.) independently checked the extracted data of all primary and secondary outcomes for accuracy. Conflicts were discussed until consensus was reached.

Two review authors (H.E., V.J.) independently assessed the quality and risk of bias in the included studies by using a predefined standardised quality assessment form based on the Cochrane and PRISMA review guidelines for assessment of quality and risk of bias. This included the Cochrane tool for bias assessment of randomised controlled trials (RCTs) and the Newcastle—Ottawa Scale for observational studies. Discrepancies were identified and resolved through discussion with a third and senior author where necessary.

If results presented high clinical heterogeneity and/or lack of appropriately described methods for randomisation, a meta-analysis of outcome comparisons was not performed.

The assessments are summarised in [Table S1](#) (see Supplementary Material). Subgroup analyses of outcomes are presented for low and high dose thrombolysis protocols, type of fibrinolytic agent used for thrombolysis, and native or bypass graft occlusions. To form high and low dose groups, cut off values were created around the median. A high dose was defined as $\geq 75,000$ IU/hour urokinase, ≥ 0.8 mg/h rtPA or ≥ 1.0 U/hour rtPA; a low dose was defined as $< 75,000$ IU/hour urokinase or < 0.8 mg/h rtPA or < 1.0 U/hour rtPA. Bleeding complications were recorded as



major or minor, as reported by the author(s). If possible, the definition of Mehran et al.⁶ was followed and type III/IV bleedings were classified as major, i.e., when transfusion or intervention was needed or when bleedings were either intracranial or fatal. As the majority of included studies reported no comparative data, the weighted means (using descriptive statistics with a 95% confidence interval [CI], weighted by number of relevant cases) were used to present outcome data of the reviewed protocols. Pooled weighted mean results for reported patient outcomes were presented for all included studies and in addition for all RCTs and prospective cohorts >100 cases separately. Data were analysed using SPSS (IBM Statistics version 20; IBM, Armonk, NY, USA).

RESULTS

Study selection

The search strategy yielded 1762 results, with 1597 articles for title and abstract screening after removal of duplicates. Of these, 159 articles were selected for consideration of full text and 106 of these articles met the defined eligibility criteria and were included in the present review (Fig. 1).

Study characteristics

Nineteen studies were RCTs; 38 were prospective, 48 were retrospective, and one was a combined cohort study. The studies comprised a total number of 10,643 cases of which 9877 received CDT for lower extremity arterial occlusion. Seven percent of the studies were published in the period 1980–89, 51% in the period 1990–99, 20% in the period 2000–09, and 23% in the period of 2010 - present. Study characteristics for individual studies are summarised in Appendix S2 (see Supplementary Material).

From the 19 RCTs, comparative data were available for fibrinolytic agents (rtPA vs. urokinase) in three studies,^{7–9} and high dose vs. low dose regimen in two studies.^{10,11}

Patients and indications for treatment

The mean \pm SD age of the patients was 66 \pm 5 years and the majority were male (64%). Studies that described comorbidities and/or risk factors reported smoking in 62%, hypertension in 56%, cardiac disease in 43%, diabetes in 30%, hypercholesterolaemia in 34%, chronic obstructive pulmonary disease in 20%, and malignancy in 11% of patients. The majority of studies (78%) did not report the

status of chronic vascular disease, but at least five studies reported patients with necrosis or ulcerative wounds at presentation. The degree of ischaemia (acute Rutherford classification) at presentation was reported in only 30% of studies. In the majority of these studies, patients with class IIb ischaemia (moderate motor loss involved) were also treated by CDT.¹²

Descriptive characteristics of patients and indications for treatment for individual studies are summarised in [Appendix S3](#) (see Supplementary Material).

Treatment characteristics

Patients were treated with urokinase (50 studies), rtPA (27 studies), tPA (17 studies) urokinase/rtPA (six studies), urokinase/tPA (one study), pro-urokinase (one study), tenecteplase (one study), alteplase (one study), and plasmin (one study) and in one study the fibrinolytic was not reported.

The potential use of bolus injections was reported in 82% of studies (48% high dose, 10% low dose, 12% high and low dose, 10% none). In 56% of studies a continuous high dose protocol was used, in 11% a low dose protocol, and in 13% both a low and high dose protocol were used (20% was not reported).

Treatment characteristics of all reported protocols are summarised in [Appendix S4](#) (see Supplementary Material), including catheters and infusion technique used, as well as total cumulative doses, therapy duration, additional interventions, peri- and post-procedural anticoagulation, peri-procedural monitoring, level of care, and hospital type (if reported).

Quality assessment and risk of bias

The risk of bias was lowest in the RCTs, whereas the observational studies suffered from all forms of bias. However, among RCTs that reported comparative data there was high clinical heterogeneity. Also, in >30% of all RCTs it was unclear how the randomisation process took place and thus selection bias was likely; furthermore, as treatments in 84% of the RCTs could not be blinded, performance and detection bias was likely. In the cohort studies that compared interventions, comparability was not sufficient as cases and controls were not matched in the designs nor were confounders adjusted for in the analyses. Only baseline characteristics were reported with statements of no differences between groups. Owing to clinical heterogeneity and/or lack of appropriately described methods for randomisation, a meta-analysis of outcome comparisons could not be performed.

The quality assessment and risk of bias of individual studies is reported for individual studies in [Appendix S5](#) (see Supplementary Material).

Outcomes and grading of evidence

In consensus, it was concluded that it was not appropriate to perform formal meta-analysis of data, owing to the lack of control groups in cohort studies and the heterogeneous inclusion criteria of patients and definition of outcomes in the currently available literature in both cohort studies and

RCTs. As no appropriate comparative RCTs were available for meta-analysis, grading of evidence of outcome comparisons could not be performed. Pooled outcome results for the different subgroups and results for all individual studies are presented in [Table S1](#) and [Appendix S6](#) (see Supplementary Material), respectively. Data from the 19 RCTs and three prospective cohorts with ≥ 100 patients are also presented separately in [Table S1](#).

Treatment duration. Seventy-four studies (70%) reported a treatment duration, of which 38 studies had a mean treatment duration up to 24 h (of which 15 studies < 6 h), 20 studies a mean duration of 24–48 h, and four studies a mean treatment duration of >48 h. Thirty-two (30%) studies did not report exact treatment durations. The overall mean treatment duration was 21.4 h (95% CI 21.0–21.8), 21.9 h (95% CI 21.4–22.5) for high dose protocols and 32.7 h (95% CI 31.4–34.0) for studies using low dose protocols. Studies in which tPA or rtPA was used had mean treatment durations of 17.3 h (95% CI 16.7–17.8) and 20.4 h (95% CI 19.7–21.1), respectively. Studies using urokinase had a mean treatment duration of 27.4 h (95% CI 26.8–28.0).

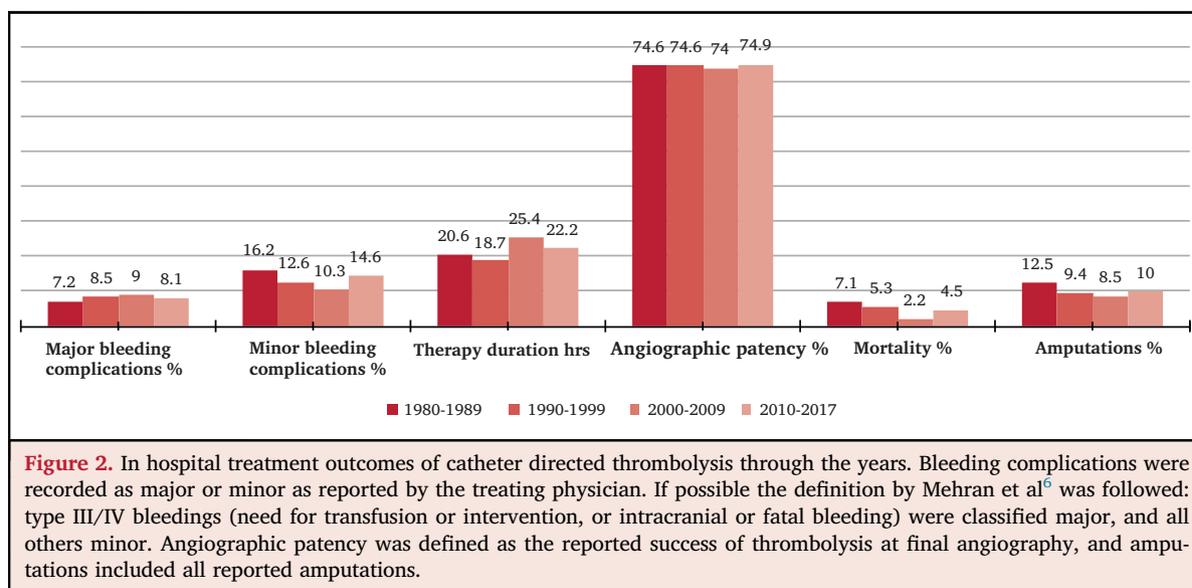
The pooled means from RCTs and prospective cohorts (≥ 100 patients) showed similar treatment durations ([Table S1](#)).

Angiographic success rates. Angiographic success rates were reported in 95% of studies with a pooled mean success rate of 74.9% (95% CI 74.6–75.1) and were 74.3% (95% CI 74.0–74.6) for high dose and 76.6% (95% CI 76.2–76.9) for low dose protocols. In addition, success rates were comparable for type of fibrinolytic agent used and for native arteries and bypasses ([Table S1](#)).

The pooled means from RCTs and prospective cohorts (≥ 100 patients) showed comparable rates around 70% (range 66.6–79.3%) for different subgroups ([Table S1](#)).

Bleeding complications. Bleeding complications were reported in 96% of studies, with pooled overall reported bleeding complications in 18.0% (95% CI 17.8–18.3) of cases among major bleeding complications in 8.4% (95% CI 8.3–8.6) and minor bleeding complications in 12.8% (95% CI 12.6–13.0). Overall more major and minor bleeding complications were reported in studies with high dose vs. low dose protocols. In studies with high dose protocols the pooled overall reported bleeding rates were 16.7% (95% CI 16.3–17.1) and 13.4% (95% CI 12.8–14.0) in low dose protocols. Pooled rates of major bleeding complications were 8.9% (95% CI 8.6–9.1) and 6.3% (95% CI 6.0–6.6). Pooled overall bleeding complication rates among fibrinolytics were 15.1% (95% CI 14.8–15.4) for urokinase, 19.2% (95% CI 18.7–19.6) for rtPA and 18.6% (95% CI 18.0–19.1) for tPA ([Table S1](#)).

The pooled means from RCTs and prospective cohorts (≥ 100 patients) showed comparable pooled overall, major, and minor bleeding rates, higher rates ($\pm 3\%$) for low dose, high dose, and urokinase subgroups and lower rates ($\pm 3\%$) for the rtPA subgroup ([Table S1](#)).



Mortality rates. In 91% of studies early (in hospital/30 days) mortality rates were reported (0–44%) and in 30% of studies late mortality rates up to one year of follow up were reported (0–26%). Fifty-three percent of studies with reported mortality rates also reported a bleeding related cause of death in 46% of cases. The pooled mean early mortality rate during admission was 4.8% (95% CI 4.7–4.9) and was equal in studies with low dose vs. high dose protocols: 3.5% (95% CI 3.4–3.7) vs. 4.5% (95% CI 4.3–4.6). Pooled mean early mortality rates for urokinase, rtPA, and tPA were 4.4% (95% CI 4.3–3.5), 4.5% (95% CI 4.3–4.7), and 8.6% (95% CI 8.2–9.1), respectively.

The pooled mean late mortality rate was 14.6% (95% CI 14.3–15.0) and was 10.9% (95% CI 10.6–11.3) for low dose and 13.2% (95% CI 12.9–13.5) for high dose protocols. Pooled mean late mortality rates for urokinase, rtPA, and tPA were 16.6% (95% CI 15.9–17.3), 14.9% (95% CI 14.3–15.4) and 15.2% (95% CI 14.9–15.6), respectively (Table S1).

The pooled means from RCTs and prospective cohorts (≥ 100 patients) showed comparable rates for early mortality and slightly higher rates ($\pm 3\%$) for late mortality.

Amputation rates. In 83% of studies amputation rates during admission were reported (0–28%) and in 24% of studies during follow up as well (0–32%). The pooled mean amputation rate during admission was 9.4% (95% CI 9.3–9.6) and at the one year follow up the pooled mean amputation rate was 14.8% (95% CI 14.3–15.3) (Table S1). The pooled means from RCTs and prospective cohorts (≥ 100 patients) showed comparable amputation rates during admission for overall and high and low dose subgroups. After one year follow up the pooled rate was higher overall (19.5%), and there were no or too few data for subgroup pooling. Only 10% of studies specified the level of amputation.

Treatment outcomes over the years

When stratified for time period the results remain comparable over the years (Fig. 2).

DISCUSSION

CDT for peripheral arterial occlusions is a widespread treatment modality performed and reported since the 1980s. The main advantages of thrombolytic therapy over surgical revascularisation of peripheral arterial occlusions include a lower morbidity, shorter length of hospital stay, and less patient discomfort.^{13,14} However, to date there has been little consensus on the optimal treatment protocol regarding fibrinolytic agent and dose regimen. This systematic literature review provides an extensive overview of different protocols and fibrinolytic agents with clinically relevant outcome parameters, i.e., treatment duration, patency rates, bleeding complications, mortality, and amputation rates.

In this systematic review, data on $> 10,000$ patients were gathered, showing real world outcomes of CDT for peripheral arterial occlusions. Acute peripheral arterial occlusion is a treacherous pathology with short-term mortality and amputation rates after thrombolytic therapy of 4.8% and 9.4%, respectively. Amputation rates increase over time and reach 15% at one year. Nevertheless, CDT is effective, with an angiographic success rate of 75%, with a mean treatment duration of only 21 h. This includes patients with Rutherford class IIa and IIb ischaemia. Interestingly, according to the recently published European Society of Cardiology/European Society for Vascular Surgery guideline on peripheral arterial disease, Rutherford class II ischaemia should not be treated by thrombolysis but by open surgery.¹⁵ Bleeding complications are the main problems of CDT, occurring in 18% of patients. Major bleeding complications affect 8.9% of all patients, contributing to an in hospital mortality of 4.8%.

When evaluating treatment outcomes, angiographic success and freedom from amputation, mortality, and bleeding complications are most important. Treatment duration is a secondary outcome. No patient reported outcome or experience measures were reported in the included studies.

Angiographic patency was achieved in 75% (95% CI 74.6–75.1) of all patients. Although no formal meta-

analysis was performed, the pooled results for subgroups suggest comparable results for low and high dose protocols, independent of type of fibrinolytic agent and vascular conduit type. The separately pooled results of RCTs and large prospective cohorts show $\pm 5\%$ lower angiographic patency rates, mainly based on lower success in the high dose groups. Bypass graft subgroups showed higher pooled success rates for prosthetic bypass grafts (82.3%; 95% CI 81.2–83.1) than for venous bypass grafts (61.4%; 95% CI 59.8–63.1).

With respect to amputation rates, pooled mean rates $\pm 10\%$ were reported during admission, comparable among all subgroups. Pooled results from RCTs and large prospective cohorts also show similar rates, although higher for UK (12.4%, 95% CI 12.0–12.8) and lower for rtPA (5.2%, 95% CI 4.9–5.4). At the one year follow up, the pooled mean amputation rate was $\pm 15\%$, showing a lower rate for low dose protocols (12.4%, 95% CI 11.3–13.4) than for high dose protocols (19.9%, 95% CI 19.0–20.8). However, amputation rates during follow up were only reported in 24% of studies. Only three RCTs/large prospective cohorts reported amputation rates after the one year follow up, with a pooled mean of 19.5% (95% CI 18.2–20.8). Amputation rates are an important determinant of short and long-term treatment success, as they reflect progression of disease and can have a major impact on quality of life. However, the level of amputation has to be taken into account in the interpretation of these rates as the impact on quality of life is mostly caused by social isolation and emotional distress due to loss of mobility after major amputation.¹⁶ Nevertheless, only 10% of studies specified amputation levels.

Regarding bleeding complications, the pooled results of all studies showed a worrying 18% major bleeding incidence in 8% of patients. The pooled results suggest a lower dose is accompanied by a lower incidence of bleeding complications: pooled mean rates in low dose protocols (13.4%; 95% CI 12.8–14.0) are lower than high dose protocols (16.7%; 95% CI 16.3–17.1), based on both minor and major bleeding rates. Also, protocols with urokinase (15.1%; 95% CI 14.8–15.4) showed fewer bleeding complications than rtPA (18.6%; 95% CI 18.0–19.1) or tPA (18.5%; 95% CI 17.9–19.0). However, differences between groups were small and pooled results from RCTs and large prospective cohorts showed higher bleeding rates in the majority of groups. Some fibrinolytics may increase bleeding complications in a dose dependent manner, while others might not.¹⁷ In addition, other factors significantly increase the bleeding risk independent of fibrinolytic dose such as concomitant systemic heparinisation.¹⁴ Following the results of the TOPAS trial, it is justified to refrain from systemic heparinisation and only give heparin through the arterial sheath. Of the 106 studies included in this review, only 52 reported (partial) details of the use of heparin, using varying protocols in terms of mode of administration (intravenous, over the sheath, or not specified), the use of boluses (different doses, different per fibrinolytic used, or not specified) and/or administration only in selected cases.

Regarding mortality, the pooled rates of all studies showed a mean early mortality of 4.8% and comparable rates among low dose/high dose and fibrinolytic subgroups, with the exception of a higher rate of 8.6% in the tPA subgroup. Pooled results from RCTs and large prospective cohorts showed comparable results, although subgroup results could not always be pooled owing to single study results. Late mortality results during follow up were only reported in the minority of studies (30%) at different intervals during follow up, but if pooled, late mortality was around 15% and comparable between subgroups, although the rate was lower in low dose protocols. Of all studies reporting mortality rates, only 53% reported causes of death. This is an important determinant in interpreting mortality rates after CDT in order to assess its impact and relatedness to a potential fatal outcome, as the patient population undergoing thrombolysis already has multiple comorbidities and a limited life expectancy due to cardiovascular risk.¹⁷

With regard to duration of treatment, the pooled mean treatment durations of all reported studies (70%) demonstrated a trend of shorter treatment duration when high doses of fibrinolytics were administered (defined as $\geq 75,000$ IU urokinase, ≥ 0.8 mg rtPA or ≥ 1.0 U rtPA) or rtPA was used as the fibrinolytic of choice.

The clinical relevance of a shorter thrombolytic treatment duration depends on the effect size of the difference and the concomitance of bleeding complications, as a more aggressive fibrinolytic regimen could implicate a higher risk of bleeding. In this perspective, faster lysis with higher doses of fibrinolytics comes at a cost of higher (overall, major, and minor) bleeding rates, as demonstrated in the bleeding complications section. In addition, the difference in the pooled mean treatment durations is relatively small (21.9 h for high dose vs. 32.7 h for low dose protocols), i.e., approximately 1.0 vs. 1.5 days of treatment. When only the pooled means of RCTs and large prospective cohorts (>100 patients) are considered, these mean treatment durations are even shorter; 13.6 h for high dose vs. 17.3 h for low dose protocols. However, this could be partially explained by predefined treatment duration limits as part of short interventional protocols in some of these studies.^{8,9,18–21}

tPA/rtPA as the fibrinolytic of choice for a shorter treatment duration compared with urokinase has been reported previously,^{7,22} and could be attributed to a higher fibrin specificity and affinity, resulting in more significant thrombolytic activity.²² However, there is a lack of large prospective comparative studies evaluating therapy duration as an outcome variable rather than as a predefined parameter as part of the treatment protocol as, for example, is the case in the STILE trial.¹³

In the past four decades, the results of CDT have not changed greatly (Fig. 2). Improvement in catheter techniques and handling have not led to higher patency rates or lower amputation rates. Selection bias may be a possible explanation. Improvements in technique could be compensated for by the inclusion of patients with more complex lesions, more profound ischaemia, and/or longer

duration of symptoms. The current data are insufficient to confirm this suspicion. Nevertheless, it is worrying that the incidence of bleeding complications has not been lowered and that efficacy has not increased over the years.

There was high clinical heterogeneity among all studies: indications for treatment of pre-existent chronic vascular disease were reported in only 22% of studies. When reported, the presence of ulcerative wounds or necrosis at presentation could have overestimated amputation rates as an amputation would be necessary anyway. Furthermore, acute Rutherford classification at presentation was only reported in 29% of studies. Although the current consensus is that CDT is only indicated in patients with viable limb ischaemia (i.e., Rutherford grade I or IIa), a lot of patients with Rutherford IIb ischaemia were included and treated by CDT in some studies. The inclusion of patients with non-viable ischaemia could underestimate success and amputation rates.²³ As there are no data from RCTs comparing these two groups of patients directly, conclusions should be drawn carefully. However, as there is a lack of reporting on these data, large prospective series with stratification of these groups is advised.

In addition, the duration of symptoms is likely to influence the efficacy of thrombolysis: the STILE trial demonstrated that patients with acute ischaemia (0–14 days) who were treated with thrombolysis had improved amputation free survival and shorter hospital stays, and that for patients with chronic ischaemia (>14 days), surgical revascularisation was more effective and safer than thrombolysis.¹³ Although the duration of symptoms was reported in 70% of studies in this review, many studies included subpopulations (e.g., <14 days of symptoms) or reported large ranges of duration of symptoms but without stratifying results for ischaemia time.

Many studies also included patients with post-intervention occlusions/emboli that were treated by CDT. As the nature of disease in these cases is different and CDT as initial treatment for emboli is controversial, these results should be analysed separately. The present authors tried to exclude these as far as possible.

The majority of studies reported the inclusion of bypass grafts, as well as native arteries, but did not specify the conduit type and did not stratify treatment results for these subgroups. This should be done as the efficacy of CDT for bypass grafts seems to differ between conduit types (Table S1).

Clinical heterogeneity between studies was also large due to several factors influencing treatment results (i.e., efficacy and treatment duration). For example, level of care was only reported in 37% of studies. Treatment duration could be highly influenced by local logistics and intervals between check angiograms, which could potentially be quicker in patients treated in a higher level of care ward. Furthermore, hospital type could also influence this and varied between studies (49% university medical hospitals, 51% general/private hospitals).

Heterogeneity in reporting of outcomes is also high in large prospective cohorts and RCTs: often only major

bleeding complications are stated without mention of minor bleeding, introducing attrition bias and underestimating the total rate of bleeding complications. In addition, only the total incidence of bleeding complications was mentioned and severity was not specified. This is highly relevant as minor local bleeding at the catheter insertion site is common with CDT and can be treated conservatively, whereas distant bleeding can be a detrimental complication. Also, consecutive interventions following bleeding are seldom reported.

Finally, widely varying definitions introduce heterogeneity between studies: treatment success is defined differently in many studies complicating comparability. Several definitions of treatment success are complete dissolution, > 95% or >50% thrombus dissolution, recanalisation with or without outflow, combined definitions like positive thrombolytic outcome, including angiographic success, relief of clinical symptoms and 30 day patency, angiographic success with and without adjunctive percutaneous treatments, and Thrombolysis in Myocardial Infarction score.

Adjunctive techniques and devices

CDT with adjunctive mechanical thrombectomy and ultrasound assisted thrombolysis have the theoretical potential to reduce treatment duration and/or thrombolytic agent dosage, thereby potentially reducing bleeding complications. Unfortunately, experience is limited to a small number of (mostly retrospective cohort) studies using different fibrinolytics, dose regimens, and techniques with varying results.^{24–27} Techniques and devices as sole treatment modality (without the use of thrombolysis) were not included in this review.

Significance of results for practice

This systematic review yielded a wide variety of literature on CDT for peripheral arterial occlusion, mainly consisting of cohort studies published in the 1990s. There is high clinical heterogeneity in the reported studies and a lack of comparative data from large prospective cohorts and RCTs that prevents formal meta-analysis. However, the pooled results suggest faster thrombolysis with higher doses of fibrinolytics and with rtPA protocols than with urokinase but potentially at the cost of higher bleeding rates. Furthermore, outcomes (i.e., angiographic patency, mortality, and amputation rates during admission) were comparable between low and high dose protocols and type of fibrinolytic agent (urokinase, tPA, rtPA). Nevertheless, there is lack of follow up data regarding long-term outcomes.

Study strength and limitations

This is the first systematic review of the literature to date to report a complete data series of RCTs, as well as observational cohorts about CDT for peripheral arterial occlusions over the years. Previous reports on this topic included only a limited number of RCTs with mainly small patient numbers and a general paucity of results focused on infusion techniques,² or included outdated techniques (intravenous

administration) and fibrinolytics (streptokinase), not relevant to current daily practice.¹

Owing to the lack of control groups and the heterogeneous inclusion criteria of patients and definition of outcomes in the studies, it was not appropriate to perform formal meta-analysis. However, in addition to the summarised results of individual studies, the pooled weighted mean results for reported patient outcomes are presented for all studies, as well as for RCTs and prospective cohorts of >100 cases, separately. Nevertheless, these results should be interpreted with caution owing to their high heterogeneity.

The results of this review suggest further research on CDT is required, with a focus on lowering bleeding complications, increasing efficacy, and adjunctive techniques/devices in a large prospective or even randomised controlled setting.

CONCLUSIONS

CDT is an effective treatment for peripheral arterial occlusion with an angiographic patency rate of 75% and freedom from amputation rate of 91%. The main concern is bleeding complications, which occur in 18% of patients. Although no formal meta-analysis could be performed, the pooled results suggest lower doses of fibrinolytics lead to similar success rates at the cost of longer treatment duration but with fewer bleeding complications. There is a large variety in treatment protocols and the available literature suffers from the absence of reporting standards and from high heterogeneity; therefore, there is a need for prospective data from large series.

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CONFLICT OF INTEREST

None.

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None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2018.11.018>.

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COUP D'OEIL

Huge Iatrogenic Pseudoaneurysm of the Profunda Femoris Artery

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An 83 year old female sustained a left femoral intertrochanteric fracture and underwent internal fixation with a dynamic hip screw plate two years previously. A pulsatile mass developed gradually in the left thigh. Pain, pallor, and poikilothermia in the distal left lower limb were noted. Computed tomography angiography demonstrated a 15 × 8 cm pseudoaneurysm of the profunda femoris artery (panel A) with compression of the left superficial femoral artery. The pseudoaneurysm was excised and the section of the first perforating artery, penetrated by the cortical screws (green arrows, panel B), was closed primarily. The patient was discharged with no complications.

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