Journal Pre-proof

Catheter directed thrombolysis for Not Immediately Threatened Acute Limb Ischaemia: a Systematic Review and Meta-Analysis

Sabrina A.N. Doelare, Thomas W.A. Koedam, Harm P. Ebben, Erik Tournoij, Arjan W.J. Hoksbergen, Kak K. Yeung, Vincent Jongkind, Collaborators

PII: S1078-5884(22)00872-3

DOI: https://doi.org/10.1016/j.ejvs.2022.12.030

Reference: YEJVS 8625

To appear in: *European Journal of Vascular & Endovascular Surgery*

Received Date: 11 April 2022

Revised Date: 29 November 2022

Accepted Date: 23 December 2022

Please cite this article as: Doelare SAN, Koedam TWA, Ebben HP, Tournoij E, Hoksbergen AWJ, Yeung KK, Jongkind V, Collaborators, Catheter directed thrombolysis for Not Immediately Threatened Acute Limb Ischaemia: a Systematic Review and Meta-Analysis, *European Journal of Vascular & Endovascular Surgery*, https://doi.org/10.1016/j.ejvs.2022.12.030.

Title-Page:

Title: Catheter directed thrombolysis for Not Immediately Threatened Acute Limb Ischaemia: a Systematic Review and Meta-Analysis

Running title: CDT for Rutherford-I ALI: a Systematic Review and Meta-Analysis

Sabrina A.N. Doelare[1,2], Thomas W.A. Koedam[1,3], Harm P. Ebben[1,2], Erik Tournoij[3], Arjan W.J. Hoksbergen[1], Kak K. Yeung[1,2], Vincent Jongkind[1,2,3] & Collaborators**

** S. Acosta[4], O. Grip[5], V.S. Kashyap[6] & D. Vakhitov[7]

[1]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Surgery, Amsterdam Cardiovascular Sciences, de Boelelaan 1117, Amsterdam, The Netherlands

[2]Vrije Universiteit Amsterdam, Department of Physiology, Amsterdam Cardiovascular Sciences, De Boelelaan 1117, Amsterdam, The Netherlands

[3]Department of Surgery, Dijklander Hospital, Maelsonstraat 3, Hoorn, Netherlands

[4]Department of Clinical Sciences Malmö, Lund University, Sweden

[5]Department of Surgical Sciences, Section of Vascular Surgery, Uppsala University, Uppsala, Sweden

[6]Division of Vascular Surgery and Endovascular Therapy, University Hospitals Cleveland Medical Center, OH

[7]Center for Vascular Surgery and Interventional Radiology, Tampere University Hospital, Tampere, Finland

Correspondence:

Sabrina Doelare (s.doelare@amsterdamumc.nl) P.O. Box 7057, Boelelaan 1117, 1007 MB, Amsterdam

Words abstract: 286, Words What this paper adds (WTPA) paragraph: 82, Words text body: 3172 (excluding WTPA, abstract, references and figure legends)

Number of tables: 3, number of figures: 3, number of supplementary tables: 1, number of supplementary figures: 3, number of supplementary appendices: 1

What this paper adds

In this systematic review, the short- and long-term outcomes of catheter-directed thrombolysis (CDT) for not immediately threatened acute lower limb ischaemia (ALI) were gathered. These findings can provide a benchmark for future research efforts and can be used by both patients and physicians involved in the decision-making process concerning thrombolytic therapy for Rutherford-I patients. A meta-analysis was also conducted, demonstrating high angiographic success of CDT in the treatment of not immediately threatened ALI, but also risk of mortality and poor long-term outcomes.

Abstract

Objectives

This systematic review and meta-analysis reports the outcomes of Catheter-directed thrombolysis (CDT) for patients with not immediately threatened (Rutherford-I) acute lower limb ischaemia (ALI).

Methods

A systematic search of PubMed, Embase and Cochrane was performed to identify observational studies and trials published between 1990 and 2022 reporting on the results of CDT in patients with Rutherford-I ALI. A meta-analysis was performed using a random effects model with 95% confidence intervals (CI). The outcomes of interests were treatment duration, angiographic success, bleeding complications, amputation- and mortality rates, primary- and secondary patency and functional outcome expressed as pain-free walking distance.

Results

Thirty-nine studies were included, comprising 1861 patients who received CDT for not immediately threatened ALI. Funnel plots showed indication for publication bias and heterogeneity was substantial. Data from 5-13 studies were included in the meta-analysis. Pooled treatment duration was 2 days (95% CI 1–2), with angiographic success of 80% (95% CI 73–86%) and 30-day freedom of amputation in 98% of patients (95% CI 92–100%). Major bleeding rate was 5% (95% CI 2–14%) with a 30-day mortality rate of 3% (95% CI 1–5%). Amputation-free survival rate was 71% (95% CI 62–80%) at 1-year and 63% (95% CI 51–73%) at 3-years follow-up. Long-term patency rates could be retrieved from 4 studies: 48% at 1 year (95% CI: 27–70%). No data could be retrieved on walking distance of the patients.

Conclusions

Although CDT in the treatment of not immediately threatened ALI showed high angiographic success, the long-term outcomes are relatively poor with low patency and substantial risk of major amputation. Further research is required to interpret the outcome of CDT in the context of potential confounders such as age and comorbidities.

Keywords

Catheter-directed thrombolysis, CDT, not immediately threatened acute limb ischaemia, Rutherford class I, peripheral arterial occlusions, systematic review

Introduction

Acute limb ischaemia (ALI) is a sudden decrease in arterial perfusion to the limb, potentially threatening its survival, especially when sensory loss or motor deficit occurs (1). In line with the Rutherford classification, there is no immediate threat to the viable limb if no sensory loss or motor deficit is present. However, an acute onset claudication and severe impairment of walking distance may occur.

Catheter-directed thrombolysis (CDT) is the first-choice treatment in many centres for patients with marginally threatened ALI (sensory loss present, Rutherford-IIA), and CDT is also performed in patients with serious disabling symptoms of not immediately threatened limb ischaemia (Rutherford-I) (2, 3). For patients with acute onset claudication (Rutherford I) that does not threaten the limb, (percutaneous) CDT is not recommended in the recently published ESVS guidelines (4). CDT for ALI has evolved in multiple directions over the years, making the data whereupon this recommendation is based limited and potentially outdated (5, 6). We therefore performed a systematic literature review to investigate short- and long-term outcomes of CDT for patients with not immediately threatened limb ischaemia.

Methods

Study eligibility

A systematic review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in the PROSPERO database (registration number CRD42021240939) (7). The Patient, Intervention, Comparison, Outcome (PICO) framework (8) was used to determine the following research question: "What is the effect of CDT using various fibrinolytic agents and devices on outcomes of interest in patients not immediately threatened limb ischaemia due to lower limb native arterial, previous bypass graft occlusions and stent occlusions?". We defined not immediately threatened limb ischaemia as Rutherford grade I ALI: a sudden decrease in arterial perfusion leading to pain during walking without sensory or motor deficit. The outcomes of interests as suggested by registry reporting standards (9) were treatment duration; angiographic success, defined as dissolution of the thrombus with restoration of antegrade blood flow (as used in the studies included in meta-analysis); bleeding complications, major bleeding was defined as Bleeding Academic Research Consortium (BARC) bleeding type III/IV; amputation rates, major amputations were defined as amputations above the tarsometatarsal joint; all-cause mortality rates, primary- and secondary patency and functional outcome expressed as pain-free walking distance. Subgroup analyses of outcomes are performed for low- and high-dose thrombolysis protocols and type of fibrinolytic agent used for thrombolysis. According to the systematic review of Ebben et al. (3), a high-dose protocol was defined as ≥75,000 IU/h UK, ≥0.8 mg/hr (r)t-PA or ≥1.0 U/h rtPA and a low-dose protocol was defined as <75,000 IU/h UK, <0.8 mg/hr (r)t-PA or <1.0 U/h rtPA.

Studies reporting results of CDT using different fibrinolytic agents and devices (ultrasound-assisted CDT and other device assisted CDT) in patients with not immediately threatened

limb ischaemia due to lower limb native arterial, previous bypass graft and stent occlusions were considered for inclusion. Excluded were reports on traumatic or iatrogenic caused thrombosis, venous thrombosis, upper limb occlusions, occlusion of arteriovenous fistula and patients treated with systemic thrombolysis and thrombolysis with streptokinase. Furthermore, studies describing paediatric populations, cohorts ≤15 patients, narrative reviews and technical descriptions were excluded as well. Authors of publications in which data were not specified for not immediately threatened limb ischaemia were contacted to retrieve further information with data specifically for these patients and on treatment protocol if not yet reported.

Search strategy

Pubmed, Embase and Cochrane databases were searched using a combination of 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), which were limited to data published since 1 January 1998. The full electronic search strategy used can be found in Supplementary Appendix 1. Reference lists of included studies were searched to identify more studies. The search was restricted to the Dutch and English languages. The search was repeated on 6 December 2021 to include recently published articles.

Data collection and analysis

Titles and abstracts of studies were independently screened by two reviewers (S.D., T.K.). Full text versions of the selected studies that met the eligibility criteria were obtained. Data of the included studies were assessed and extracted (S.D., T.K.) using a predefined standardised data extraction form. Extracted information included study characteristics, patients and

indications, treatment characteristics, outcomes with definitions and times of measurement, information for risk of bias assessment and specification of missing data. The extracted data of all outcomes of interest were checked independently by a senior author (V.J.) for accuracy. Disagreements between reviewers were solved by discussion and subsequent consensus.

Risk of bias

Quality scoring was assessed using the Newcastle-Ottawa scoring system for observational studies, which is a quality assessment tool that awards stars based on 3 categories: "Selection", "Exposure/Outcome", and "Comparability". A score with a range of 0-9 was allocated to each study. Studies with a quality score ≤5 were categorized as low-quality studies, 6-7 were categorized as moderate-quality studies and those with a score of ≥8 were considered to be high-quality studies. Each study was analysed by two reviewers (S.D., T.K.), establishing for each item the value "0" (if the item was not contemplated) or "1" (if the item was contemplated); a maximum score of 2 could be given for the category "Comparability". The quality of reporting was independently assessed, and disagreements were resolved by consensus or consultation with a senior author (V.J.).

Statistical analysis

If data was not specifically reported for the Rutherford-I group, data could be reproduced by reported means and standard deviation of normal distributed studies (10). Data were pooled with a random effects model to calculate the pooled risk and 95% confidence interval (CI) using The R Project for Statistical Computing (R Foundation for Statistical Computing version 3.6.1, Vienna, Austria). The amount of statistical heterogeneity between studies was assessed by the Cochrane's Q (x^2) test and inconsistency was quantified by calculating I^2.

Publication bias was evaluated by funnel plots along with the Egger linear regression test and Begg and Mazumdar rank correlation test if ≥10 studies were pooled in one analysis.

Results

Study selection

The search retrieved 1,819 potentially relevant articles, of which 1,814 eligible articles remained for title and abstract screening after removing duplicates. 174 articles were selected for full text evaluation, of which 39 articles fulfilled the inclusion criteria and were included (Figure 1). Outcome data from 6 studies could be directly incorporated into the meta-analysis (11-16). To enquire about missing data, the corresponding authors of the included studies were contacted. Additional data on the outcomes in Rutherford-I patients could be retrieved from 8 articles (17-24). Eventually, 14 articles were included in this meta-analysis.

Study characteristics

The included studies reported on a total of 5,529 patients who received CDT for ALI, of whom 1,861 (34%) presented with not immediately threatened limb ischaemia (Rutherford-I). The severity of ischaemia at presentation was categorized according to the acute Rutherford classification in 20 studies. The proportion of Rutherford-I patients could be determined in the remaining studies based on the provided clinical features at baseline. Eight Randomized Controlled Trials and 31 observational (4 prospective- and 27 retrospective) cohort studies were selected for inclusion in the current review and were published between 1998 and 2021. In 19 studies rtPA was the thrombolytic agent of choice, UK in 14 studies, tPA in 2 studies, whereas rtPA/UK, Pro-urokinase/UK, Alfimeprase and Plasmin were used in the remaining 4 studies. Dosing protocols were variable, a high-dose protocol was used in 49% of studies, a low-dose protocol in 23%, in 13% both a low- and high-dose protocol were used and in the remaining articles the protocol was not mentioned.

Risk of bias assessment

The Newcastle-Ottawa Scale for assessing the quality of the nonrandomized studies is presented in Supplementary Table S1. The minimum and maximum scores were, respectively, 4 and 8. High scores (≥8) were recorded in 2 studies only.

Assessment of publication bias

Publication bias was investigated for angiographic success, short-term amputation and all-cause mortality, as these were the outcomes that were reported by 10 or more studies. The funnel plot on short-term morality was visually asymmetrical, suggesting publication bias, and could be statistically confirmed by the Egger linear regression test (p=.023) and the Begg and Mazumdar rank correlation test (p=.040) (Supplementary Figure S1). The funnel plots on short-term amputation and angiographic success were suggestive of publication bias as they appeared asymmetrical (Supplementary Figures S2 and S3).

Synthesis of results and outcome

Results for meta-analysis of the studies included are shown in Table 1. Different thrombolytic agents and protocols were used in the included articles. Heterogeneity was high for all outcomes except for short-term mortality. Of the included studies, 4 studies reported on the long-term outcomes. None of the studies reported on pain-free walking distance during follow-up. Outcomes for different protocols could be retrieved from limited number of studies and are presented in Table 3.

Angiographic success rates. Eleven studies comprising 708 patients reported on the angiographic success which ranged between 64% and 90%. The pooled success rate after treatment with thrombolysis in Rutherford-I patients was 80% (95% CI 73 – 86%). In the studies using UK as the thrombolytic agent of choice angiographic success rates were 74%

(95% CI 64 – 82%) whereas for rtPA this was 83% (95% CI 75 – 89%). The use of additional interventions following CDT in Rutherford-I patients was reported in five studies (17, 18, 21, 23, 24).

Treatment duration. Seven studies reported the total treatment duration; 5 studies (12, 18, 20, 21, 24) had a treatment duration of 24-48 hours and 2 studies (17, 19) had a duration of >48 hours. The overall pooled treatment thrombolysis duration of Rutherford-I patients was 2 days (95% CI 1 – 2); 1 day (95% CI 1 – 1) for high-dose protocols and 3 days (95% CI 1 – 4) for studies with low-dose protocols.

Bleeding complications. Data on bleeding complications were reported in 6 studies, which included 508 patients, with an overall reported bleeding complication rate of 15% (95% CI 9 – 25%). Minor bleedings occurred in 11% (95% CI 6 – 19%) and major bleeding complications in 5% of patients (95% CI 2 – 14%) (Table 1). In view of the considerable study heterogeneity, the major bleeding incidence of 49% reported by Swischuk et al. (25) was a clear outlier. Removal of this study from the meta-analysis showed results similar to the overall pooled analysis, but with a moderate degree of heterogeneity (4%, 95% CI 2 – 8%, I^2 = 52%, p = .042). Overall bleeding complications were 7% (95% CI 2 – 21%) in studies using low-dose protocols and 22% (95% CI 17 – 27%) in studies using high-dose protocols with overlapping confidence intervals.

All-cause mortality rates. Ten studies reported short-term (in-hospital/30 days) mortality data and 6 studies reported on the mortality rate after one year or more of follow-up. The pooled mean short-term mortality rate was 3% (95% CI 1 – 5%) (Figure 2), 12% (95% CI 8 – 18%) at 1 year and 22% (95% CI 12 – 37%) at 3 years (Table 1). Pooled short-term mortality

rates were comparable for overall and low- (3%, 95% CI 1 – 10%) and high (3%, 95% CI 1 – 7%) dose subgroups.

Amputation rates. Thirteen studies reported on short-term amputation rates, which was 2% (95% CI 0 – 8%) (Figure 3). The level of amputation was specified in 7 studies. The pooled amputation rate at 1 year follow-up, as reported in 6 studies was 21% (95% CI 16 – 27%). The analysis of 4 studies on the three-year outcome of CDT in Rutherford-I patients demonstrated a probability of amputation of 24% (95% CI 16 – 34%).

Amputation-free survival (AFS) rates. Six studies, comprising 558 patients, reported on the short-term AFS which was 84% (95% CI 80 – 88%) and showed comparable rates for all subgroups (Table 1). The pooled AFS at 1 year follow-up was 71% (95% CI 62 – 80%) and 63% (95% CI 51 – 73%) at 3-years.

Patency. Long-term patency could be retrieved from 4 studies (12, 20, 21, 24), in all rtPA was used (Table 2). Pooled primary patency rates at 1-year were 48% (95% CI 27 – 70%) and 14% (95% CI 5 – 33%) at 5-years. Secondary patency rates were 56% (95% CI 37 – 74%) at 1-year and 31% (95% CI 11 – 63%) at 3-years. Two studies reported on secondary patency at 5-years of follow-up: 35% (95% CI 24 – 48%).

Discussion

To our knowledge, this study represents the first systematic report of CDT for acute peripheral arterial occlusions in patients with not immediately threatened ALI. This meta-analysis demonstrated that CDT can be performed in Rutherford-I patients with high angiographic success (80%). However, after one year, all-cause mortality and amputation rates paint a sobering picture for these patients (3). Notably, the present long-term outcomes were primarily based on the results of 4 retrospective studies (17, 18, 20, 22), which included patients presenting with significant comorbidities and a history of peripheral vascular disease. Although not separately evaluated in this review given the limited reporting, it is well known that these risk factors have a great influence on the course of the affected limb and survival (26-29). The magnitude of the long-term risks after CDT cannot be determined in this study due to a lack of data on causes of death and functional outcomes.

Some criticism against a standard policy of initial thrombolysis for all patients with not immediately threatened limb ischaemia has already been voiced elsewhere (5, 6). Many of those authors also advocated conservative treatment i.e., prescription of anticoagulation agents. An interesting, although small case series of eight patients with not immediately threatened limb ischaemia, showed a successful outcome of initial anticoagulation treatment and were all discharged home without the need for surgery angioplasty (30). During the 18 months of follow-up, debilitating claudication required surgical intervention in only 2 patients. Despite the small number of patients in this series, the data suggest that conservative treatment may be an option in the treatment of not immediately threatened limb ALI. In a recent population-based study on 161 citizens from Malmö, Sweden, with ALI, 15 patients with Rutherford-I ALI were treated conservatively with anticoagulation alone, resulting in an AFS at 1 year of 80% (31). Newly designed percutaneous thrombectomy and aspiration

devices have been put forward as an effective treatment alternative for ALI patients due to rapid vessel recanalization and decreased bleeding risk. In many patients additional thrombolysis is not even needed. Future, preferably comparative studies need to assess the benefits of these techniques over other treatment strategies. The results of this meta-analysis call for improving outcome of ALI on longer-term. Potential improvements can be made in patient selection, proper management of cardiovascular risk factors, directed follow-up protocols with frequent imaging, optimal anticoagulation and most probably a combination of all of these.

In this meta-analysis we looked at the different protocols used. As no comparative studies were performed, direct comparison between high- or low-dose and UK or rtPA was not possible. Even though mortality and amputation rates in the short-term were low in all subgroups, pooled treatment duration and incidence of bleeding complications differed between groups resulting in wide and overlapping confidence intervals. Due to this and the large variety in treatment protocols, no definite conclusions can be drawn. The importance of different treatment protocols is further demonstrated by Swischuk et al. In their study, the first 10 patients were treated with a high infusion rate e.g., 3-6 mg/h, which was then lowered to 1.5 mg/h due to a perceived increase in bleeding complications. This very high dose protocol and the small sample size may have contributed to the increased major bleeding incidence (25). Ideally, large studies comparing treatment protocols are performed to investigate optimal dosage of thrombolytic drugs and anticoagulants.

The review is strengthened by a recently performed literature search identifying studies conducted in different geographical regions in high-income countries, making the results broadly representative. Most studies presented the results of the outcomes for the entire

population but were unfortunately not subdivided for Rutherford staging. Extensive attempts were made to contact the authors for detailed data, which could, ultimately, be retrieved from 8 articles (17-24). Unfortunately, funnel plot analysis showed signs of publication bias.

There are some limitations to this systematic review that need to be addressed. The results of CDT in Rutherford-I patients have been primarily evaluated in observational studies with relatively small cohorts. All articles that were not in the English or Dutch language were excluded from this meta-analysis. None of the studies accounted for competing risks to mortality (as major bleeding may increase risk of amputation and both may increase risk of mortality), which could have affected long-term amputation and patency rates. Different patient level covariables such as bypass conduits and aetiology of the occlusion, may have had some impact on effect estimates; however, the available data did not allow to perform a subgroup analyses. Another limitation is the moderate to high statistical heterogeneity across the studies in the meta-analysis, and therefore, these results should be interpreted with caution. Importantly, none of the included studies had the primary aim to report the results of CDT for Rutherford grade I ALI. Therefore, we lack functional outcome which is especially important in this patient group. Furthermore, classification of patients may be difficult as the symptoms of ALI are subject to change over time and the distinction between Rutherford grade I and Rutherford grade IIA can be difficult in clinical practice. Nevertheless, the results of this systematic review provide valuable insights into the treatment results of CDT for not immediately threatened ALI.

While the traditional outcomes of different revascularization modalities have been widely reported, data concerning the impact of such care on the functional status is roughly non-existent, yet, we think functional outcomes are essential in defining the optimal treatment

approach for the ALI population (4). Both publication bias and selection bias are expected. Conservatively treated patients could very well be less symptomatic, potentially improving their outcome, with CDT reserved for very symptomatic patients who are included in this systematic review. Hence, comparative studies for this patient group are required to accurately assess the beneficial effects (i.e., relief of symptoms and functional status) of conservative management and CDT in patients with not immediately threatened ischaemia. Furthermore, it is important to better identify risk factors for long-term adverse events and find strategies to improve long-term outcome. Until then, the findings of this study can provide a benchmark for future research efforts and can be used by both patients and physicians involved in the decision-making process concerning thrombolytic therapy for Rutherford-I patients. The recommendation from the recent ESVS guidelines against thrombolysis in Rutherford-I ALI is strengthened by the results from the current meta-analysis (4).

In conclusion, this meta-analysis shows high angiographic success of catheter-directed thrombolysis in the treatment of not immediately threatened limb ischaemia, but also risk of mortality and poor long-term outcomes. Further investigations are necessary to ultimately determine whether CDT should be used to revascularize not immediately threatened limb ischaemia.

Acknowledgements

We would like to thank statistician S. van Dieren for the statistical support.

References

1. Darwood R, Berridge DC, Kessel DO, Robertson I, Forster R. Surgery versus thrombolysis for initial management of acute limb ischaemia. Cochrane Database Syst Rev. 2018;8:CD002784.
2. Thrombolysis in the management of lower limb peripheral arterial occlusion--a consensus document. Working Party on Thrombolysis in the Management of Limb Ischemia. Am J Cardiol. 1998;81:207-18.
3. Ebben HP, Jongkind V, Wisselink W, Hoksbergen AWJ, Yeung KK. Catheter Directed Thrombolysis Protocols for Peripheral Arterial Occlusions: a Systematic Review. Eur J Vasc Endovasc Surg. 2019;57:667-75.
4. Björck M, Earnshaw JJ, Acosta S, Bastos Gonçalves F, Cochennec F, Debus ES, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. Eur J Vasc Endovasc Surg. 2020;59:173-218.
5. Braithwaite BD, Tomlinson MA, Walker SR, Davies B, Buckenham TM, Earnshaw JJ. Peripheral thrombolysis for acute-onset claudication. Thrombolysis Study Group. Br J Surg. 1999;86:800-4.
6. Korn P, Khilnani NM, Fellers JC, Lee TY, Winchester PA, Bush HL, et al. Thrombolysis for native arterial occlusions of the lower extremities: clinical outcome and cost. J Vasc Surg. 2001;33:1148-57.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906.
8. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16.
9. Behrendt CA, Björck M, Schwaneberg T, Debus ES, Cronenwett J, Sigvant B. Editor's Choice - Recommendations for Registry Data Collection for Revascularisations of Acute Limb Ischaemia: A Delphi Consensus from the International Consortium of Vascular Registries. Eur J Vasc Endovasc Surg. 2019;57:816-21.
10. Wessa P. Free Statistics Software, Office for Research Development and Education, version 1.2.1 2022, Available from: https://www.wessa.net/.
11. Castañeda F, Swischuk JL, Li R, Young K, Smouse B, Brady T. Declining-dose study of reteplase treatment for lower extremity arterial occlusions. J Vasc Interv Radiol. 2002;13:1093-8.
12. Disini L, Wilson P, Cockburn JF. Successful intra-arterial alteplase infusion is a predictor of 12-month limb survival in patients with lower limb arterial occlusion. Clin Radiol. 2008;63:636-41.
13. Hundt W, Kalinowski M, Stamm AC, Portig I, Swaid Z, Dietz C, et al. Combined treatment of subacute and acute synthetic and venous bypass-graft occlusions with percutaneous mechanical thrombectomy and thrombolysis. Eur J Radiol. 2013;82:e807-15.
14. Kröger K, Buss C, Rudofsky G. Retrospective analysis of Rt-pa thrombolysis combined with PGE1 in patients with peripheral arterial occlusions. Angiology. 2000;51:377-84.
15. Taha AG, Byrne RM, Avgerinos ED, Marone LK, Makaroun MS, Chaer RA. Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia. J Vasc Surg. 2015;61:147-54.

16. Yuan B, Li T, Zhang Y, Zhang W, Ren T, Yang B. Effects of delivering recombinant tissue plasminogen activator on a new infusion system during endovascular intervention in patients with lower limb ischemia. Thorac Cardiovasc Surg. 2013;61:445-52.
17. Ebben HP, Nederhoed JH, Lely RJ, Meijerink MR, van der Meijs BB, Wisselink W, et al. Low-dose thrombolysis for thromboembolic lower extremity arterial occlusions is effective without major hemorrhagic complications. Eur J Vasc Endovasc Surg. 2014;48:551-8.
18. Ebben HP, van Burink MV, Jongkind V, Mouwen DE, Udding J, Wisselink W, et al. Efficacy versus Complications in Arterial Thrombolysis. Ann Vasc Surg. 2018;48:111-8.
19. Ebben HP, Yang HT, Hoksbergen AWJ, Wisselink W, Ko PJ, Yeung KK. Catheter-Directed Thrombolysis for Acute Limb Ischemia in an Asian Population. Ann Vasc Surg. 2019;55:246-50.
20. 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.
21. Kashyap VS, Gilani R, Bena JF, Bannazadeh M, Sarac TP. Endovascular therapy for acute limb ischemia. J Vasc Surg. 2011;53:340-6.
22. Kuoppala M, Åkeson J, Svensson P, Lindblad B, Franzen S, Acosta S. Risk factors for haemorrhage during local intra-arterial thrombolysis for lower limb ischaemia. J Thromb Thrombolysis. 2011;31:226-32.
23. Vakhitov D, Suominen V, Korhonen J, Oksala N, Salenius J-P. Independent Factors Predicting Early Lower Limb Intra-arterial Thrombolysis Failure. Ann Vasc Surg. 2014;28:164-9.
24. Vakhitov D, Oksala N, Saarinen E, Vakhitov K, Salenius JP, Suominen V. Survival of Patients and Treatment-Related Outcome After Intra-Arterial Thrombolysis for Acute Lower Limb Ischemia. Ann Vasc Surg. 2019;55:251-9.
25. Swischuk JL, Fox PF, Young K, Hussain S, Smouse B, Castañeda F, et al. Transcatheter intraarterial infusion of rt-PA for acute lower limb ischemia: results and complications. J Vasc Interv Radiol. 2001;12:423-30.
26. Grip O, Wanhainen A, Acosta S, Björck M. Long-term Outcome after Thrombolysis for Acute Lower Limb Ischaemia. Eur J Vasc Endovasc Surg. 2017;53:853-61.
27. Kuoppala M, Franzén S, Lindblad B, Acosta S. Long-term prognostic factors after thrombolysis for lower limb ischemia. J Vasc Surg. 2008;47:1243-50.
28. Stewart D, Kong M, Novokhatny V, Jesmok G, Marder VJ. Distinct dose-dependent effects of plasmin and TPA on coagulation and hemorrhage. Blood. 2003;101:3002-7.
29. Hess CN, Wang TY, Weleski Fu J, Gundrum J, Allen LaPointe NM, Rogers RK, et al. Long-Term Outcomes and Associations With Major Adverse Limb Events After Peripheral Artery Revascularization. J Am Coll Cardiol. 2020;75:498-508.
30. Mokete MM, Earnshaw JJ. Management of acute-onset claudication. Cardiovasc Surg. 2001;9:209-10.
31. Kulezic A, Acosta S. Epidemiology and Prognostic Factors in Acute Lower Limb Ischaemia: A Population Based Study. Eur J Vasc Endovasc Surg. 2022;63:296-303.

Tables

Table 1. Outcomes of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI) in all patients

Outcome	N patients (studies)	Pooled data, random effects model (95% CI)	Heterogeneity
Angiographic success	708 (11)	80% (73-86%)	I^2=71%, p<.001
Treatment duration (in days)	565 (7)	2 (1-2)	I^2=98%, p<.001
Bleeding complications	508 (6)	15% (9-25%)	I^2=80%, p<.001
Minor bleedings	451 (5)	11% (6-19%)	I^2=74%, p=.004
Major bleedings	585 (9)	5% (2-14%)	I^2=87%, p<.001
Short-term amputation	949 (13)	2% (0-8%)	I^2=20%, p=.24
Short-term mortality	838 (10)	3% (1-5%)	I^2=0%, p=.88
Short-term amputation-free survival	558 (6)	84% (80-88%)	I^2=44%, p=.11
Amputation rates at 1 year	484 (6)	21% (16-27%)	I^2=51%, p=.069
Amputation rates at 3 years	425 (4)	24% (16-34%)	I^2=77%, p=.005
Mortality at 1 year	484 (6)	12% (8-18%)	I^2=59%, p=.032
Mortality at 3 years	425 (4)	22% (12-37%)	I^2=89%, p<.001
Amputation-free survival at 1 year	558 (6)	71% (62-80%)	I^2=77%, p<.001
Amputation-free survival at 3 years	425 (4)	63% (51-73%)	I^2=79%, p=.003

CI = confidence interval

Table 2. Pooled results for reported long-term patency of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Outcome	N patients (studies)	Pooled data, random effects model (95% CI)	Heterogeneity
Primary patency at 1 year	297 (4)	48% (27-70%)	I^2=93%, p<.001
Primary patency at 3 years	258 (3)	18% (5-51%)	I^2=94%, p<.001
Primary patency at 5 years	258 (3)	14% (5-33%)	I^2=87%, p<.001
Secondary patency at 1 year	258 (3)	56% (37-74%)	I^2=89%, p<.001
Secondary patency at 3 years	255 (3)	31% (11-63%)	I^2=95%, p<.001
Secondary patency at 5 years	170 (2)	35% (24-48%)	I^2=61%, p=.11

CI = confidence interval

568 Table 3. Outcomes of CDT for not immediately threatened acute limb ischaemia (Rutherford-
569 I ALI) in patients treated by different protocols

Outcome	N patients (studies)	Pooled data, random effects model (95% CI)	Heterogeneity
Angiographic success			
low-dose protocol	261 (5)	82% (69-91%)	I^2=72%, p=.007
high-dose protocol	344 (5)	77% (64-87%)	I^2=81%, p<.001
rtPA	353 (6)	83% (75-89%)	I^2=60%, p=.030
urokinase	355 (5)	74% (64-82%)	I^2=60%, p=.040
Treatment duration (in days)			
low-dose protocol	206 (3)	3 (1-4)	I^2=97%, p<.001
high-dose protocol	271 (4)	1 (1-1)	I^2=92%, p<.001
rtPA	267 (4)	1 (1-2)	I^2=97%, p<.001
urokinase	298 (3)	2 (1-4)	I^2=99%, p<.001
Bleeding complications overall			
low-dose protocol	205 (3)	7% (2-21%)	I^2=72%, p=.028
high-dose protocol	302 (4)	22% (17-27%)	I^2=6%, p=.37
rtPA	152 (2)	16% (9-29%)	I^2=49%, p=.16
urokinase	299 (3)	14% (6-29%)	I^2=83%, p=.003
Bleeding complications minor			
low-dose protocol	149 (2)	8% (2-23%)	I^2=66%, p=.088
high-dose protocol	303 (4)	13% (7-21%)	I^2=59%, p=.064
rtPA	152 (2)	16% (9-29%)	I^2=49%, p=.16
urokinase	300 (3)	8% (5-13%)	I^2=37%, p=.20
Bleeding complications major			
low-dose protocol	238 (4)	1% (0-6%)	I^2=0%, p=.99
high-dose protocol	347 (6)	10% (4-24%)	I^2=88%, p<.001
rtPA	251 (4)	10% (2-40%)	I^2=93%, p<.001
urokinase	335 (5)	3% (1-11%)	I^2=64%, p=.024
Short-term amputation			
low-dose protocol	367 (8)	1% (0-16%)	I^2=0%, p=.91
high-dose protocol	493 (5)	2% (0-10%)	I^2=0%, p=.86
rtPA	617 (9)	1% (0-11%)	I^2=0%, p=.65
urokinase	331 (4)	7% (4-12%)	I^2=0%, p=.69
Short-term mortality			
low-dose protocol	238 (4)	3% (1-10%)	I^2=54%, p=.089
high-dose protocol	447 (5)	3% (1-7%)	I^2=0%, p=.92
rtPA	435 (6)	3% (1-6%)	I^2=0%, p=.99
urokinase	403 (5)	2% (1-6%)	I^2=0%, p=.45
Short-term amputation-free survival			
low-dose protocol	206 (3)	82% (69-90%)	I^2=70%, p=.036

high-dose protocol	264 (3)	88% (83-91%)	I^2=0%, p=.85
rtPA	258 (3)	82% (72-89%)	I^2=69%, p=.040
urokinase	300 (3)	87% (83-90%)	I^2=0%, p=.96
Amputation at 1 year			
low-dose protocol	174 (3)	33% (26-40%)	I^2=42%, p=.18
high-dose protocol	190 (3)	14% (10-20%)	I^2=0%, p=.39
rtPA	184 (3)	24% (18-32%)	I^2=24%, p=.27
urokinase	300 (3)	17% (10-28%)	I^2=68%, p=.043
Amputation at 3 year			
low-dose protocol	186 (2)	33% (26-40%)	I^2=0%, p=.92
high-dose protocol	151 (2)	12% (8-18%)	I^2=0%, p=1.0
rtPA	145 (2)	29% (19-41%)	I^2=53%, p=.14
urokinase	280 (2)	19% (8-39%)	I^2=89%, p=.003
Mortality at 1 years			
low-dose protocol	175 (3)	13% (7-24%)	I^2=55%, p=.11
high-dose protocol	190 (3)	12% (7-19%)	I^2=29%, p=.25
rtPA	184 (3)	15% (9-23%)	I^2=39%, p=.19
urokinase	252 (3)	16% (7-18%)	I^2=36%, p=.21
Mortality at 3 years			
low-dose protocol	186 (2)	31% (11-63%)	I^2=94%, p<.001
high-dose protocol	151 (2)	12% (3-38%)	I^2=78%, p=.034
rtPA	145 (2)	28% (6-68%)	I^2=94%, p<.001
urokinase	280 (2)	17% (13-23%)	I^2=13%, p=.28
Amputation-free survival at 1 year			
low-dose protocol	206 (3)	65% (50-77%)	I^2=64%, p=.060
high-dose protocol	264 (3)	81% (75-85%)	I^2=0%, p=.64
rtPA	258 (3)	67% (47-82%)	I^2=88%, p<.001
urokinase	300 (3)	74% (68-80%)	I^2=9%, p=.33
Amputation-free survival at 3 years			
low-dose protocol	186 (2)	51% (39-63%)	I^2=61%, p=.11
high-dose protocol	151 (2)	77% (66-85%)	I^2=38%, p=.20
rtPA	145 (2)	56% (33-76%)	I^2=87%, p=.006
urokinase	280 (2)	68% (57-77%)	I^2=68%, p=.077

570 CI = confidence interval

571
572
573
574
575
576
577
578
579

Figures

Figure 1. Flow chart of the study selection process

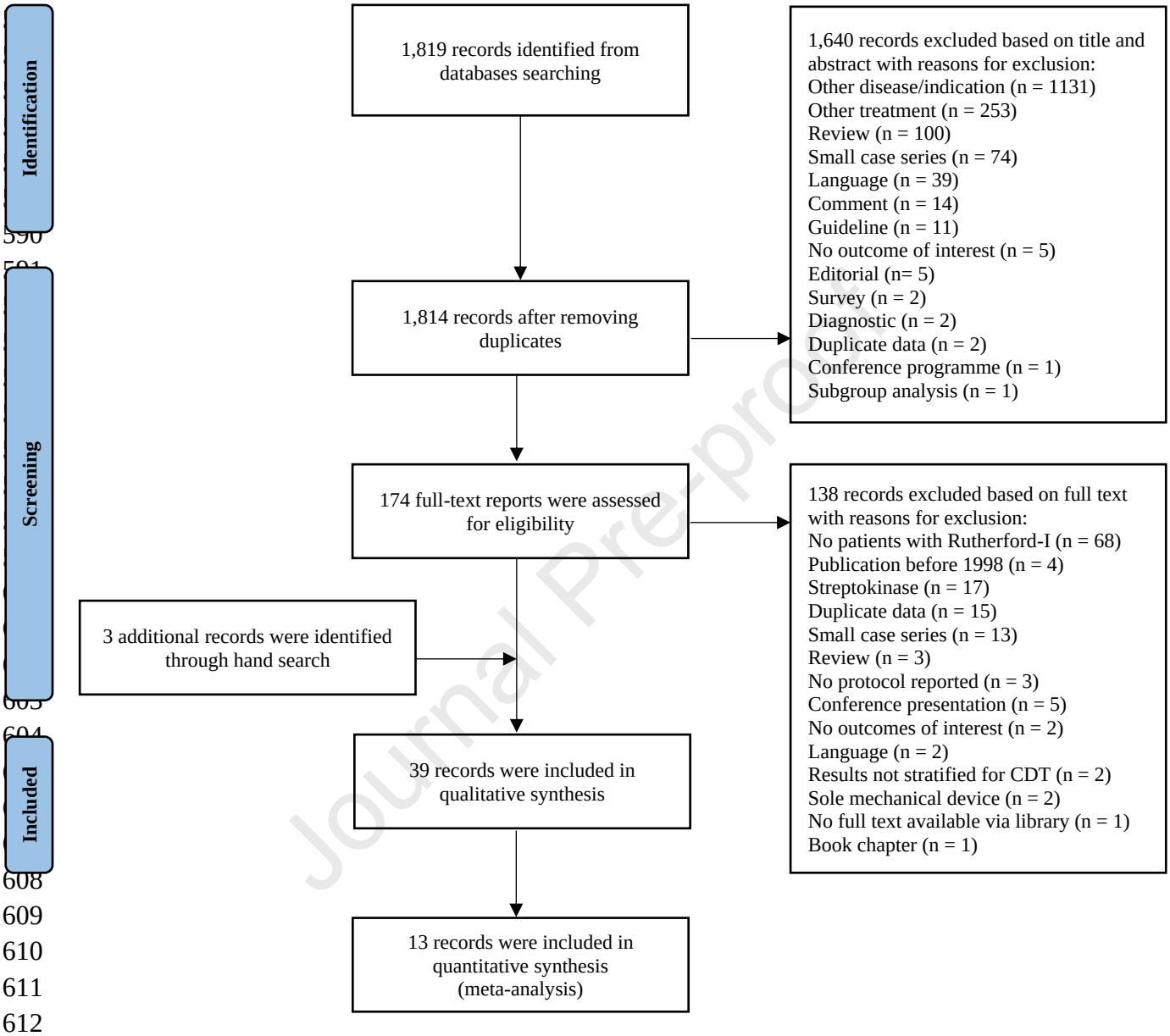


Figure 2. Forrest plot for short-term mortality reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Legend:
CI = confidence interval

*Data of both articles were provided as a combined cohort by the authors

Figure 3. Forrest plot for short-term amputation reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Legend:
CI = confidence interval

*Data of both articles were provided as a combined cohort by the authors

Supplementary Figure S1. Funnel plot for short-term mortality reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Legend:
Linear regression test of funnel plot asymmetry: t = -2.82, df = 8, p = .023; rank correlation test of funnel plot asymmetry: z = -2.06, p = .040.

Supplementary Figure S2. Funnel plot for short-term amputation reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Legend:
Linear regression test of funnel plot asymmetry: t = -3.90, df = 11, p = .003; rank correlation test of funnel plot asymmetry: z = -0.49, p = .63.

Supplementary Figure S3. Funnel plot for angiographic success reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)

Legend:
Linear regression test of funnel plot asymmetry: t = 2.81, df = 9, p = .021; rank correlation test of funnel plot asymmetry: z = 1.01, p = .31.

Appendix

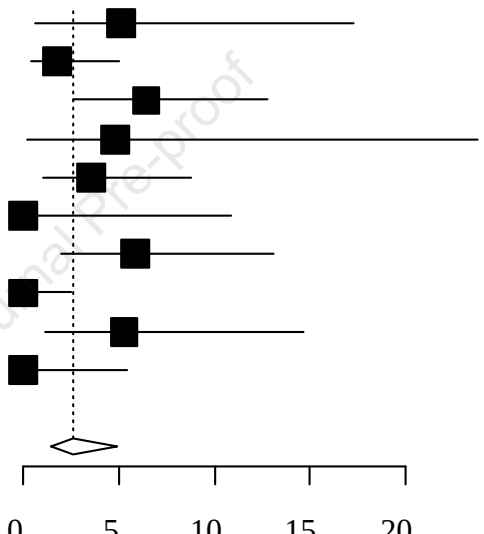
Supplementary Appendix 1. Database specific search queries

List of titles/legends of the supplementary material:

- Supplementary Table S1. Risk of bias assessment using the Newcastle-Ottawa quality assessment scale criteria
- Supplementary Figure S1. Funnel plot for short-term mortality reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)
    - Legend: Linear regression test of funnel plot asymmetry: t = -2.82, df = 8, p = .023; rank correlation test of funnel plot asymmetry: z = -2.06, p = .040.
- Supplementary Figure S2. Funnel plot for short-term amputation reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)
    - Legend: Linear regression test of funnel plot asymmetry: t = -3.90, df = 11, p = .003; rank correlation test of funnel plot asymmetry: z = -0.49, p = .63.
- Supplementary Figure S3. Funnel plot for angiographic success reported in studies of CDT for not immediately threatened acute limb ischaemia (Rutherford-I ALI)
    - Legend: Linear regression test of funnel plot asymmetry: t = 2.81, df = 9, p = .021; rank correlation test of funnel plot asymmetry: z = 1.01, p = .31.
- Supplementary Appendix 1. Database specific search queries

Study	Events	Total	Proportion (95% - CI)
Disini 2008	2	39	0.05 (0.01; 0.17)
Ebben 2014	3	171	0.02 (0.00; 0.05)
Ebben 2018	7	109	0.06 (0.03; 0.13)
Ebben 2019	1	21	0.05 (0.00; 0.24)
Grip 2014/Kuoppala 2011*	4	113	0.04 (0.01; 0.09)
Hundt 2013	0	32	0.00 (0.00; 0.11)
Kashyap 2011	5	86	0.06 (0.02; 0.13)
Mahler 2012	0	144	0.00 (0.00; 0.03)
Vakhitov 2019	3	57	0.05 (0.01; 0.15)
Yuan 2013	0	66	0.00 (0.00; 0.05)
Random effects model		**838**	**0.03 (0.01; 0.05)**

Heterogeneity: I^2 = 0%, τ = 0.4238, p = 0.88



Study	Events	Total	Proportion	(95% - CI)
Castañeda 2002	0	30	0.00	(0.00; 0.12)
Castañeda 2002	0	19	0.00	(0.00; 0.18)
Disini 2008	0	39	0.00	(0.00; 0.09)
Ebben 2014	20	171	0.12	(0.07; 0.17)
Ebben 2018	6	109	0.06	(0.02; 0.12)
Ebben 2019	2	20	0.10	(0.01; 0.32)
Grip 2014/Kuoppala 2011*	10	113	0.09	(0.00; 0.11)
Hundt 2013	0	32	0.00	(0.01; 0.11)
Kashyap 2011	4	88	0.05	(0.00; 0.02)
Kröger 2000	0	190	0.00	(0.00; 0.22)
Taha 2015	0	15	0.00	(0.13; 0.36)
Vakhitov 2019	13	57	0.23	(0.00; 0.05)
Yuan 2013	0	66	0.00	(0.04; 0.16)
Random effects model		**949**	**0.02**	**(0.00; 0.08)**

Heterogeneity: I^2 = 20%, τ = 3.3720, p = 0.24