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Short-term complications and outcomes in pharmaco-mechanical thrombolysis first and catheter-directed thrombolysis first in patients with acute lower limb ischemia

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Author contribution

SA, EK, FE, TB contributed to the design and implementation of the research

SA, FE to the statistical analysis,

SA, EK, FE, TB to the interpretations of the results, and writing of the manuscript.

SA, EK, TB performed the data collection.

Abstract

Background

Pharmaco-mechanical thrombolysis (PMT) has emerged as a treatment option in patients with acute lower limb ischemia (ALI), especially Rutherford IIb (motor deficit) for rapid revascularization, but supportive data is scarce. The aim of the present study was to compare effect of thrombolysis, complications, and outcomes of PMT first versus catheter-directed thrombolysis (CDT) first in a large cohort of patients with ALI.

Basic procedures

All endovascular thrombolytic/thrombectomy events in patients with ALI performed between January 1st 2009 and December 31st 2018 (n=347) were included. Successful thrombolysis/thrombectomy was defined as complete or partial lysis. Reasons for use of PMT was described. Complications such as major bleeding, distal embolization, and new onset of renal impairment, and major amputation and mortality at 30 days were compared between PMT (AngioJet™) first and CDT first groups in a multi-variable logistic regression model with adjustment for age, gender, atrial fibrillation, and Rutherford IIb.

Main findings

The most common reason for initial use of PMT was need of rapid revascularization, and the most common reason for use of PMT after CDT was insufficient effect of CDT. Presentation of Rutherford IIb ALI was more common in the PMT first group (36.2% vs 22.5%, respectively, p=0.027). Among 58 patients receiving PMT first, 36 (62.1%) were terminated within a single session of therapy without need of CDT. The median duration of thrombolysis was shorter (p<0.001) for the PMT first group (n=58) compared to the CDT first (n=289) group (4.0 hours vs 23.0 hours, respectively). There was no significant difference in amount of tissue plasminogen activator given, successful thrombolysis/thrombectomy (86.2% and 84.8%), major bleeding (15.5% and 18.7%), distal embolization (25.9% and 16.6%), major amputation or mortality at 30-day (13.8% and 7.7%) in the PMT first compared to the CDT first group, respectively. The proportion of new onset of renal impairment was higher in the PMT first compared to the CDT first group (10.3% versus 3.8%, respectively), and the increased odds (Odds ratio 3.57, 95% CI 1.22 – 10.41) was maintained in the adjusted model. In Rutherford IIb ALI, no difference in rate of successful thrombolysis/thrombectomy (76.2% and 73.8%), complications or 30-day outcomes was found between PMT first (n=21) and CDT (n=65) first group.

Conclusion

PMT first appears to be a good treatment alternative to CDT first in patients with ALI, including Rutherford IIb. The found renal function deterioration in the PMT first group needs to be evaluated in a prospective, preferably, randomized trial.

Key words: acute lower limb ischemia, pharmaco-mechanical thrombolysis, catheter-directed thrombolysis, major bleeding, distal embolization, renal function, Rutherford IIb

1.1 Introduction

Acute lower limb ischemia (ALI) can be treated with similar efficacy and outcome after open vascular surgery and local thrombolysis[1]. Low dose continuous catheter-directed thrombolysis (CDT) has for decades been an established treatment option for ALI, but fast-track thrombolysis protocols, using high dose thrombolytic regimens[2] and/or pharmaco-mechanical thrombolysis (PMT)[3], for faster thrombus clearance has challenged this view.

The AngioJet™ peripheral thrombectomy system is a pharmaco-mechanical peripheral thrombectomy device with power pulse™ lytic delivery and active aspiration for rapid restoring of blood perfusion. There is, however, insufficient data to suggest superior outcome of this rheolytical thrombectomy system compared to low dose CDT[4].

Major concerns regarding CDT are bleeding complications[5], and most feared is intra-cranial hemorrhage[6]. Acute kidney injury due to iodine contrast exposure during computed tomography angiography (CTA) followed by repetitive iodine contrast administration during low dose CDT[7], and intravascular hemolysis with hemoglobinemia after mechanical thrombolysis[8], particularly in patients with already compromised renal function at admission, are other well-known adverse effects. In fact, several observational studies have found an increased risk of renal dysfunction with PMT compared to CDT[9-11].

Although the European Society of Vascular Surgery (ESVS) 2020 Guidelines on the management of ALI[12] recommends combined percutaneous thrombectomy with CDT for Rutherford IIb ALI, there are very little supportive data. The aim of the present study was to explore reasons to use PMT, and to compare effect of thrombolysis, complications, and outcomes of PMT first versus CDT first in a large cohort of patients with ALI. A secondary aim was to compare complications and outcomes in Rutherford IIb ALI between groups.

2.1 Methods

2.1.1 Setting

Skåne University Hospital is the third largest hospital in Sweden, located in Malmö and Lund. Vascular Centre, located in Malmö, has a primary catchment population of 800 000 inhabitants. Vascular Centre does not only serve these patients but also acts as a tertiary referral centre for the southern part of Sweden.

2.1.2 Study sample

All consecutive endovascular thrombolytic/thrombectomy events in patients with ALI performed between January 1st 2009 and December 31st 2018 (n=347) were included. Patients undergoing emergency open revascularization procedures (thrombo-embolectomy [n=152], bypass [n=21]) during this study period were excluded. Among these 173 procedures, 112 had Rutherford IIb.

2.1.3 Thrombolysis

Before thrombolysis treatment is begun, several conditions must be met. Absolute contraindications are described in a local memo; operation or organ biopsy ≤ 2 weeks, cerebral infarction ≤6weeks, cerebral metastasis, known arteriovenous cerebral malformations and epidural catheter or puncture of the dura ≤ 3days. If none of these, absolute contraindications, are present several blood tests are performed including creatinine, hemoglobin, aspartate aminotransferase, alanine aminotransferase, bilirubin, lactate dehydrogenase, activated partial thromboplastin time, prothrombin complex and platelet count.

2.1.3.1 Low dose catheter-directed thrombolysis

Preferably an ultrasound guided puncture is made in the contralateral common femoral artery. A flush catheter is placed in the occlusion and the lytic agent, alteplase a recombinant tissue plasminogen activator (tPA), is deposited. Heparin bolus 5000 IE is given primarily and during treatment continuous heparin infusion was monitored by regular activated partial thromboplastin time (APTT) measurement. Low molecular weight heparin (Klexane® 40 mg subcutaneously once daily) and acetyl salicylic acid (ASA) 75 mg once daily, substituted heparin infusion from 2012 and onwards. This shift in treatment strategy without continuous heparin infusion was based on a report[13] where continuous heparin was judged to offer no

advantage. Total sum of amount of iodine contrast administration during the angiographic sessions together with any immediately (within one day) preceding or subsequent computed tomography angiography for diagnostic purposes or complication, respectively, was calculated.

2.1.3.2 AngioJet™ pharmaco-mechanical thrombolysis

When using the AngioJet™ Ultra device (Boston Scientific, Marlborough, Massachusetts, US) an ultrasound guided puncture of the common femoral artery (CFA) and an introducer of suitable length and diameter (minimum 6 French) is placed. The target clot lesion must be passed with a guide wire. The AngioJet™ Solent Omni (6 French), AngioJet™ Solent Proxi (6 French) and AngioJet™ Solent dista (4 French) catheters for arterial use are available. The most used thrombolytic solution is 20 mg of alteplase in a 50 ml saline solution. A power-pulsed spray technique is most often used and delivers 0.6 ml of the thrombolytic solution with every pulse and the catheter is passed through the thrombus at a speed of 4-5 mm per pulse. It is recommended to let the solution work for about 20 minutes before proceeding with the treatment. After 20 minutes of dwell time, the AngioJet™ catheter is re-introduced to perform a mechanical rheolytic thrombectomy of the clot with pacing technique (approximately ten seconds on, and a few second off) to avoid cardiac arrhythmia (adenosine and potassium release from the clot). The patients are closely monitored with electrocardiogram (ECG) during the procedure. This thrombectomy sequence can be repeated until satisfactory results or reaching the maximum effective working time of 300 seconds. The mechanical rheolytic thrombectomy method relies on the fact that an increase in the speed of a fluid occurs simultaneously with a decrease in static pressure – the Bernoulli effect. High pressure of saline jets travels backwards causing a vacuum effect allowing the thrombus to be drawn into the catheter and fragmented by the jets and evacuated from the body. During the procedure multiple angiographies are performed to monitor the results of treatment and to evaluate if any distal embolization has occurred.

2.1.4 Red blood cell transfusion data

Data over transfusion of units of red blood cell were retrieved from the hospital blood bank registry.

2.1.5 Definitions

Acute lower limb ischaemia was defined as sudden decrease in or worsening of limb perfusion causing a potential threat to viability of the extremity, and with symptoms for less than 14 days. Symptom duration was defined as the time from start of symptoms until the start of thrombolytic procedure. Degree of ischemia was defined according to Rutherford classification[14] at admission, and Rutherford IIb means motor deficit. Degree of lysis was defined as complete, partial, lysis but no run-off or no lysis[15]. Run off after lysis was determined by using angiographic images that were evaluated at both the beginning and end of thrombolytic procedure. One was considered to have ischemic heart disease if one had a history of myocardial infarction, angina pectoris, coronary artery bypass or percutaneous coronary angioplasty. Patients with a history of stroke (cerebral bleeding or infarction) or transient ischemic attack were considered to have had a cerebrovascular disease. Anemia was considered when hemoglobin (Hb) levels was below 134g/L in men and 117g/L in women. Estimated glomerular filtration rate (e-GFR) calculation was based on serum creatinine, age and gender[16] (www.efgr.se). Acute kidney injury (AKI) was considered if the patient had a 25% increase in serum creatinine within 72 hours after latest contrast administration[17]. Major bleeding was defined as bleeding requiring at least two units of red blood cell transfusion, re-operation or resulting in cessation of thrombolytic therapy[18]. Major adverse events (MAE) were defined as stroke, acute myocardial infarction, acute pulmonary embolism, major bleeding, or distal embolization. Major amputation was defined as amputation above foot-level.

2.1.6 Follow- up

All patients were followed from the time of inclusion to amputation or death, or end of-follow up 1st March 2021. Information on amputations was retrieved from medical charts and survival was followed-up with record-linkage to the National Population Registry.

2.1.7 Ethics

This study was approved by the Swedish Ethical Review Authority (Dnr 2020-00 764).

2.1.8 Statistical methods

Proportions of complications and outcomes were expressed with 95% confidence intervals (CI). Differences in proportions were analysed with Pearson's chi square or Fisher´s exact test for nominal outcomes or Kendall´s tau-b test for ordinal outcomes. Continuous data that

was not normally distributed was expressed in median and interquartile range, and group differences evaluated with the Mann-Whitney U test. Normally distributed data were expressed with mean and standard deviation, and group differences evaluated with independent samples t-test. Paired samples T-test was used to analyse the change in e-GFR in between two different timepoints from admission to discharge in the PMT and CDT groups. The mean change in e-GFR from admission to discharge was compared between the PMT and CDT groups using analysis of variance (ANOVA), adjusting for e-GFR at admission, Rutherford IIb and atrial fibrillation. A uni-variable logistic regression model was applied to express Odds ratios (OR) with 95% confidence intervals (CI) of complications and outcomes in all patients treated by PMT first compared to CDT first for ALI, and a multi-variable logistic regression model were performed for adjustment for potential confounding factors (age, gender, atrial fibrillation, and Rutherford IIb). Significance level was set to < 0.05. The statistical analysis was performed using SPSS version 27 and 28 (IBM, Armonk, New York, USA).

3.1 Results

3.1.1 Reasons to use pharmaco-mechanical thrombolysis

The most common reason for initial use of PMT was need of rapid revascularization, often due to motor deficit (Table 1). Among 58 patients receiving PMT first, 36 (62.1%) were terminated within a single session of therapy without need of CDT. The most common reason for use of PMT after CDT was insufficient effect of CDT (Table 1).

3.1.2 Comparison between patients undergoing PMT first and CDT first

3.1.2.1 Patient characteristics

Presence of atrial fibrillation was higher in the PMT first than in the CDT first group (25.9% vs 12.1%, p=0.006, Table 2), and medication with acetyl salicylic acid was lower in the PMT first than in the CDT first group (46.6% vs 60.6%, p=0.048; Table 2).

3.1.2.2 Aetiology of arterial occlusion, preoperative imaging and severity of ALI

The most common aetiology of arterial occlusion in PMT treated patients were thrombosis in a native artery (36.2%), endoprosthesis occlusion (32.8%) and embolism in a native artery (19.0%), and the most common aetiology in the CDT treated group were endoprosthesis occlusion (39.8%), thrombosis (24.2%) and embolism (18.0%) (Table 3). There was no difference in use of preoperative non-invasive imaging between groups. Presentation of Rutherford IIb ALI was more common in the PMT first group (36.2% vs 22.5%, respectively, p=0.027).

3.1.2.3 Details of endovascular therapy

The median duration for the PMT first group was shorter (p<0.001) compared to the CDT first group (4.0 hours vs 23.0 hours, respectively) (Table 4). The total amount of t-PA and iodine contrast administered, gram iodine contrast/e-GFR ratio and degree of lysis were similar for the two groups. Successful thrombolysis/thrombectomy were achieved in 86.2% and 84.8%, respectively.

3.1.2.4 Change in renal function

There was no significant difference in change of e-GFR from admission to hospital discharge in the PMT first compared to the CDT first group in adjusted analysis (p=0.06) (Table 5). The proportion of new onset of renal impairment was higher in the PMT first compared to the

CDT first group (10.3% versus 3.8%, respectively, Supplementary Table 1), and the increased odds (OR 3.57, 95% CI 1.22 – 10.41; Table 6) was maintained in the adjusted model.

3.1.2.5 Complications and outcomes

The proportion of major bleeding (15.5% and 18.7%) was not significantly different in the PMT first and CDT first group, respectively. Interruption of thrombolysis due to bleeding occurred in 16 (4.6%) patients. There were six in-hospital strokes, three hemorrhagic and three ischemic embolic strokes, of which three were fatal. None of the three hemorrhagic strokes were on concomitant intravenous heparin infusion. Among the three patients with concomitant ischemic embolic strokes, all had atrial fibrillation and one were on anticoagulation therapy. There were four fatal bleedings due to two hemorrhagic strokes, one retroperitoneal bleeding and one perioperative bleeding after below knee amputation. There were nine in-hospital fatalities due to major bleeding (n=4), ischemic embolic stroke (n=1), acute myocardial infarction (n=1), acute aortic occlusion (n=1), pulmonary embolism (n=1), persistent limb ischemia due to refusal of major amputation (n=1). The median in-hospital stay for the PMT first and CDT first group were 5 days (IQR 4 -10) and 6 days (IQR 5 – 10), respectively (p=0.75). The major amputation or mortality rate at 30-day were 13.8% and 7.7%, respectively, Supplementary Table 1, and there was no difference between groups in the adjusted model (Table 6).

3.1.2.6 Complications and outcomes in Rutherford IIb ALI

Patients treated with PMT first (n=21) were older (p=0.034) than the CDT first (n= 65) group (mean age 75.9 [SD 12.8] vs 69.9 [SD 10.4], respectively). The proportions of females in the PMT first and CDT first group were 57.1% (12/21) and 38.5% (25/65), respectively (p=0.13). The anatomical level of arterial occlusion was infra-inguinal in 66.7% (14/21) and 70.8% (46/65), respectively (p=0.72). Successful thrombolysis was achieved in 76.2% (16/21) and 73.8% (48/65), respectively (p=0.83). Adjunctive aspiration thrombo-embolectomy was performed in 23.8% (5/21) and 16.9% (11/65), respectively (p=0.48). There were no significant differences in odds of complications and outcomes between patients with Rutherford IIb ALI treated with PMT first (n=21) and CDT first (n=65) (Table 7). There was no significant difference in odds between PMT first and risk of major amputation or mortality at 30 days adjusted for age and gender (OR 3.42, 95% CI 0.92 – 12.7; p=0.067).

4.1 Discussion

The present retrospective observational study showed that PMT was used for various reasons, mainly due to need of initial rapid revascularization or insufficient effect of CDT, which means that the reasonable comparators should be PMT first versus CDT first in a study evaluating the effect of PMT, its complications and outcomes. Notably, the PMT first group had more severe ALI compared to the CDT group, including a higher proportion of patients with Rutherford IIb. The risk for major amputation or mortality at 30 days was, however, not significantly increased for the PMT first compared to the CDT group in the unadjusted analysis, and the HR was further attenuated in adjusted analysis after entry of covariates, including presence of Rutherford IIb. In the subgroup analysis of patients with Rutherford IIb ALI, there was a non-significant association between PMT first and major amputation or mortality at 30 days, after adjusting for age and gender.

The obvious advantage with PMT first in the present study was the shorter duration of treatment. The median time of PMT first was 4 hours and 62% of patients were terminated within a single session of therapy without need of continuous CDT at an intensive or intermediate care unit. However, one report using the AngioJet™ mechanical thrombectomy device without the pulse-spray-technique mode, found no difference in duration of treatment in the PMT plus CDT group compared to the CDT alone group, which may be due to that some patients in the former group actually were treated with CDT first plus PMT, insufficient effect by mechanical thrombectomy alone, or this unit´s strategy to perform overnight infusion of tPA to dissolve distal thrombus for improvement of outflow[19]. Like the present study, another comparative study first used the AngioJet™ power pulse mode with deposition of 6 – 10 mg tPA within the thrombus for 12 – 15 min, followed by reactivation in thrombectomy mode. There was no difference in duration of lysis time between the PMT and CDT groups, which may be explained by that any patient receiving PMT was classified in the PMT group including those with residual thrombus after CDT, and that 79% in the PMT group required adjunctive CDT[20].

Results from the PEARL registry[21] with data from 283 patients at 34 institutions in the US and Europe showed that 52% underwent PMT only, and the registry data was divided into PMT only versus PMT plus CDT, whereafter a 1:1 propensity-score matched adjusted analysis was performed for analysis of outcome. PMT alone was found to be superior to PMT

plus CDT in procedure success, 12-month amputation-free survival, and 12-month freedom from amputation. Again, a major limitation was that the PMT plus CDT group was heterogenous, and the order of treatments was not documented in phase 1 of the registry and 25% were treated with CDT prior to PMT in phase 2. It can be assumed that the decision to proceed to CDT after PMT and the decision to proceed to PMT after CDT was insufficient thrombus removal. The mixed group PMT plus CDT is simply an inappropriate comparator to PMT alone. Ignoring or being unaware of the sequence of treatments is a major bias, and data from the PEARL registry should therefore be interpreted with great caution.

The major bleeding rate was high in both groups, especially the CDT first group, whereas the rate of interruption of thrombolysis due to bleeding was 4.6%. The strict definition of major bleeding, and retrieval of robust data from the hospital register of red cell blood transfusions, ensured accurate identification of this complication. Patients with anemia at admission might seem more likely to receive blood transfusions after thrombolysis, but the frequency of anemia at admission in the two groups was similar, not apparently acting as a confounder when estimating odds of major bleeding between patients treated by PMT first compared to CDT first. Fatal bleeding related to the thrombolytic procedure occurred in three patients, of which two were due to intracranial hemorrhage. The high fatality rate in patients with intracranial hemorrhages related to thrombolysis has been reported previously[13]. In the Thrombolysis Or Peripheral Arterial Surgery (TOPAS) trial[1], comparing thrombolysis with surgery for ALI, heparin was found to be an independent risk factor for major bleeding, and owing to the high rate of intracranial hemorrhage, heparin use was stopped prematurely in the trial. However, none of the three patients with intracranial hemorrhage in the present study were administered concomitant intravenous heparin infusion.

The rates of PMT and CDT-related distal embolization was high without significant difference between groups. However, the 26% distal embolization rate in the PMT group is of concern, and similar high distal embolization rate has been reported[22]. A large proportion of patients with complication of distal embolization were complementary treated with endovascular aspiration thrombo-embolectomy, whereas filter devices to protect from embolization rarely was used. A variety of distal embolic protection devices or filters has been developed but not yet advocated in endovascular treatment of ALI. Of note, these protection devices were originally developed for treatment of deep venous thrombosis, where minor embolization probably has less severe consequences[12]. Of interest, embolic protection

devices used in atherectomy procedures in patients with chronic peripheral arterial disease were not associated with less rate of distal embolization, better technical success, or clinical outcomes, whereas fluoroscopy time was longer when these filter devices were used[23].

There was a difference in renal outcomes between PMT first and CDT first groups. Odds for new onset of renal impairment was increased in the PMT first group after adjustment for important confounders. The e-GFR was virtually the same from admission to discharge in the PMT first group, whereas e-GFR was improved from admission to discharge in the CDT first group, and in adjusted analysis, the difference in change of e-GFR from admission to hospital discharge in the PMT first compared to the CDT first group was close to significant. It can be assumed that all patients with ALI to some degree, were dehydrated at admission, but it was only possible to show an increase in e-GFR in the CDT first group. The fact that the PMT first group had more severe ischemic leg injuries and the median in-hospital stay in this group was one day shorter, compared to CDT first group, time from treatment to discharge was perhaps too short to allow for renal recovery in the PMT first group. Several previous observational studies have warned for renal dysfunction after PMT[9-11], but a prospective study, preferably randomized, allowing longer postinterventional time for the evaluation of renal function recovery, is needed to compare a PMT first with CDT first strategy.

The limitations of the study were attributed to the retrospective design, the small sample size in the PMT first group, risk for statistical type II error, and the limited number of covariates that were deemed possible to adjust for in the multivariable analysis. For instance, in this sample PMT first had higher combined major amputation/mortality at 30 days in Rutherford IIb ALI than the CDT first group, but without reaching statistical significance, and adjustment for confounders was not justified in this small subgroup. The strength was the meticulous division of the thrombolytic procedures into two comparative study groups, PMT first versus CDT first. This categorization was found necessary since approximately half of patients undergoing PMT, underwent PMT first and half underwent CDT first due to the completely different reasons to choose PMT first or CDT first. The preoperative calf arterial outflow status was not determined in the present retrospective study due to use of inconsistent imaging modalities. It should be acknowledged that severe ALI categorized as Rutherford IIb, vary in severity and extent of motor paralysis, which may induce treatment selection bias. Since there is a clinical reason to choose PMT first over CDT first, and that the proportion of Rutherford IIb ALI was higher in the PMT first group, it is not unlikely that patients treated

with PMT first due to motor deficit in the present study had a more advanced limb paralysis than corresponding patients treated with CDT first. Prospective studies in patients with ALI need a preset protocol, including evaluation by computed tomography angiography[24] of preoperative calf arterial outflow, and of motor function variables for better evaluation of differences in motor deficits between treatment groups. Comparison of complications and outcomes between PMT first and CDT first with a third group, emergency open revascularization procedures, was out of scope in this study. The majority of patients with ALI underwent endovascular therapy during the study period, but it is acknowledged that a higher proportion of patients with ALI Rutherford IIb were treated with emergency open revascularization procedures (65%), mainly thrombo-embolectomy, compared to the PMT first group (36%).

In conclusion, both PMT first and CDT first have high technical success rates, and PMT first appears to be a good treatment alternative in Rutherford IIb ALI. The found renal function deterioration in the PMT first group needs to be evaluated in a prospective, preferably, randomized trial.

5.1 Funding

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6.1 Declaration of interest

None

7.1 References

1. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. N Engl J Med 1998; 338: 1105 – 11.
2. Plate G, Jansson I, Forssell C, et al. Thrombolysis for acute lower limb ischaemia e a prospective, randomised,multicentre study comparing two strategies. Eur J Vasc Endovasc Surg 2006 ;31: 651 – 60.
3. Ascher E, Kibrik P, Rizvi SA, et al. Fast-track thrombolysis protocol for acute limb ischemia. J Vasc Surg 2021; 73: 950 – 9.
4. Veenstra EB, van der Laan MJ, Zeebregts CJ, et al. A systematic review and meta-analysis of endovascular and surgical revascularization techniques in acute limb ischemia. J Vasc Surg 2020; 71: 654 – 68.
5. Ouriel K, Shortell CK, DeWeese JA, , 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.
6. Kuoppala M, Åkeson J, Svensson P, et al. Risk factors for haemorrhage during local intra-arterial thrombolysis for lower limb ischaemia. J Thromb Thrombolysis “011; 31: 226 – 232.
7. Butt T, Lehti L, Apelqvist J, et al. Contrast-associated acute kidney injury in patients with and without diabetes mellitus undergoing computed tomography angiography and local thrombolysis for acute lower limb ischemia. Vasc Endovasc Surg 2022; 56: 151 – 157.
8. Soares R, Matielo MF, Neto FCB, et al. Analysis of the safety and efficacy of the endovascular treatment for acute limb ischemia with percutaneous pharmacomechanical thrombectomy compared with catheter-directed thrombolysis. Ann Vasc Surg 2020; 66: 470 – 478.
9. Escobar G, Burks D, Abate MR, , et al. Risk of acute kidney injury after percutaneous pharmamechanical thrombectomy using AngioJet in venous and arterial thrombosis. Ann Vasc Surg 2017; 42: 238 – 245.
10. Shen Y, Wang X, Jin SS, et al. Increased risk of acute kidney injury with percutaneous mechanical thrombectomy using AngioJet compared with catheter-directed thrombolysis. J Vasc Surg: Venous and Lym Dis 2019; 7: 29 – 37.

11. Morrow KL, Kim AH, Plato SA, , et al. Increased risk of renal dysfunction with percutaneous mechanical thrombectomy compared with catheter-directed thrombolysis. J Vasc Surg 2017; 65: 1460 – 6.
12. Björck M, Earnshaw JJ, Acosta S, , 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 Feb;59(2):173-218.
13. Grip O, Kuoppala M, Acosta S, et al. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. Br J Surg 2014; 101: 1105 – 1112.
14. Rutherford RB, Baker JD, Ernst C, , et al. Recommended standards for reports dealing with lower extremity ischemia: revised version: J Vasc Surg 1997; 26: 517 – 538.
15. Earnshaw JJ, Whitman B, Foy C. National audit if thrombolysis for acute leg ischemia (NATALI): clinical factors associated with early outcome. J Vasc Surg 2004; 39: 1018 – 1025.
16. Björk J, Grubb A, Sterner G, et al. Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. Scand J Clin Lab Invest 2011; 71: 232 – 239.
17. Mehran R, Aymong ED, Nikolsky E, , et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. J Am Coll Cardiol 2004; 44: 1393 – 1399.
18. Schulman S, Angerås U, Bergqvist D, et al. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202e4.
19. Gandhi SS, Ewing JA, Cooper E, et al. Comparison of low-dose catheter-directed thrombolysis with and without pharmacomechanical thrombectomy for acute lower extremity ischemia Ann Vasc Surg 2018; 46: 178 – 186.
20. Byrne RM, Taha AG, Avgerinos E, et al. Contemporary outcomes of endovascular interventions for acute limb ischemia. J Vasc Surg 2014; 59: 988 – 95.
21. Leung DA, Blitz LR, Nelson T, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: Results from the PEARL Registry. J Endovasc Ther 2015; 22: 546 – 557.

22. Gong M, He X, Boxiang Z, et al. Endovascular revascularization strategies using catheter-based thrombectomy versus catheter-directed thrombolysis for acute limb ischemia. Thrombosis Journal 2021; 19: 96.
23. Fereydooni A, Bai H, Baril D, et al. Embolic devices are not associated with improved outcomes of atherectomy for lower extremity revascularization. Ann Vasc Surg 2022; 86: 168 – 176.
24. Saphir E, Svensson-Björk R, Acosta S. Performance of computed tomography angiography before revascularization is associated with higher amputation-free survival in Rutherford IIb acute lower limb ischaemia. Front Surg 2021;8:744721.

Table 1. Reasons for using PMT in patients treated with PMT only, PMT + CDT, or CDT + PMT for acute lower limb ischemia

	PMT only (n=36)	PMT + CDT (n=22)	CDT + PMT (n=21)
Reasons (%)			
Rapid revascularization due to motor deficit	11 (30.6)	10 (45.5)	-
Rapid revascularization wanted (not due to motor deficit)	19 (52.8)	12 (54.5)	-
Motor anxiety and judged uncapable of lying still during thrombolysis	2 (5.6)	-	-
Termination of treatment in a single session	2 (5.6)	-	-
Advanced cancer disease	1 (2.8)	-	-
Older thrombotic occlusion	1 (2.8)	-	-
Previous bleeding complications during CDT and no candidate for open surgery	1 (2.8)	-	-
Bleeding complication and need of termination of CDT	-	-	1 (4.8)
Insufficient effect of CDT	-	-	17 (81.0)
Clinical deterioration during CDT	-	-	3 (14.3)

PMT; Pharmaco-mechanical thrombolysis, CDT; Catheter-directed thrombolysis.
A few patients had multiple reasons.

Table 2. Comparison of characteristics in patients treated with PMT first and CDT first for acute lower limb ischemia

	PMT first (n=58)	**CDT first (n=289)**	**P-value**
Women (%)	29 (50.0)	113 (39.1)	0.12
Age (mean [SD])	71.5 (13.1)	69.0 (10.4)	0.10
Comorbidities (%)			
Hypertension	41 (70.7)	234 (81.0)	0.078
Ischemic heart disease	12 (20.7)	77 (26.6)	0.34
Atrial fibrillation	15 (25.9)	35 (12.1)	0.006
Cerebrovascular disease	11 (19.0)	46 (15.9)	0.57
Diabetes Mellitus	14 (24.1)	73 (25.3)	0.86
Anemia	14 (24.1)	69 (23.9)	0.97
Claudication	34 (58.6)	165 (57.1)	0.83
Presence of foot ulcer	13 (22.4)	60 (20.8)	0.78
Medications at admission (%)			
Acetyl salicylic acid	27 (46.6)	175 (60.6)	0.048
Clopidogrel	3 (5.2)	28 (9.7)	0.27
Anticoagulation	8 (13.8)	43 (14.9)	0.83
Symptom duration prior to start of treatment (h) (median [IQR])	64 (24 – 234; n=56)	72 (24 – 168; n=278)	0.94

PMT; Pharmaco-mechanical thrombolysis, CDT; Catheter-directed thrombolysis;

Table 3. Comparison of aetiologies of arterial occlusion, preoperative imaging and severity of acute lower limb ischemia in patients treated with PMT first and CDT first.

	PMT first (n=58)	CDT first (n=289)	P-value
Etiology (%)			
Thrombosis	21 (36.2)	70 (24.2)	0.058
Embolism	11 (19.0)	52 (18.0)	0.86
Popliteal artery aneurysm with thromboembolism	1 (1.7)	16 (5.5)	0.32
Vein bypass occlusion	2 (3.4)	17 (5.9)	0.75
Synthetic bypass occlusion	5 (8.6)	25 (8.7)	0.99
Endoprosthesis occlusion	19 (32.8)	115 (39.8)	0.32
Primary infra-inguinal / aorto-iliac occlusion	33 / 25	189 / 100	0.22
Preoperative non-invasive imaging (%)	51 (87.9)	256 (88.6)	0.89
Computed tomography angiography	34 (58.6)	173 (59.9)	0.86
Magnetic resonance tomography angiography	12 (20.7)	46 (15.9)	0.37
Duplex	10 (17.2)	65 (22.5)	0.38
Degree of ischemia - Rutherford Class (%)			
I	21 (36.2)	97 (33.6)	
IIa	16 (27.6)	127 (43.9)	
IIb	21 (36.2)	65 (22.5)	
III	0 (0)	0 (0)	0.056

PMT; Pharmaco-mechanical thrombolysis, CDT; Catheter-directed thrombolysis.

Multiple aetiologies possible

Table 4. Comparison of characteristics of endovascular therapy in patients treated with PMT first and CDT first for acute lower limb ischemia.

	PMT first (n=58)	**CDT first (n=289)**	**P-value**
Duration of thrombolysis (h) (median [IQR])	4.0 (3.0 – 20.0)	23.0 (17.0 – 34.5)	< 0.001
Amount of t-PA (mg) (median [IQR])	20 (11.4 – 25.0)	21.4 (15.0 – 32.0)	0.15
Pulse spray technique (%)	39 (67.2)	4 (1.4)	NA
Mechanical thrombectomy (%)	57 (98.3)	21 (7.3)	NA
Mechanical thrombectomy only (%)	8 (13.8)	-	NA
Iodine contrast			
Total amount of iodine contrast (gram) (median [IQR])	47.9 (25.7 – 60.1)	48.7 (33.2 – 67.4)	0.20
Gram iodine contrast dose/e-GFR admission ratio (median [IQR])	0.63 (0.43 – 0.89)	0.69 (0.48 – 1.02)	0.28
Degree of lysis (%)			
Complete lysis	11 (19.0)	98 (33.9)	
Partial lysis	39 (67.2)	147 (50.9)	
Lysis, but no run-off	6 (10.3)	12 (4.2)	
No lysis	2 (3.4)	32 (11.1)	0.045
Successful thrombolysis/thrombectomy	50 (86.2)	245 (84.8)	0.78
Adjuvant revascularization (%)			
Endovascular	51 (87.9)	215 (74.4)	0.026
Aspiration thrombo-embolectomy	11 (19.0)	46 (15.9)	0.57
Open	0 (0)	14 (4.8)	0.14
Hybrid	4 (6.9)	16 (5.5)	0.76

PMT; Pharmaco-mechanical thrombolysis, CDT; Catheter-directed thrombolysis,

IQR; inter-quartile range, e-GFR; estimated glomerular filtration rate

Table 5. Development of e-GFR over in-hospital period in patients treated with PMT first and CDT first for acute lower limb ischaemia.

	Admission e-GFR, mean (SD)	**Discharge e-GFR, mean (SD)**	**Change in e-GFR (95% CI)**	**P-value**
PMT first (n=58)	64.7 (21.4))	64.3 (22.7)	-0.40 (-4.1 – 3.3)	0.83
CDT first (n=289)	65.7 (19.6)	68.0 (20.1)	2.3 (1.1 – 3.5)	<0.001
*Difference in e-GFR between PMT first and CDT first			- 3.0 (-6.2 – 0.1)	0.060

PMT; Pharmaco-mechanical thrombolysis, CDT; Catheter-directed thrombolysis

CI=confidence interval, eGFR= estimated glomerular filtration rate ml/min/1.73m^2 (calculated from e-GFR.se), SD=standard deviation, *= Analysis of Variance (General Linear Model – adjusted for Rutherford IIb, atrial fibrillation and admission e-GFR).

Table 6. Odds ratios of complications and outcomes in all patients treated by PMT first compared to CDT first for acute lower limb ischaemia

	Crude model			**Adjusted model***	
	OR (95% CI)	p-value		**OR (95 % CI)**	p-value
Major bleeding	0.80 (0.37 – 1.73)	0.57		0.65 (0.29 – 1.46)	0.29
Distal embolization	1.75 (0.90 – 3.40)	0.098		1.72 (0.87 – 3.42)	0.12
Fasciotomy	1.07 (0.30 – 3.85)	0.92		1.03 (0.27 – 3.93)	0.96
Acute kidney injury	1.35 (0.69 – 2.64)	0.38		1.21 (0.60 – 2.43)	0.59
New onset of renal impairment at discharge (e-GFR<60 ml/min/1.73m^2)	2.92 (1.03 – 8.23)	0.043		3.57 (1.22 – 10.41)	0.020
30-day MAE	1.20 (0.66 – 2.18)	0.54		1.09 (0.58 – 2.02)	0.80
In-hospital stay (days) ≤ 4 days	1.16 (0.61 – 2.21)	0.66		1.38 (0.70 – 2.70)	0.35
30-day major amputation	1.50 (0.53 – 4.24)	0.45		1.30 (0.45 – 3.76)	0.63
30-day mortality	2.20 (0.55 – 8.76)	0.26		1.61 (0.37 – 7.03)	0.53
Major amputation or mortality at 30 days	1.93 (0.81 – 4.57)	0.14		1.51 (0.62 – 3.72)	0.36

PMT; Pharmaco-mechanical thrombolysis, CDT; catheter-directed thrombolysis, OR; Odds ratio, CI=confidence interval, e-GFR= estimated glomerular filtration rate, MAE = major adverse events.

*Including age, gender, atrial fibrillation, and Rutherford IIb

Table 7. Odds ratios of complications and outcomes in patients treated by PMT first (n=21) compared to CDT first (n=65) for acute lower limb ischemia with Rutherford IIb at admission

	Crude model	
	OR (95% CI)	p-value
Major bleeding	0.35 (0.09 – 1.32)	0.12
Distal embolization	1.60 (0.52 – 4.93)	0.41
Fasciotomy	1.03 (0.19 – 5.56)	0.97
Acute kidney injury	1.67 (0.57 – 4.88)	0.35
New onset of renal impairment at discharge (e-GFR<60 ml/min/1.73m^2)	3.2 (0.19 – 53.5)	0.42
Successful thrombolysis/thrombectomy	1.13 (0.36- 3.57)	0.83
30-day MAE	0.81 (0.30 – 2.23)	0.69
30-day major amputation	2.27 (0.57 – 9.00)	0.24
30-day mortality	6.74 (0.58 – 78.4)	0.13
Major amputation or mortality at 30 days	3.26 (0.95 – 11.14)	0.060

PMT; Pharmaco-mechanical thrombolysis, CDT; catheter-directed thrombolysis, OR; Odds ratio, CI=confidence interval, e-GFR= estimated glomerular filtration rate, MAE = major adverse events.

Highlights

- Patients undergoing thrombolysis for acute lower limb ischemia (ALI) were evaluated
- Pharmaco-mechanical thrombolysis (PMT) first was successful in 86% of patients
- PMT first and catheter-directed thrombolysis first had similar 30-day outcomes
- There was an increased odds for new onset of renal impairment after PMT first
- In Rutherford IIb ALI, outcomes and complications were the same in the two groups