Endovascular Revascularization Strategies Using Catheter-Based Thrombectomy Versus Conventional Catheter-Directed Thrombolysis for Acute Limb Ischemia

Maofeng Gong  
Nanjing First Hospital

Xu He  
Nanjing First Hospital

Boxiang Zhao  
Nanjing First Hospital

Jie Kong  
Nanjing First Hospital

Jianping Gu  
Nanjing First Hospital

Guoping Chen (✉️ 175899321@qq.com)  
Nanjing First Hospital

Research

Keywords: Acute limb ischemia, Endovascular treatment, Catheter-based thrombectomy, Percutaneous mechanical thrombectomy, Catheter-directed thrombolysis

DOI: https://doi.org/10.21203/rs.3.rs-733076/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

Acute limb ischemia (ALI) is an important clinical event threatening both life and the affected limbs, but the optimal treatment for ALI remains undefined. The aim of this study was to compare the safety and effectiveness of thrombectomy approaches via either catheter-based thrombectomy (CBT) or catheter-directed thrombolysis (CDT).

Methods

A total of 98 patients (mean age 69.7 years, 60 male) who underwent endovascular intervention for ALI from January 2015 to August 2018 were included. Of these, 57 were treated with primary CBT via a large-bore catheter, an AngioJet catheter or Rotarex catheter, and/or underwent low-dose CDT, and 41 were treated with primary CDT. The safety and effectiveness of CBT compared to conventional CDT and other various endovascular techniques were evaluated.

Results

More Rutherford IIb patients were treated with primary CBT (68.4%) than CDT (26.8%; P < .001). Patients who underwent primary CBT achieved a higher technical success rate than those who underwent primary CDT in a shorter procedure time (P < .001), whereas 42.1% of patients who underwent CBT did not need adjunctive CDT. The duration and dosage of adjunctive CDT in the CBT group were significantly decreased compared with those in the primary CDT group (both P < .001), and the CBT group achieved a shorter in-hospital length of stay (P < .001). Subgroup analysis revealed that patients treated with AngioJet and Rotarex catheters achieved slightly lower dosages, shorter CDT durations and shorter in-hospital stay lengths than those treated with large-bore catheters (P > .05). Clinical success was estimated to be achieved in 98.2% of patients who underwent CBT, which is similar to the 97.6% estimated in those who underwent primary CDT (P = 1.000), and this finding was similar among the CBT subgroups. Patients who underwent primary CBT had slightly fewer complications than those who underwent primary CDT (P = .059), especially minor complications (P = .036). The freedom from amputation at 6 and 12 months for CBT and CDT was assessed (93.0% vs 90.2% respectively, P = .625; 89.5% vs 82.5%, respectively, P = .34). Comparable limb salvage was found for different techniques of large bore catheters, AngioJet catheters and Rotarex catheters. The Kaplan-Meier table analysis also showed similar limb salvage rates between groups.

Conclusions
Endovascular treatment of ALI with the use of catheter-based therapies is a safe and effective modality with similar safety and clinical outcome to conventional CDT alone, and this treatment modality overcomes the common shortcomings of CDT alone. Different CBT techniques have comparable efficacy but different adverse event profiles.

**Article Highlights**

Type of Research: Single-center retrospective cohort study.

Key Findings: CBT was successful as a stand-alone first-line endovascular technique in close to one-half of patients, with the remainder of patients requiring adjunctive CDT due to residual thrombus or emboli into distal small arteries where the CBT catheters could not safely reach. CBTs had the advantages of pronounced reduction of large volumes of thrombus in a moderate time and quicker return of blood flow and had comparable limb salvage rates. In contrast, primary CDT had greater technical success but was associated with more bleeding complications, including one bleeding-related death. Moreover, comparisons among CBT techniques revealed comparable outcomes in ALI patients regardless of which of the 3 modalities were used as first-line treatment but showed that the modalities had different adverse event profiles.

Take Home Message: Endovascular treatment of ALI with the use of catheter-based therapies is a safe and effective modality that can reduce the requirement for thrombolysis, with expected reductions in hemorrhagic complications. It has a safe and similar clinical outcome to conventional CDT alone but helps to overcome the usual shortcomings of CDT alone. Regarding Rutherford IIb ischemia, CBT may be a preferred option over CDT. In terms of CBT modalities, different techniques have comparable efficacy but have different adverse event profiles.

**Table of Contents Summary**

This retrospective single-center study analyzed the endovascular revascularization and outcomes of 98 acute limb ischemia patients. The study suggests that catheter-based thrombectomy (CBT) is a safe and effective modality that can reduce the requirement for thrombolysis, with expected reductions in hemorrhagic complications. It has a safe and similar clinical outcome to conventional catheter-directed thrombolysis (CDT) alone but can overcome the usual shortcomings of CDT alone. Regarding Rutherford IIb ischemia, CBT may be a preferred option over CDT. In terms of CBT modalities, different techniques have comparable efficacy but have different adverse event profiles.

**Introduction**

Acute limb ischemia (ALI), referred to as ischemia symptoms that emerge within two weeks, is one of the most common arterial emergencies [1,2]. The most common causes of ALI are embolism, thrombosis of native arteries or reconstructions, peripheral arterial aneurysm, dissection and traumatic arterial injury [3]. ALI manifesting as “6P syndrome” can be catastrophic, with a potential threat to limb viability due
to insufficient time for new vessel growth to compensate for the sudden interruption of limb perfusion [4,5]. Ischemia is graded clinically according to the Rutherford ALI classification system. For acute, viable or marginally threatened ALI, timely recognition and revascularization aiming at restoring perfusion is recommended (Class I) [1,2,5].

ALI is a potential lethal event leading to not only amputation (12-50% of cases) but also death (20-40% of cases) without prompt treatments [4]. A majority of adverse outcomes occur within the initial days after presentation, indicating that intervention time is limited. Therefore rapid and effective revascularization following an episode of ALI is pivotal, as it will most likely improve the prognosis. However, determination of the optimal option for revascularization remains particularly challenging [1]. Surgical and endovascular approaches have been a longstanding topic of debate; both appear equally effective in the ALI patient population [6,7] but have different adverse event profiles. Two recent guidelines, the European Society of Cardiology (ESC) and the European Society for Vascular Surgery (ESVS) guidelines [1,8], have put a spotlight on ALI, and an evolution towards less invasive interventions has taken place, which may be an opportunity to encourage endovascular interventions in addition to surgery [9].

For endovascular approaches, conventional catheter-directed thrombolysis (CDT) is one of the most well established and employed techniques [10,11]. Recently, a variety of new endovascular modalities aimed at mechanical disruption of the thrombus have emerged, and catheter-based thrombectomy (CBT) techniques, including thromboaspiration, microfragmentation, pharmacomechanical thrombectomy and ultrasound-accelerated CDT, have emerged and been made more available [12]. Even if all of the above techniques have been widely applied in clinical practice, relatively little is known about critical points such as safety and competitive device performance. Thus, the primary objective of this study was to compare the safety and effectiveness of CBT to conventional CDT in the management of ALI, as well as to evaluate various endovascular techniques with large bore catheters, Rotarex catheters and AngioJet catheters.

### Methods

#### Patients and Study Design

This was a retrospective cohort study which included confirmed ALI patients who underwent endovascular revascularization as first-line treatment at a single academic center from January 2015 to July 2019. All patients underwent treatment via the CBT and/or CDT approach, and data were retrospectively derived from the medical database system and paper records. This data collection protocol was approved by the institutional review board, and the need for informed consent was waived owing to the retrospective nature of this study. A study flow-chart is shown in Fig. 1.

#### Management Strategies Details

ALI was initially assessed in the majority of patients with urgent duplex ultrasound and CT arteriography (CTA). Then, the therapeutic approach was left to the discretion of the treatment group, consisting of 3
interventional radiologists with at least 15 years of experience. The decision to proceed with either CBT or CDT as the first-line treatment was determined by the interventional radiologist operators based mainly on the degree of ischemia, experience and devices available. Although the procedural details varied slightly in different cases depending on individuality therapy, procedures were largely similar, and the exact CBT reperfusion details are shown in **Supplementary Table 1**. If residual *in situ* thrombus or distal embolization was found after embolectomy, further widely used alternative conjunction with CDT was considered.

Patients who underwent conventional CDT as first-line treatment were infused a bolus dose of 5 mg of recombinant tissue-type plasminogen activator (rt-PA) (Actilyse; Boehringer Ingelheim; Ingelheim, Germany) *via* a multiple-side hole thrombolytic catheter (Uni*Fuse*; Angio-Dynamic; Latham, NY). Both CDT techniques subsequently received a continuous infusion of reduced-dose rt-PA for further treatment. Thrombolytic therapy with rt-PA was administered as follows: 20 mg of actilyse in 500 ml of 0.9% saline was administered through the reserved thrombolysis catheter at an infusion rate of 0.01 mg/kg/h; the maximum rate was no more than 1.0 mg/h. Thrombolysis with actilyse was only administered when the fibrinogen level, which was monitored at 12-24 hourly intervals, was greater than 1.0 g/L. Follow-up angiography was performed to assess efficacy every 24 hours. In the absence of any contraindications, CDT was continued if the thrombus load remained and discontinued when treatment was complete or in the event of an adverse event.

If more than the indicated minimum of 50% stenosis remained after thrombus removal, balloon angioplasty and/or stenting was performed. During each thrombolysis therapy or at the end of CDT, low molecular weight heparin (Hebei Chang Shan Biochemical Pharmaceutical; Shijiazhuang, China) therapy at a dose of 100 IU/kg per 12 hours was started immediately. In the absence of local hemorrhagic complications, dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d) and statin therapy (atorvastatin, 20 mg/d) were prescribed after discharge. Outpatient follow-ups were conducted by our center at 1, 3, 6, and 12 months postprocedure *via* ankle-brachial index (ABI), duplex ultrasound and/or CTA; additional procedures and complications were recorded during follow-up.

**Definitions of Outcome and Safety Measures**

The clinical severity of ALI was classified by the Rutherford classification system details are listed in **Supplementary Table 2** [5]. Technical success of the primary procedure was defined as complete *in situ* thrombus clearance of CBT or CDT alone, and adjunctive treatment of CDT to achieve thrombus clearance for CBT was considered to indicate assistant technical success. Clinical success (improvement in clinical status) was defined as the absence and/or relief of symptoms related to ALI according to accepted guidelines [5,11], or an improvement in the Rutherford grade of at least one category with objective evidence of hemodynamic change (at least 0.1 increase in ABI). Limb salvage was defined as freedom from major amputation (performed above the ankle), and maintained functional autonomy (walking or standing) was determined in accordance to accepted guidelines [5]. The need for necessary additional techniques (such as balloon angioplasty and/or stenting) to treat underlying chronic disease
to obtain sufficient distal perfusion within the same hospital stay was recorded but not considered clinical failure. Safety was classified as major or minor complications in accordance with the criteria of the Society of Interventional Radiology (SIR) classification scale [13].

Statistical Analysis

The SPSS statistical software package (version 23.0; SPSS statistical software, Chicago, Illinois, USA) was used to perform all statistical analyses in this study. Continuous variables are expressed as the mean ± standard deviation. Qualitative variables are presented as numbers and percentages. When assessing the correlation between pre- and postprocedural variables, a paired t-test was used. The significance of qualitative variables was tested with a chi-square test or Fisher's exact test. Findings with a P value less than 0.05 were deemed statistically significant.

Results

Baseline Characteristics and Ischemia Classification of Patients

A total of 98 patients [mean age 69.7 years, 61.2% male (n=60)] with ALI who underwent endovascular revascularization with either CBT or CDT were included. Of those patients who underwent CBT as first-line treatment, 28 were treated with large-bore catheters, 16 with AngioJet catheters, and 13 with Rotarex catheters, and 41 underwent conventional CDT solely as the first-line treatment. The demographics, comorbidities, presentation and lesion characteristics of 98 patients are summarized in Table 1. Procedure characteristics and outcomes are outlined in Table 2, and Table 3 summarizes outcomes by subgroups of interest.

The mean duration of ischemia symptoms before presentation was slightly longer in the CBT group of than that in the CDT group (37.2±32.8 hours vs 31.0±28.2 hours, respectively; P=.332). Within the CBT group, the Rotarex subgroup had a longer duration of ischemia (50.8±30.0 hours, P=.208). With regard to etiology, the major risk factors for the development of ALI were hypertension (70.4%), diagnosed atrial fibrillation (63.3%) and coronary artery disease (32.7%). In the majority of cases, the thrombosed segment resided in the iliac or iliofemoral arteries; three cases in the CBT group had iliofemoral thrombus of existing stents, and two cases in the CDT group had distal artery thrombus. There were no statistically significant differences in baseline characteristics between the two groups or among the subgroups of large-bore catheters, AngioJet catheters and Rotarex catheters (P>.05). With regard to the ischemia classification of patients, the primary CDT group had a slightly higher proportion of patients with Rutherford grade I ischemia (P=.076); there were fewer Rutherford grade IIa patients treated with primary CBT (n=17, 29.8%) than those treated with CDT (n=26, 63.4%; P=.001), and more Rutherford grade IIb patients were treated with the use of primary CBT (n=39, 68.4%) than those treated with CDT (n=11, 26.8%; P<.001).

Outcomes of Technical and Clinical Success
Procedure characteristics and outcomes are outlined in Table 2 and Table 3. Patients who underwent primary CDT achieved a higher technical success rate (n=39, 95.1%) than those who underwent primary CBT (n=24, 42.1%) in a shorter time [1.32±0.44 hours versus 1.89±0.52 hours; \( P < .001 \)]. In the subgroup analysis, large-bore catheters had slightly shorter procedure lengths than AngioJet or Rotarex catheters. In the remaining 57 patients who underwent primary CBT and experienced technical failure, 33 patients required adjunctive CDT due to either residual \textit{in situ} thrombus (n=19) or dislodged distal thrombus (n=14). At completion, additional balloon angioplasty and/or secondary stenting for underlying chronic disease to obtain sufficient distal reperfusion was performed in 81.6% of patients (n=80), without a significant difference between the two groups (\( P = .804 \)).

The duration and dosage of adjunctive CDT were significantly when compared to those for primary CDT (duration was 1.74±.98 days vs 3.07±1.38 days, mean dosage rt-PA 14.14±5.75mg vs 29.27±11.70 mg, both \( P < .001 \)). The CBT group also demonstrated a shorter in-hospital length of stay (\( P < .001 \)). In the subgroup analysis, AngioJet and Rotarex catheters achieved slightly lower dosages, shorter CDT durations and shorter length of in-hospital stay than large-bore catheters. Clinical success estimates were achieved in 98.2% of patients (n= 56) who underwent primary CBT, which was similar to the 97.6% (n=40) success in those who underwent primary CDT (\( P=1.000 \)). These were similar among the subgroups of CBT, despite differences in the proportions of patients with Rutherford Ila and Rutherford Ilb ischemia treated with each modality. Of these, the clinical success rates of patients in Rutherford Ila and Ilb were 100% and 96.0%, respectively (\( P=1.000 \)). In both groups, ABI was significantly improved from preprocedure measurements to those after treatment completion (\( P<.001 \)); however, the difference was not statistically significant between each other or among the subgroups (\( P > .05 \)).

Complications and Treatment Therapy

The 30-day complications recorded are listed in Table 2 and Table 3. Patients who underwent primary CBT had slightly fewer complications than those who underwent primary CDT (\( P=.059 \)), especially for minor complications (\( P=.036 \)). Minor complications for the CBT group included vessel spasm (n=3), dissection of the superficial femoral artery (n=1), hematuria (n=1) and hematoma of the puncture site (n=1); the rate of complications was significantly lower than that for CDT. Minor complications in the CDT group were presented mainly as hemorrhage events, including hematoma of the puncture site (diameter 3-5 cm, n=6), pseudoaneurysm (n=2), hematuria (n=2) and calf hematoma (n=1). Local pressure dressing was applied for observation and treatment of minor hemorrhage, and minor complications experienced less serious adverse consequences. The major complication of the CBT group was compartment syndrome (n=3) requiring surgery for calf fasciotomy. Two patients in the CDT group required transfusion of two units of red blood cell suspension due to major gastrointestinal hemorrhage. Fortunately, all these events resolved without permanent sequelae. One death in each group was recorded: one subject in the CBT group died from cardiac failure after amputation, which was unrelated to the procedure, and the one subject in the CDT group died from intracranial hemorrhage after CDT despite surgical decompression.

In the subgroup analysis, large-bore catheters and Rotarex catheters had more procedure-related distal emboli than AngioJet catheters, yet the difference was not statistically significant among the 3 groups.
(P = .430). Owing to the small size of these vessels and underlying chronic disease, the dislodged thrombus was treated with adjunctive CDT.

**Follow-up and Limb freedom from Amputation**

No patients were lost to follow-up, and 96% (94/96) of patients were alive when discharged from the hospital. The reintervention rates at 6 months and 12 months were 9.6% (n=9) and 18.1% (n=17), respectively. A total of four and five patients suffered major amputations at 6 months for the CBT and CDT groups and six and seven at 12 months, respectively. The freedom from amputation at 6 months in the CBT and CDT groups was 93.0% and 90.2%, respectively, and at 12 months was 89.5% and 82.5%, respectively (P > .05). The Kaplan-Meier analysis also showed similar limb salvage rates between groups (Fig. 2). Similarly, no significant differences were seen among groups (P > .05). Additionally, a total of eight deaths (two versus four at 6 months; two versus zero at 12 months) were recorded during follow-up.

**Discussion**

The present study demonstrated that CBT is successful as a stand-alone first-line endovascular technique in close to one-half of patients with ALI, with the remainder requiring adjunctive CDT due to residual thrombus or emboli into distal small arteries where the CBT catheters could not safely reach. CBTs had the advantages of pronounced reduction of large volumes of thrombus in a moderate time, speedy recanalization of blood flow and comparable limb salvage. In contrast, primary CDT had greater technical success but with more bleeding complications (statistically significant for minor bleeds), including one bleeding-related death. Moreover, the comparison among CBTs revealed comparable outcomes in ALI patients regardless of which of the 3 modalities were used as first-line treatment, but had different adverse event profiles. Because ALI might threaten limbs and life, especially quality of life, shared decision making between clinicians, patients and families based on the best available option for ALI patients seems to be important [2, 14].

A recent meta-analysis study of 21 studies including 4689 patients found comparable result with endovascular versus surgical revascularization [6]. With regard to therapies for endovascular revascularization, treatment for ALI has initially been performed via CDT over the years, but in recent years the CBT approach has been widely favored and can be performed with equivalent results to surgery [1,4,6]. The strategy options for ALI treatment in our study depended mainly on the severity of ischemia. CDT for revascularization often takes time, and ischemia may progress during treatment if the thrombus is not removed in a timely manner [1,2,6]. In this study, 73.2% of CDT therapy was applied in patients with Rutherford grade I and IIa ischemia considering its inherent defects of slow opening of the lumen. In 68.4% of patients with Rutherford grade IIb, more emergency revascularization techniques, including large-bore catheters, Rotarex catheters and AngioJet catheters, were used as the preferred first-line methods to restore perfusion. Although clinical success and freedom from amputation in the Grip et al. [7] study were inferior in patients with Rutherford grade IIb than IIa ischemia, the present study
demonstrates that outcomes were no worse for patients with Rutherford grade IIb ischemia. Patients who underwent CBT achieved similar outcomes, removing emboli/thrombus and opening the lumen with shorter procedure times than CDT. The strategy of CBT for Rutherford grade IIb ischemia seems to be a suitable alternative when initiated promptly.

In the present cohort study of patients treated by CDT and CBT, both techniques were shown to be useful. We compared CBT and CDT as the primary endovascular procedures, and the results indicated that technical success rates of CBT were 42.1%, which was lower than that of CDT as 57.9% of CBT patients underwent conjunctive CDT. This number was lower than that reported by Zehnder et al. [15], which may be attributed to a more stringent definition (not including adjunctive CDT) of technical success in the present study. A matched analysis comparing clinical success and limb salvage between the two groups showed slightly better outcomes and comparable limb salvage (albeit not statistically significant) in the CBT group. The patients who were free from amputation at 6 months and 12 months was approximately 93.0% versus 90.2% and 89.5% versus 82.9% in both groups, which was similar to those of other published studies [16,17]. While more patients with Rutherford grade IIb ischemia were considered, CBT attained a better outcome. These results indicated that it might be better to perform CBT initially than CDT. A limitation of CBTs was the inability to use the devices in the small-caliber arteries of the lower limbs; however, it was managed by conjunctive low-dose CDT. Even if adjuvant therapy was possible, and the procedure time tended to be shorter in CDT, CBT seemed to have the advantages of a lower CDT duration and rt-PA dosages than conventional CDT. Several studies have examined whether the risk factors for bleeding risk during CDT are related to the duration and dosages of CDT used [18,19]. Approximately one-half of patients with ALI did not require adjunctive CDT, and the present study supported the major potential advantage of CBT, which, if successful as a stand-alone treatment, obviates the requirement for CDT with a concomitant reduction in the risk of hemorrhagic complications.

One study that compared CDT with or without pharmacomechanical thrombolysis using the AngioJet device showed that CBT increased technical success rates but at the cost of more distal emboli, causing embolization of both large and small particles. Notably, patients treated with CBT in our study also encountered distal emboli events, similar to a published study [20]. It should be noted that a variety of distal embolic protection devices have been developed for carotid artery stenosis and deep vein thrombosis, a situation of minor embolization and less serious consequences [21]. The use of distal embolic protection devices has been considered suitable but not yet advocated in ALI treatments. The mean rt-PA dosage was lower in CBT than in CDT. Although there was no significant difference in the frequency of major complications between the two groups, two cases of major hemorrhage and one death complication were noted in CDT, while no such cases were recorded in CBT. Furthermore, three patients who underwent CBT required calf compartment decompression due to compartment syndrome after reperfusion, which was not recorded in CDT. A possible explanation for this may lie in the differences in ischemia grade at presentation for each group; more patients with Rutherford grade IIb ischemia were present in the primary CBT group, and more ALI patients with Rutherford Ila ischemia were present in the primary CDT group. In addition to the severity of ischemia, another possible explanation may be related to the shorter time taken to achieve reperfusion with CBT compared
with CDT, which may result in massive blood perfusion and exudation [22,23]. The risks of CBT may lead to hyperkalemia, hemoglobinuria, and renal damage [16], but these risks were not recorded in the present study.

Subgroup analysis evaluated within distinct patients showed that three techniques exhibited comparable outcomes in patients with ALI but had different adverse event profiles. There are studies in the literature that evaluate percutaneous aspiration thrombectomy (PAT), Rotarex catheters and AngioJet catheters alone. The PEARL registry study showed AngioJet catheter as a modality for treating ALI, with a technical success rate of 52%, and adjuvant CDT improved this success rate to 83% [16]. Rotarex devices were described with a technical success rate of 68.7% as a stand-alone technique when examined in 147 patients but with additional thrombolysis in 90.5% [24]. Patients with ALI assigned to an initial large-bore catheter and AngioJet catheter tended to have improved technique success rates in the present study and had less need for adjunctive intervention. The rotaex device revealed a lower technical success rate and a greater need for additional CDT due to distal artery emboli. A physiological circulation model study [25] revealed that the Rotarex system had slight advantages, but significantly more thromboemboli and vascular injuries were observed in the Rotarex group; however, the AngioJet was more tissue preserving. Similar to our subgroup analysis, AngioJet had slightly first pass recanalization when compared to Rotarex catheter, and lower distal emboli when compared to large bore catheter in a “real-world” contemporary clinical setting.

As reported by Heller et al. [24], the success of thromboaspiration depends on the relation of the diameter of the catheter used and the diameter of the artery treated. A mismatch between the size of the catheter and arterial diameter may be the main cause of distal emboli, which is more frequent in the above iliac versus the below arteries. One of the potential drawbacks of large-bore catheters and Rotarex catheters is their frequent need for large access sheaths. In the majority of patients, larger access diameters were applied, and the rate of access bleeding and pseudoaneurysm formation remained low in the present study. Several other commercially available CBT devices, such as Penumbra/Indigo and EKOS devices, have been shown to be useful tools for the endovascular approach of ALI. Unfortunately, they were not applied in our study.

Some limitations of the present study should be mentioned. The strategy employed mainly depended on the severity of ischemia and the expertise and facilities of the treating team, and the study was not randomized, which could have resulted in potential selection biases and confounding variables. Although the outcome in the subgroup analysis of PAT with a large-bore catheter and PMT with an AngioJet/Rotarex catheter was conducted, the conclusion was limited to a small subgroup of cases, which may need to be confirmed, and there is a need for future research in this field. Meanwhile, devices such as Penumbra/Indigo had not been utilized in the present study. Therefore, the thromboaspiration device used in the present study was limited to a simple large-bore catheter. Nevertheless, this study hopes to help clinicians choose between approaches for individual patients, but is inevitably hampered by a lack of robust data. The conclusions of the present study are limited due to the small, retrospective
and nonrandomized analysis from a single center. These data may help prompt the design of RCTs that may differ from the guidelines.

**Conclusion**

This study demonstrates that endovascular treatment of ALI with the use of catheter-based therapies is a safe and effective modality that can reduce the requirement for thrombolysis, with expected reductions in hemorrhagic complications. It has a safe and similar clinical outcome to conventional CDT alone but helps to overcome the often encountered shortcomings. Regarding Rutherford IIb ischemia, CBT may be a preferred option over CDT. In terms of CBT modalities, different techniques have comparable efficacy, but have different adverse event profiles. Insufficient data are available to determine a preference for a specific technique among CBTs. Future trials regarding ALI need to be designed carefully, ensuring comparable study groups, and should follow standardized practices of outcome reporting.

**Abbreviations And Acronyms**

ABI, ankle-brachial index; ALI, acute limb ischemia; ESC, European Society of Cardiology; ESVS, European Society for Vascular Surgery; LMWH, Low molecular weight heparin; MALE, Major adverse limb events; PTA, percutaneous transluminal angioplasty; PAT, percutaneous aspiration thrombectomy; RCT, Randomized controlled trial; rt-PA, recombinant tissue plasminogen activator; SFA, superficial femoral artery.

**Declarations**

**Ethical approval and consent to participate** The study protocol was reviewed and approved by the institutional review board (IRB) of the Nanjing First Hospital, Nanjing Medical University (Nanjing, China). In addition, the study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies.

**Consent to publish** Not applicable.

**Availability of data and materials** The datasets generated and analyzed during the current study are not publicly available, as the experimental data are related to other experiments that are progressing but are available from the corresponding author upon reasonable request.

**Competing interests** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The content of the manuscript is original, and it has not been published or accepted for publication.

**Funding** This work was supported by the National Natural Science Foundation of China (8187 1463).
Authors’ contributions MF Gong: contributed to data collection, manuscript writing/editing. X He and BX Zhao: contributed to project development, data collection, data analysis. J Kong: contributed to project development, data collection, data analysis, manuscript editing. JP Gu: contributed to project development. GP Chen: contributed to project development.

References

1. 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.

2. Hess CN, Huang Z, Patel MR, Baumgartner I, Berger JS, Blomster JI, et al. Acute limb ischemia in peripheral artery disease: insights from EUCLID. Circulation. 2019;140:556–65.

3. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. Circulation. 2015;132:1805–15.

4. Korabathina R, Weintraub AR, Price LL, Kapur NK, Kimmelstiel CD, Iafrati MD, et al. Twenty-year analysis of trends in the incidence and in-hospital mortality for lower-extremity arterial thromboembolism. Circulation. 2013;128:115–21.

5. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517–38.

6. Kolte D, Kennedy KF, Shishehbor MH, Mamdani ST, Stangenberg L, Hyder ON, et al. Endovascular versus surgical revascularization for acute limb ischemia: a propensity-score matched analysis. Circ Cardiovasc Interv. 2020 Jan;13(1):e008150.

7. Grip O, Wanhainen A, Michaelsson K, Lindhagen L, Bjorck M. Open or endo-vascular revascularization in the treatment of acute lower limb ischaemia. Br J Surg. 2018;105:1598–606.

8. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T et al Editor’s choice e-2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55: 305 – 68.

9. Davis FM, Albright J, Gallagher KA, Gurm HS, Koenig GC, Schreiber T, et al. Early outcomes following endovascular, open surgical, and hybrid revascularization for lower extremity acute limb ischemia. Ann Vasc Surg. 2018;51:106–12.

10. 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.

11. Lian WS, Das SK, Hu XX, Zhang XJ, Xie XY, Li MQ. Efficacy of intra-arterial catheter-directed thrombolysis for popliteal and infrapopliteal acute limb ischemia. J Vasc Surg. 2020;71(1):141–8.

12. Byrne RM, Taha AG, Avgerinos E, Marone LK, Makaroun MS, Chaer RA. Contemporary outcomes of endovascular interventions for acute limb ischemia. J Vasc Surg. 2014;59:988–95.
13. Rajan DK, Patel NH, Valji K, Cardella JF, Brown DB, Brountzos EN, et al. Quality improvement guidelines for percutaneous management of acute limb ischemia. J Vasc Intervent Radiol. 2009;20:208-18.

14. Tsang JS, Naughton PA, O'Donnell J, Wang TT, Moneley DS, Kelly CJ, et al. Acute limb ischemia in cancer patients: should we surgically intervene? Ann Vasc Surg. 2011;25:954–60.

15. Zehnder T, Birrer M, Do DD, Baumgartner I, Triller J, Nachbur B, et al. Percutaneous catheter thrombus aspiration for acute or subacute arterial occlusion of the legs: how much thrombolysis is needed? Eur J Vasc Endovasc Surg. 2000;20:41–6.

16. Leung DA, Blitz LR, Nelson T, Amin A, Soukas PA, Nanjundappa A, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: results from the PEARL registry. J Endovasc Ther. 2015;22(4):546–57.

17. Kwok CHR, Fleming S, Chan KKC, Tibballs J, Samuelson S, Ferguson J, et al. Aspiration thrombectomy versus conventional catheter-directed thrombolysis as first-line treatment for non-iatrogenic acute lower limb ischemia. J Vasc Interv Radiol. 2018;29:607–13.

18. Kuoppala M, Akeson 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.

19. Lee K, Istl A, Dubois L, DeRose G, Forbes TL, Wiseman D, et al. Fibrinogen level and bleeding risk during catheter-directed thrombolysis using tissue plasminogen activator. Vasc Endovascular Surg. 2015;49:175–9.

20. Kwok CHR, Fleming S, Chan KKC, Tibballs J, Samuelson S, Ferguson J, et al. Aspiration thrombectomy versus conventional catheter-directed thrombolysis as first-line treatment for non-iatrogenic acute lower limb ischemia. J Vasc Interv Radiol. 2018;29:607–13.

21. Harada K, Morioka J, Higa T, Saito T, Fukuyama K. Significance of combining distal filter protection and a guiding catheter with temporary balloon occlusion for carotid artery stenting: clinical results and evaluation of debris capture. Ann Vasc Surg. 2012;26(7):929–36.

22. Funke C, Pfiffner R, Husmann M, Pffmmatter T. The use of the “preclosure” technique for antegrade aspiration thrombectomy with large catheters in acute limb ischemia. Cardiovasc Interv Radiol. 2013;36:377–84.

23. von Keudell AG, Weaver MJ, Appleton PT, Bae DS, Dyer GSM, Heng M, et al. Diagnosis and treatment of acute extremity compartment syndrome. Lancet. 2015;386:1299–310.

24. Heller S, Lubanda JC, Varejka P, Chochola M, Prochazka P, Rucka D, et al. Percutaneous mechanical thrombectomy using Rotarex S device in acute limb ischemia in infrainguinal occlusions. Biomed Res Int 2017; 2017:2362769.

25. Rusch R, Trentmann J, Hummitzsch L, Rusch M, Aludin S, Haneya A, et al. Effectiveness and safety of percutaneous thrombectomy devices: comparison of Rotarex and Angiojet in a physiological circulation model. Eur J Vasc Endovasc Surg. 2020;59(6):983–9.
Table 2. Procedure Characteristics by Treatment Approach and Outcomes

| Characteristics                                                                 | Primary CBT (n=57) | Primary CDT (n=41) | p value |
|---------------------------------------------------------------------------------|-------------------|--------------------|---------|
| Technical success of thrombus/embolus removal                                    |                   |                    |         |
| With primary intervention only                                                  | 24 (42.1)         | 39 (95.1)          | .000    |
| Including adjuvant thrombolysis                                                 | 57 (100)          | 41 (100)           | 1.000   |
| Adjunctive angioplasty/stenting after thrombus/embolus removal                  | 47 (82.5)         | 33 (80.5)          | .804    |
| Duration of operation procedure, h                                              | 1.89±.52          | 1.32±.44           | .000    |
| Total duration of thrombolysis, d                                               | 1.74±.98          | 3.07±1.38          | .000    |
| Rt-PA dose, mg                                                                  | 14.14±5.75        | 29.27±11.70        | .000    |
| ABI scores                                                                      |                   |                    |         |
| Pretreatment                                                                     | .29±.09           | .31±.08            | .747    |
| Treatment completion                                                             | .72±.16           | .66±.13            | .101    |
| Clinical success                                                                 | 56 (98.2)         | 40 (97.6)          | 1.000   |
| Limb salvage at 6 months                                                        | 53 (93.0)         | 37(90.2)           | .625    |
| Limb salvage at 12 months                                                       | 51 (89.5)         | 34 (82.9)          | .346    |
| 30-day complications                                                             | 10 (17.5)         | 14 (34.1)          | .059    |
| Minor (SIR A, B: nominal or no therapy, no consequence)                         | 6 (10.5)          | 11(26.8)           | .036    |
| Major (SIR C, D, E: requires therapy or permanent sequelae)                     | 3 (5.3)           | 2 (4.9)            | 1.000   |
| Major-death (SIR F: death)                                                      | 1 (1.8)           | 1 (2.4)            | 1.000   |
| Procedure- related distal embolization                                           | 14 (24.6)         | 2 (4.9)            | .090    |
| In-hospital length of stay, d                                                   | 4.97±.13          | 6.04±.95           | .000    |

CBT= catheter-based thrombectomy; CDT= catheter-directed thrombolysis.

Continuous data are presented as the means ± standard deviations; categorical data are given as the
Table 1. Demographics, Comorbidities, Presentation and Lesion Characteristics of ALI Patients.

| Characteristic                                           | Primary CBT (n=57) | Primary CDT (n=41) | p value |
|---------------------------------------------------------|--------------------|--------------------|---------|
| Age, y, mean ± SD (range)                               | 68.89±11.88        | 70.63±10.87        | .461    |
| Male sex                                                | 35 (61.4%)         | 25 (61.0%)         | .966    |
| Duration of symptoms at presentation, h, mean ± SD (range) | 37.2±32.8          | 31.0±28.2          | .332    |
| Risk factors                                            |                    |                    |         |
| Diabetes mellitus                                       | 20 (35.1)          | 12 (29.3)          | .545    |
| Coronary artery disease                                 | 19 (33.3)          | 13 (31.7)          | .886    |
| Rheumatic heart disease                                 | 9 (15.8)           | 5 (12.2)           | .616    |
| Previous cerebrovascular accident                       | 7 (12.3)           | 3 (7.3)            | .644    |
| Renal insufficiency                                     | 5 (8.8)            | 3 (7.3)            | 1.00    |
| Hypertension                                            | 38 (66.7)          | 31 (75.6)          | .339    |
| Hyperlipidemia                                          | 18 (31.6)          | 13 (31.7)          | .989    |
| Diagnosed atrial fibrillation                           | 35 (61.4)          | 27 (65.9)          | .652    |
| Current diagnosis of cancer                             | 3 (5.3)            | 1 (2.4)            | .858    |
| History of smoking                                      | 17 (29.8)          | 13 (31.7)          | .842    |
| History of peripheral artery disease                    | 20 (35.1)          | 12 (29.3)          | .545    |
| Thrombosed segment                                      |                    |                    |         |
| Iliac                                                   | 6 (10.5)           | 3 (7.3)            | .851    |
| Iliofemoral (including iliofemoral stents)              | 42 (73.7)          | 24 (58.5)          | .115    |
| Femoropopliteal                                         | 8 (14.0)           | 12 (29.3)          | .065    |
| Crural and Tibial                                        | 0 (0)              | 2 (4.9)            | .173**  |
| Ischemia level (Rutherford category)                    |                    |                    |         |
| I (viable limb)                                         | 1 (1.8)            | 4 (9.8)            | .076    |
| II a (marginally threatened limb)                       | 17 (29.8)          | 26 (63.4)          | .001*   |
| II b (immediately threatened limb)                      | 39 (68.4)          | 11 (26.8)          | .000*   |

ALI=Acute limb ischemia; CBT= Catheter-based thrombectomy; CDT= catheter-directed thrombolysis.

Continuous data are presented as the means ± standard deviations; categorical data are given as the counts (percentage).
*P<.05** Fisher exact.

Includes two patients of thrombus in stents.

Counts (percentages).
**Table 3. Comparisons of Outcomes by Treatment Approach (large bore catheter and Rotarex and AngioJet devices)**

| Characteristic                                      | Large bore catheter | Rotarex catheter | AngioJet catheter | p value |
|-----------------------------------------------------|---------------------|------------------|-------------------|---------|
| Age, y, mean ± SD (range)                           | 69.7±13.2           | 67.6±9.9         | 68.8±11.7         | .862    |
| Sex, male                                           | 17 (60.7)           | 9 (56.3)         | 9 (69.2)          | .768    |
| Duration of symptoms at presentation, h, mean ± SD (range) | 31.2±36.5           | 50.8±30.0        | 36.7±25.8         | .208    |
| Ischemia level (Rutherford category)                |                     |                  |                   |         |
| I (viable limb)                                     | 1 (3.6)             | 0 (0)            | 0 (0)             | .590    |
| II a (marginally threatened limb)                   | 11 (39.3)           | 3 (18.8)         | 3 (23.1)          | .292    |
| II b (immediately threatened limb)                  | 16 (57.1)           | 13 (81.3)        | 10 (76.9)         | .186    |
| Procedure length (h, mean ± SD)                     | 1.74±.54            | 2.03±.53         | 2.04±.38          | .103    |
| Technical and clinical success with initial endovascular procedure only | 13 (46.4)           | 3 (18.8)         | 6 (46.2)          | .157    |
| Total duration of thrombolysis, d                   | .775±.20            | .56±.16          | .61±.22           | .092    |
| rt-PA dosage, mg                                     | 16.67±5.56          | 12.31±5.63       | 12.1±4.88        | .076    |
| In-hospital length of stay, d                       | 5.21±.92            | 4.78±.71         | 4.69±1.18        | .165    |
| ABI scores                                          |                     |                  |                   |         |
| Pre procedure                                        | .30±.11             | .29±.09          | .28±.04           | .743    |
| Treatment completion                                 | .68±.15             | .75 ±.17         | .75 ±.16         | .179    |
| Limb salvage at 6 months                            | 26 (92.9)           | 15 (93.8)        | 12 (92.3)        | .988    |
| Limb salvage at 12 months                           | 25 (89.3)           | 14 (87.5)        | 12 (92.3)        | .915    |
| Procedure-related complications                      |                     |                  |                   |         |
| Minor (SIR A, B: nominal or no therapy, no consequence) | 3 (10.7)             | 2 (12.5)         | 2 (15.4)          | .916    |
| Major (SIR C, D, E: requires therapy or permanent sequelae) | 0 (0)              | 0(0)              | 0 (0)             | -      |
| Major-death (SIR F: death)                          | 0 (0)               | 0 (0)            | 0 (0)             | -      |
| Procedure-related distal embolization               | 6 (21.4)            | 5 (38.5)         | 3 (18.8)          | .430    |

Data are presented as the mean ± standard deviation or number (percentage).
Study Flowchart CBT = catheter-based thrombectomy; CDT = catheter-directed thrombolysis.
Figure 2

Kaplan-Meier estimates of limbs salvage for the CBT and CDT cohort at 12 months. CBT= catheter-based thrombectomy; CDT= catheter-directed thrombolysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.docx