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Improvement of rheolytic thrombectomy for acute deep vein thrombosis of the whole lower limb by primary popliteal vein thrombosis clearance: protocol for a prospective, multicenter, randomized controlled trial (the Reformation study)

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ABSTRACT

Introduction Pharmacomechanical thrombectomy (PMT) can be a useful treatment for restoring vein patency quickly, especially for extensive acute deep vein thrombosis (DVT). However, previous evidence failed to validate the effectiveness of PMT in reducing the incidence of post-thrombotic syndrome (PTS). To address this controversy, the reformation study aims to improve rheolytic thrombectomy for acute DVT of the lower limb through primary popliteal vein thrombosis clearance.

Method and analysis Reformation is a prospective randomised multicentre trial. It has 160 patients in two groups: the modified access group (80 patients) and the traditional access group (80 patients). The purpose of this study is to assess whether the modified access approach for removing inflow thrombus in a one-stage procedure is more effective in enhancing the success rate of the procedure and reducing the incidence of PTS during a 24-month follow-up period, for patients with acute whole limb DVT.

Ethics and dissemination The reformation study has been registered at www.clinicaltrials.gov. The study protocol has been approved by the Institutional Review Board and Human Research Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approved number: KY2021-067-A). The results will be disseminated by publication in a peer-reviewed journal.

Trial registration number NCT05286710.

Protocol version and date V.1.2, 20 August 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, the reformation study is the first randomised controlled trial to determine whether inflow deep vein thrombosis (DVT) burden affects the clinical efficacy of pharmacomechanical thrombectomy (PMT) in patients with extensive DVT over the long term.
⇒ This study will provide high-quality evidence for the clinical application of PMT in the treatment of extensive DVT.
⇒ This study is an evaluator-blind trial. The participants and surgeons cannot be blinded.
⇒ The 24-month follow-up period is not relatively long enough for evaluating the incidence of post-thrombotic syndrome in patients with DVT.

INTRODUCTION

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] VTE is the third most common cardiovascular disease after myocardial infarction and stroke.[2–4] Up to 50% of the patients suffering from DVT will develop post-thrombotic syndrome (PTS), which may be accompanied by major disability.[5 6] The pathophysiologic mechanism of PTS involves the development of venous hypertension and venous valve incompetence. Following DVT, serious PTS, including venous ulcers, develops in up to 10% of patients.[7–9]

The standard strategy for preventing further clot formation and recurrent PE is systemic anticoagulation.[10–12] However, this method cannot eliminate existing thrombus, which can result in PTS and venous valvular insufficiency. In contrast, catheter-directed thrombolysis (CDT) directly infuses thrombolytic agents into the occluded vein, reducing systemic drug exposure and the necessary therapeutic dose. Current evidence supports the utility of endovascular methods, which may be useful for patients who have

severe symptoms, extensive DVT, high physiologic reserve and long-life expectancy, low bleeding risk and who do not respond well to initial oral anticoagulation therapy, particularly within the acute time frame of 2–4 weeks after symptom onset.[10–13] Although there are certain benefits associated with CDT, recent trials such as Acute Venous Thrombolysis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) and ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation (CAVA) have not been able to confirm them. Moreover, CDT has a relatively longer infusion time, ranging from 8 to 87 hours, which increases the risk of major bleeding during the procedure.[14–16]

Pharmacomechanical thrombectomy (PMT) is an alternative method to remove acute DVT.[17] The AngioJet rheolytic thrombectomy system is one of the most widely used PMT catheters.[18] The system uses high-pressure saline or thrombolytic agent jets to create a pressure gradient based on the Bernoulli effect, which fragments and aspirates the thrombus. Previous comparative case series studies show that PMT has demonstrated potential benefits compared with CDT alone, including lower doses of thrombolytic agents and shorter infusion times. This results in a reduced risk of haemorrhagic events and, in turn, less use of hospital resources.[19]

Moreover, owing to newly modified approaches, it is now possible to eliminate DVT in all segments simultaneously. Our previous study demonstrated that using a contralateral femoral vein or tibial vein for one-stage inflow DVT removal resulted in a significantly higher rate of thrombus clearance in a single session compared with the traditional ipsilateral popliteal venous approach.[20] Furthermore, patients who required further CDT and PTS treatment at the 2-year follow-up were significantly lower in the modified access group. However, a study conducted by Jeyabalan *et al* revealed that inflow thrombosis did not affect the outcomes of thrombolysis in patients with popliteal and tibial clots who underwent PMT from thrombosed popliteal vein (PV) access. After treatment, 90% of the patients regained patency of the popliteal vein, but more than 60% of the patients needed additional treatment after PMT.[21]

It is uncertain whether removing inflow venous thrombus from the tibial and distal popliteal areas would improve venous drainage, maintain patency and reduce venous reflux. Although these results are promising, there is still no conclusive evidence from multicentre randomised controlled trials (RCTs) to support them. Therefore, we have initiated the reformation study to address this controversy by improving rheolytic thrombectomy for acute DVT of the lower limb through primary popliteal vein thrombosis clearance.

METHODS

Study objective

The primary study objective is to determine whether removing blood clots in the distal popliteal vein using a modified approach can reduce the incidence of PTS over a 24-month follow-up period in patients with extensive acute DVT involving the iliac and femoropopliteal veins when compared with performing PMT through the traditional approach of the ipsilateral popliteal vein. Secondary objectives include: (a) patency rate immediately after lonely mechanical thrombectomy, (b) total time of interventional surgery (including duration of subsequent CDT), (c) total dosage of urokinase used for the procedure, (d) patency rate of lower limb vein at postinterventional 12 and 24 months, (e) deep venous valve function evaluation by ultrasound at postinterventional 12 and 24 months, (f) quality of life (QOL) score evaluated by 36-Item Short Form Health Survey (SF-36), venous insufficiency epidemiological and economic study quality of life (VEINES-QOL) score, and European quality of life 5-dimension 5-level (EQ-5D-5L) score at postinterventional 3, 6, 12 and 24 months, (g) re-intervention rate within 24 months after operation and (h) treatment rate of CDT after mechanical thrombectomy.

The safety outcomes include procedural complications such as haematoma at the puncture site, haemoglobinuria or haemolytic jaundice. The major bleeding events according to the International Society on Thrombosis and Haemostasis and all-cause death will also be recorded during the follow-up period.[22]

Study design

Reformation is an ongoing, multicentre, randomised, open-label, two-arm controlled trial sponsored by Boston Scientific. The study design, execution and data analysis are independent of the sponsor. 160 patients will be recruited from and randomised at nine participating hospitals in China. The study started in September 2022 and is planned to end in December 2027. The study protocol has been approved by the Institutional Review Board and Human Research Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approved number: KY2021-067-A). All participants will provide written informed consent before enrolment. Patients will be randomly allocated in a 1:1 ratio by central stratification and block randomisation method to receive either modified or traditional PMT treatment. The patients flow diagram is shown in figure 1. The statistical analyst of this study generates the random allocation table through SAS software. The block length and random allocation table of each centre will be kept blind and not be opened during the whole study period. The study was overseen by an independent Data Safety Monitoring Board and was conducted in accordance with Good Clinical Practices.

Patient and public involvement

No patient or public involvement.

Patient population

To be eligible for inclusion, patients must be between 18 and 80 years old and have a first-time symptomatic DVT

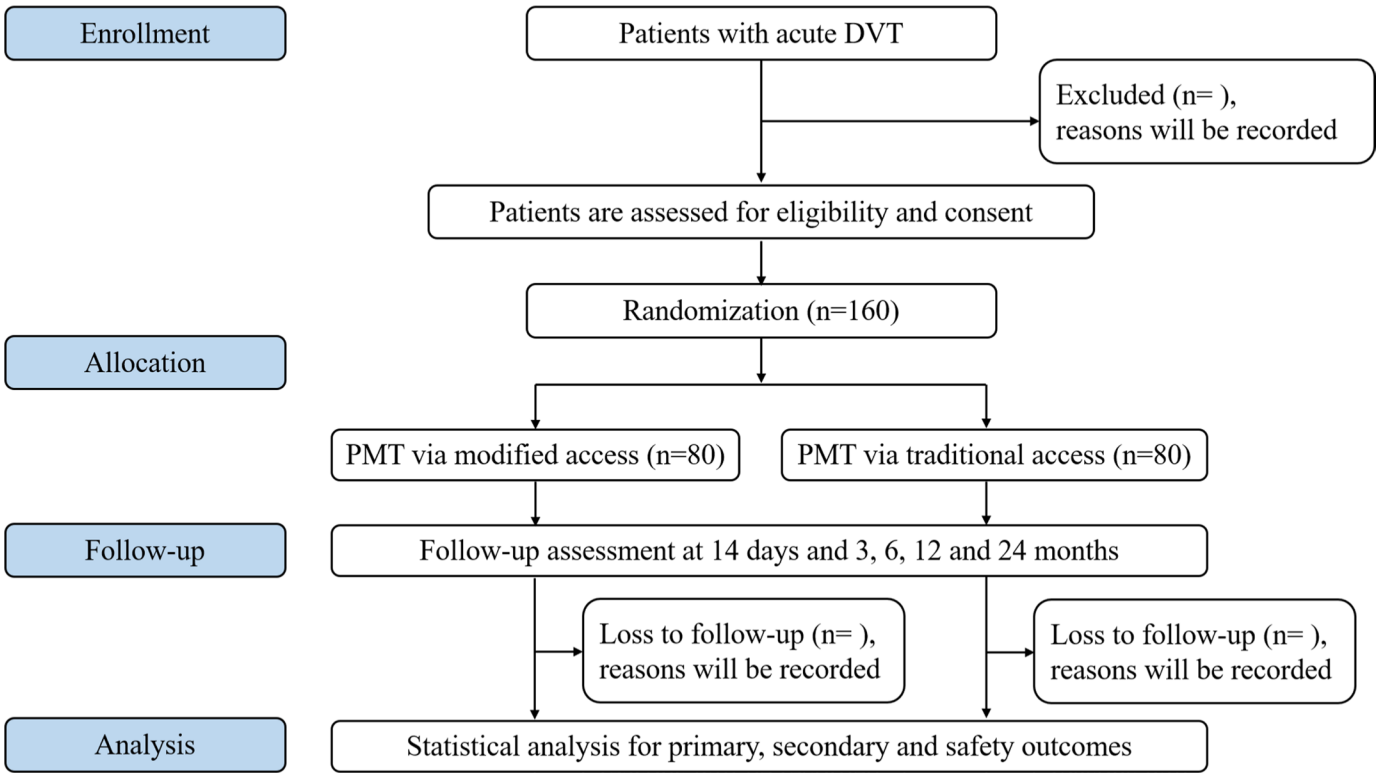

Figure 1 Patients flow diagram. DVT, deep vein thrombosis; PMT, pharmacomechanical thrombectomy.

involving the iliac and femoropopliteal vein, verified by compression ultrasonography or venography. The study aims to recruit a total of 160 individuals with entire-limb acute DVT. Out of these, 80 participants will be treated with PMT via the contralateral femoral vein, jugular vein or ipsilateral tibial vein, which is referred to as the modified access group. The remaining 80 participants will be treated with PMT via the ipsilateral popliteal vein, which is referred to as the traditional access group.

Inclusion criteria

1. Age between 18 and 80 years old.
2. Acute DVT occurred less than 14 days from the onset of the disease.
3. DVT with thrombosis involving the iliac vein, common femoral vein, distal popliteal vein and/or calf vein.
4. The patient must have signed an informed consent form.

Exclusion criteria

1. Patients with a history of DVT in the same lower limb.
2. Plasma creatinine level greater than 180 µmol/L.
3. Patients who are contraindicated for thrombolysis treatment.
4. Patients with thrombosis in inferior vena cava.
5. Patients who have a known allergy to heparin, low molecular weight heparin or contrast agent.
6. Patients who have participated in a clinical trial within the past 3 months.
7. Women who are pregnant or in lactation.
8. Patients with other diseases that may interfere with the study or significantly reduce their life expectancy (less than 2 years).
9. Patients with autoimmune thrombopathy or thrombocytopenia (platelets $<80\times10^{9}$/L).
10. Patients who are unwilling or unable to participate in the study.

Conduct of the study

Patients who meet the inclusion criteria and do not have any exclusion criteria will be invited to participate in this study. Once they provide written informed consent, they will be randomly assigned to receive PMT treatment through either modified or traditional access. Anticoagulation will begin with full therapeutic anticoagulation with two times per day weight-based low molecular weight heparin (LMWH) for at least 8 hours, followed by oral anticoagulation therapy for at least 6 months. The oral anticoagulation therapy will be administered through new oral anticoagulants or warfarin (maintaining international normalized ratio (INR) between 2 and 3). Warfarin will only be used in patients (such as patients with antiphospholipid syndrome) who are not recommended for new oral anticoagulants. The individual duration of anticoagulation is determined by the risk factors of DVT according to guidelines.[10 11] Patients with persistent risk factors or unprovoked DVT will continue anticoagulation therapy after 6 months. For patients taking edoxaban, LMWH will be used for at least 5 days. For patients taking warfarin, LMWH will be used until INR reaches 2–3.

Additional antithrombotic agents such as aspirin will not be routinely used for DVT or stenting. However, patients with prior coronary disease who are previously taking antiplatelet will continue and receive a single antiplatelet agent. Phlebotonics such as diosmine and calcium dobesilate are allowed, and the dosage will be recorded in Clinical Research Form tables. 30–40 mm Hg, thigh-length and sized-to-fit elastic compression stockings will be used at (10±3) days after interventions as a standard adjunctive treatment, daily for 24 months.

PMT procedure

All endovascular treatments will be done using local anaesthesia. Preprocedure and postprocedure venography from a dorsal foot vein will be conducted to assign a thrombus score to each of the six venous segments (common iliac, external iliac, common femoral, proximal superficial femoral, distal superficial femoral and popliteal veins) according to the following criteria: complete occlusion of the venous segment was given a score of 3, substantial occlusion (50%–99%) of the venous segment was given a score of 2, partial occlusion (0–50%) of the venous segment was given a score of 1 and a patent venous segment was given a score of 0. Thrombus scores were totalled for each enrolled patient with the potential range of 0–18. The degree of thrombus removal was graded by calculating the percentage reduction in the patient's total thrombus score.[23]

During the PMT procedure, it is recommended to use a retrievable inferior vena cava filter (IVCF) that should be removed 14–21 days after treatment. To establish venous access, ultrasound or venography guidance will be used. For the modified approach, the decision to use contralateral femoral vein, jugular vein or ipsilateral tibial vein access will be at the discretion of the operating interventionist. For the traditional approach, the ipsilateral popliteal venous access will be obtained. Pulse spray thrombolysis using the 6F Angiojet device will initially be employed to treat the occluded veins, with a maximum of 250 000 UI Urokinase administered. After a 15-min dwell time, the Angiojet catheter will be used to eliminate residual thrombus, by employing the standard mechanical aspiration thrombectomy technique. CDT will be used selectively as needed for residual thrombus, using a multiple-side hole catheter (Angiodynamic, USA), with the maximum allowable CDT duration being 72 hours. During the CDT procedure, haemostasis will be monitored by analysing haemoglobin, fibrinogen, D-dimer, INR and platelet counts three times a day. The dose of urokinase will be adjusted according to the result of fibrinogen. The effect of treatment will be assessed daily by venography, and percutaneous balloon angioplasty (PTA) will be performed if the stenosis of the iliac vein diameter is greater than 50%. A stent will be placed if the residual stenosis exceeds 50% after PTA treatment.

Outcome evaluation

After their intervention, patients will have follow-up at scheduled 14±7 days, 12 months and 24 months after their intervention. At the 14±7 day follow-up, venography will be conducted to evaluate the technical success rate during their return for IVCF removal. At each visit, physicians who are not familiar with the patient's history will conduct a clinical evaluation and a duplex ultrasound (DUS) assessment of the affected lower limb. Additionally, a telephone interview will be conducted 3, 6 and 18 months after the intervention (table 1).

The clinical evaluation of the patient's status includes the clinical-etiologic-anatomic-pathophysiologic (CEAP) classification of chronic venous disease and the PTS scale using Villalta score. PTS was defined and graded by the Villalta scale as follows: 0–4 (no PTS), 5–9 (mild PTS),

Table 1 Enrolment, intervention and follow-up schedule

	Enrolment (Day −1)	Allocation (Day 0)	Follow-up (14 days)	Follow-up (3 months)	Follow-up (6 months)	Follow-up (12 months)	Follow-up (24 months)
Eligibility screen	×						
Informed consent	×						
Allocation		×					
Venography		×	×				
Clinical evaluation						×	×
CEAP classification						×	×
PTS scale by Villalta score						×	×
Duplex ultrasound assessment						×	×
Venous patency						×	×
Deep venous valve function						×	×
EQ-5D-5L score				×	×	×	×
QOL score				×	×	×	×
VEINES/QOL score				×	×	×	×

CEAP, clinical-etiologic-anatomic-pathophysiologic; EQ-5D-5L, European quality of life 5-dimension 5-level; PTS, post-thrombotic syndrome; QOL, quality of life; VEINES-QOL, venous insufficiency epidemiological and economic study quality of life.

10–14 (moderate PTS) and ≥15 or presence of venous ulcer (severe PTS). Health-related quality of life is evaluated using the generic questionnaire EQ-5D-5L, QOL and the disease-specific VEINES/QOL scores.

The venous flow, compressibility and insufficiency will be evaluated by DUS. Venous flow can be categorised as spontaneous, forced (when peripheral compression is applied) or absent. Iliac-femoral-popliteal vein patency is defined as the following findings: flow in the pelvic, femoral and popliteal vein, compressibility of the femoral and popliteal vein and no functional venous obstruction at any level. The patency of the iliac vein will be preliminarily assessed by DUS and confirmed by CT angiography or antegrade venography for patients with suspected obstruction. To assess insufficiency, the patient is examined while standing, and reflux is identified as a reversal of the velocity curve that lasts for more than 0.5 s following distal pneumatic decompression.

Sample size determination

According to the results of previous studies and literature review, the sample size is calculated based on the incidence of PTS evaluated by Villalta score. Assuming that the incidence of PTS in the test group is 16.7% and 38.2% in the control group,[20] at the α level of 0.05 and the power of 0.8, 64 patients will be included in each group calculated by PASS V.15.0 software. Considering the 20% abscission rate, 80 participants will be included in each group. Finally, 160 patients will be included in the study.

Statistical analysis

Continuous data will be presented as means and SD if normally distributed, while categorical data will be presented as numbers and percentages. Dichotomous variables between groups will be compared by a two-sided χ^2 test or Fisher's exact test, and continuous variables will be compared using a two-sided t-test. Univariate and multivariate analyses will be performed by logistic regression analysis. P value <0.05 is considered to be statistically significant. Statistical analysis will be performed with SPSS V.21.0. Subgroup analysis will be performed for whether there is a thrombus in tibial/calf veins and patients with different anticoagulants.

DISCUSSION

Patients with an extensive thrombus burden, which extends from the iliofemoral to the distal popliteal or tibial veins, are at a higher risk of developing phlegmasia compared with those with proximal iliofemoral DVT. This risk is due to insufficient collateral venous drainage, particularly at the important confluence of veins at both the popliteal and common femoral zones. A larger thrombus burden is associated with a more severe clinical presentation and a greater propensity for PTS.[24] PMT may be more effective for rapidly restoring vein patency, quality of life and clinical scores. However, the recently published and the largest ATTRACT trial did not validate these improvements. In the ATTRACT study, there was no difference in PTS incidence or QOL at 2 years between those randomised to PMT plus anticoagulation and those receiving anticoagulation alone. Furthermore, PMT led to statistically significantly more major bleeding compared with the anticoagulation group (1.7% vs 0.3%, p=0.049%).[14] The ATTRACT trial failed to identify the benefits of PMT, possibly due to the inclusion of femoropopliteal DVT along with the more extensive iliofemoral DVTs, which may have diluted the potential outcomes. However, it is worth noting that in patients with extensive DVT, positive endovascular treatment can yield greater benefits compared with those with femoropopliteal disease alone. This observation is supported by the subgroup analysis of the ATTRACT study conducted by Comerota *et al*[15] The study demonstrated that PMT significantly reduced early leg symptoms in patients with acute iliofemoral DVT. Over a 24-month period, it also reduced PTS severity scores, decreased the proportion of patients who developed moderate or severe PTS and resulted in greater improvement in venous disease-specific QOL. Furthermore, according to the guidelines for the choice of initial PMT technique in the ATTRACT study, physicians were required to use 'infusion-first PMT' for subjects with poor popliteal vein inflow. This technique started with recombinant tissue plasminogen activator (rt-PA) infusion through a multiside hole catheter for ≤30 hours. However, there were no stratified data available for the number of patients who underwent initial CDT due to occluded PV, which could prolong the duration of intervention and increase the risk of bleeding complications caused by more doses of thrombolytic drugs.

Based on the reasons mentioned above, we therefore hypothesise that the advantages of PMT will be more significant if we limit the enrolment of patients to those with proximal DVT. Additionally, for individuals with femoropopliteal DVT that extends to the iliofemoral zone, rapid thrombus removal in a single procedure session using a modified approach could further reduce the incidence of CDT and preserve the function of the venous valve.

The routine use of IVCF in patients undergoing PMT and/or CDT is still controversial in clinical practice. Lee *et al* suggested that IVCF placement should be considered as a preventive measure against life-threatening PE.[25] Conversely, Avgerinos *et al* advocated for a more selective approach, recommending IVCF use primarily for patients with preoperative clinical PE, female patients, patients with multiple DVT risk factors or single PMT treatment.[26] In this study, patients may have a high risk of clinical PE during PMT procedures due to the substantial thrombus burden. Furthermore, the majority of patients may receive single PMT treatment in our previous study.[20 27] Thus, we recommend using retrievable IVCF and retrieving at 14–21 days after the intervention.

It is crucial to understand the impact of inflow DVT on the outcome of PMT in extensive DVT. To our knowledge, the reformation study is the first RCT that has been

implemented to evaluate the clinical effectiveness of removing inflow DVT in a single stage during the endovascular treatment of patients with extensive acute DVT. Due to the COVID-19 pandemic, the trial was delayed for 1 year. Currently, 21 patients have been recruited in this study, and nine hospitals have participated. With the current study, it is possible to achieve the necessary number of patients (n=160) within a reasonable timeframe.

Based on the analysis of previous studies, our primary outcome is to measure the proportion of patients who develop PTS in a 2-year period. We will also evaluate the patency rate after treatment, Villalta score for diagnosing PTS and CEAP classification for clinical situations as secondary outcomes. Additionally, we will use EQ-5D-5L, QOL and VEINES-QOL score to measure the general and disease-specific health-related quality of life. To reduce the potential for bias in an open-label study design, the evaluating physician will be blinded to the patient's history and treatment allocation during the end-point assessment. Additionally, all patients will be explicitly instructed not to disclose their treatment allocation while they are hospitalised.

CONCLUSION

In conclusion, the reformation study is the first RCT that aims to determine the long-term clinical impact of inflow DVT burden on the clinical efficacy of PMT in patients with extensive DVT. The results of this study will be valuable for determining the appropriate treatment for patients with extensive DVT.

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