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Effects of Intravenous and Catheter Directed Thrombolytic Therapy with Recombinant Tissue Plasminogen Activator (Alteplase) in Non-Traumatic Acute Limb Ischemia; A Randomized Double-Blind Clinical Trial

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ABSTRACT

Objective: To evaluate the efficacy and safety of intravenous and catheter directed thrombolysis by recombinant tissue plasminogen activator (Alteplase) in the patients with non-traumatic acute limb ischemia (ALI).
Methods: This was a randomized clinical trial being performed between 2009 and 2011 in Mashhad University of Medical Sciences. We included those patients who were<75 years, with symptoms of less than 14 days duration, ALI of grade IIa and IIb (according to Rutherford classification) and absence of distal run off. Baseline assessment of peripheral circulation performed in all the patients. Patients were randomly assigned to undergo intravenous (n=18) or catheter directed thrombolysis (n=20) with Alteplase. The primary endpoint of the study was improvement of clinical status measured by Rutherford classification, ankle brachial index (ABI), visual analogue scale (VAS) score measured at 1, 3 and 6 months. The secondary endpoint of the study was complete or near complete recanalization of the occluded artery.
Results: A total number of 38 patients with mean age of 54.13±13.5 years were included in the study. There were 23 (60.5%) men and 15 (39.5%) women among the patients. Overall 3 (7.9%) patients had upper and 35 (92.1%) lower extremity ischemia. There was no significant difference between two study groups. None of the patients experienced major therapeutic side effects. Both ABI and VAS score improved in patients who have received first dose of t-PA within 24-hourof ALI. There was no significant difference between two study groups regarding the 6-month clinical grade (p=0.088), VAS score (p=0.316) and ABI (p=0.360). The angiographic improvement was significantly higher in CDT group (p<0.001).
Conclusion: Intravenous and catheter directed thrombolysis with t-PA is a safe and effective method in treatment of acute arteriolar ischemia of extremities. However there both intravenous thrombolysis and CDT are comparable regarding the clinical outcome.
Clinical Trial Registry: The current study is registered with Iranian Registry for Clinical Trials (www.irct.ir; IRCT2014100719427N1)

Keywords: EThrombolytic therapy; Tissue plasminogen activator (t-PA); Acute limb ischemia; Catheter-directed thrombolysis; Intravenous thrombolysis; Alteplase.

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Introduction

Acute limb ischemia (ALI) is a life-threatening condition, defined as sudden decrease in limb perfusion resulting in a potential threat to the viability of the limb. ALI is considered an event occurring less than 14 days from presentation [1-3]. The hospital admissions due to ALI has increased significantly from 60.3 to 94.3 per 100,000 of the population between 2000 and 2011, with an average annual increase of 6.2% since 2003 in England [4]. In United States, however, the incidence of hospitalization for ALI decreased from 45.7 per 100,000 to 26.0 per 100,000 population between 1998 and 2009 [5]. Symptoms progress over a period of hours to days, pain in the extremity at rest, paresthesia, muscle weakness, and paralysis [1]. The classical "6 Ps" are the typical presentation of the patients with ALI: paresthesia, pain, pallor, paralysis, poikilothermia, and pulselessness [6]. Non-traumatic causes of ALI include acute thrombotic occlusion of a pre-existing stenotic artery, and embolism from the heart or a diseased artery [7]. The clinical status of the patients and the physical findings of the affected limb are of great importance in planning the treatment. Rutherford *et al*., [6] proposed a classification which is the most commonly used method to describe ALI. According to the Rutherford classification, ALI is categorized into three major grades: Patients with viable limbs (grade I), do not require emergent intervention. It is reasonable to admit, start anticoagulation, continue clinical evaluation, and considering treatment urgently but not emergently [6]. Catheter-directed thrombolysis (CDT) is indicated urgently for patients with marginally threatened (grade IIa) limbs, if there is no contraindication. Patients with immediately threatened limbs (grade IIb) require emergent operation to salvage the limb [6]. However, improved endovascular techniques have made it possible to perform endovascular interventions in this group of patients [7-11]. Thrombolysis may be the best option when the risk of general anesthesia outweighs the risk of delay in reperfusion. Primary amputation is the only option for limb salvage in patients with irreversible ischemia (grade III) [6].

Catheter-directed thrombolysis (CDT) has been shown to be an effective armamentarium to salvage the ischemic limb resulting from acute embolism and acute thrombosis of native artery. However bleeding complication is a major problem of this treatment. Although CDT is usually applied for ALI patients with ischemic symptom onset less than 14 days, it also provides technical success for those with the symptom onset between the second and the sixth weeks [12-14]. CDT is reserved for patients with non-life-threatening ALI due to occlusion of less than 14 days duration, and patients with thrombosis of more than 30 days duration are unlikely to respond to local fibrinolysis [13,14]. Several pharmacologic regimens have been used. Each agent facilitates thrombolysis by converting plasminogen to plasmin, which then degrades fibrin and fibrinogen to their fragmented byproducts [1,11]. Streptokinase was once the most commonly used thrombolytic agent which has been replaced by urokinase, and recombinant t-PAs [15]. Direct delivery of a thrombolytic agent to the desired location has been associated with greater success than systemic lytic therapy [8,12-14]. As there is still controversy on this issue, the current study was designed to evaluate the efficacy and safety of intravenous and catheter directed thrombolysis by recombinant tissue plasminogen activator (Alteplase) in the patients with non-traumatic ALI.

Materials and Methods

Study Population

This was a randomized single blind clinical trial being performed between October 2009 and December 2011 in emergency departments of Imam Reza and Ghaem hospitals, both tertiary healthcare centers affiliated with Mashhad University of Medical Sciences, Mashhad, Iran.We included consecutively presenting patients with initial diagnosis of acute limb ischemia.The inclusion criteria was age of less than 75 years, symptoms of less than 14 days duration, ALI of grade IIa and IIb according to the Rutherford classification (Table 1) [6], and absence of distal run off in angiography before the intervention. The exclusion criteria were severe anemia (Hb<8gr/dl), thrombocytopenia (platelet<80000/µl), low serum fibrinogen (fibrinogen<100mg/dL), sever hypertension (systolic>160mmHg, diastolic>100mmHg), trauma or surgery within the previous 14 days before intervention, history of subarachnoid hemorrhage, life expectancy of less than 14 months, major internal bleeding less than 6 months before intervention, pregnancy, and

Table 1. Clinical grades of acute limb ischemia according to the Rutherford classification [6].

Category	Description	Findings		Doppler signals	
		Sensory loss	Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
II. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

lumbar puncture 2 weeks before intervention. The study protocol was approved by both institutional review boards (IRB) and medical ethics committee of Mashhad University of Medical Sciences. All the patients gave written informed consent before inclusion to the study. The study protocol was also registered with Iranian registry for clinical trials (IRCT2014100719427N1; www.irct.ir).

Study Protocol

The baseline characteristics of the patients including demographic information, risk factors, clinical presentation, drug history, and imaging studies were recorded. Baseline assessment of peripheral circulation was performed in all the patients. The assessment included grading of acute limb ischemia according to the Rutherford classification, measurement of the ankle-brachial index (ABI), scoring the pain severity according to the visual analogue scale (VAS) and limb angiography.The patients were randomly assigned to two study groups using a computer-based random digit generator. The first group was treated with systemic intravenous alteplase (Activase®, Genentech, Inc., San Francisco, USA) and the other treated through CDT and with intra-arterial alteplase (Activase®, Genentech, Inc., San Francisco, USA) administration. The first group was treated intravenously with 0.6 mg/kg (with an upper limit of 50 mg) of alteplase. Of the total dose, 20% was administrated as a bolus, and the remainder was given through intravenous infusion over a period of 2 hours. A same administration was done a day after initial dose, if there was an improvement in peripheral circulation assessment parameters. Post intervention angiography was not performed in this group. Patients in the CDT group were transferred to angiography room. First, a guide wire passed through the occlusion and then a side-hole catheter was imbedded into the occluded artery. The length of catheter which had side holes were fitted with the length of occlusion. CDT with Alteplase was done with infusion rate of 0.05mg/kg/hr. First, 5 mg of alteplase was administrated as a bolus and the remainder was given in divided doses every 2 hours over a period of 24 hours. A similar dosage of alteplase was given a day after initial dose, if an improvement was seen in peripheral circulation assessment parameters. After completion of thrombolysis regimen, all the patients were transferred to surgical intensive care unit. The patients' clinical status was closely monitored for the first 24 hours and daily prothrombin time (PT), prothromboplastin time (PTT), hemoglobin (Hb), and fibrinogen were measured. Patients were discharged from hospital after completing the thrombolysis treatment and the required care. They were followed for 6 months after the thrombolysis therapy. The interventionists and the patients were not blinded to the route of therapy. However those recording the outcome and measuring the indices were blinded to the study groups.

The patency and clinical outcome were measured according to the Rutherford classification, ABI and VAS scale. Adverse events related to the intervention including hemorrhage, hematoma, and hypersensitivity reaction were recorded. Adverse events were categorized as major and minor. Adverse events were considered major if the patient required infusion of pack cell or accompanied with a disability for the patient and the others were considered minor. The primary endpoint of the study was improvement of clinical status, defined as upward shift of at least one grade in Rutherford grading of the patient, improvement of ABI (≥0.1), and upward shift of at least 2 scores in VAS. The secondary endpoint of the study was complete or near complete recanalization of the occluded artery in angiography.

Statistical Analysis

All the statistical analysis was performed using statistical package for social sciences (SPSS Inc., Chicago, USA) version 16.0. All the data are presented as mean±SD or proportions as appropriate. The parametric data was compared between two study groups using independent t-test while paired t-test was used for comparing the results within the groups. Proportions were compared using chi-square test. A two-sided p-value of less that 0.05 was considered statistically significant.

Results

Overall we included 40 patients with ALI, out of whom 2 were excluded from the study. Thus 38 patients were assigned to undergo intravenous (n=18) or CDT (n=20). All the patients finished the study and thus the number of the patients for final analysis was 38 (Figure 1).

The mean age of the patients was 54.13±13.5 (ranging from 20 to 75) years. There were 23 (60.5%) men and 15 (39.5%) women among the patients. Only 3 (7.9%) patients had upper limb ischemia while 35 (92.1%) had lower extremity ischemia. The cause of ALI in 34 (89.4%) patients was found to be thrombosis while 4 (10.6%) patients were diagnosed to suffer from embolism from another source. The baseline characteristics of the patients are summarized in Table 2. There was no significant difference between two study groups regarding the baseline characteristics.

The patients' outcome in two study groups is demonstrated in Table 3. Overall 10 (26.3%) patients underwent limb amputations due to severe ischemia. There was no significant difference between two study groups regarding the incidence of limb amputations (p=0.096). None of the patients experienced major therapeutic side effects including extensive hematoma or emergency of pack cell injection while 4 (10.5%) experienced minor side effects, all in CTD group. However there was no

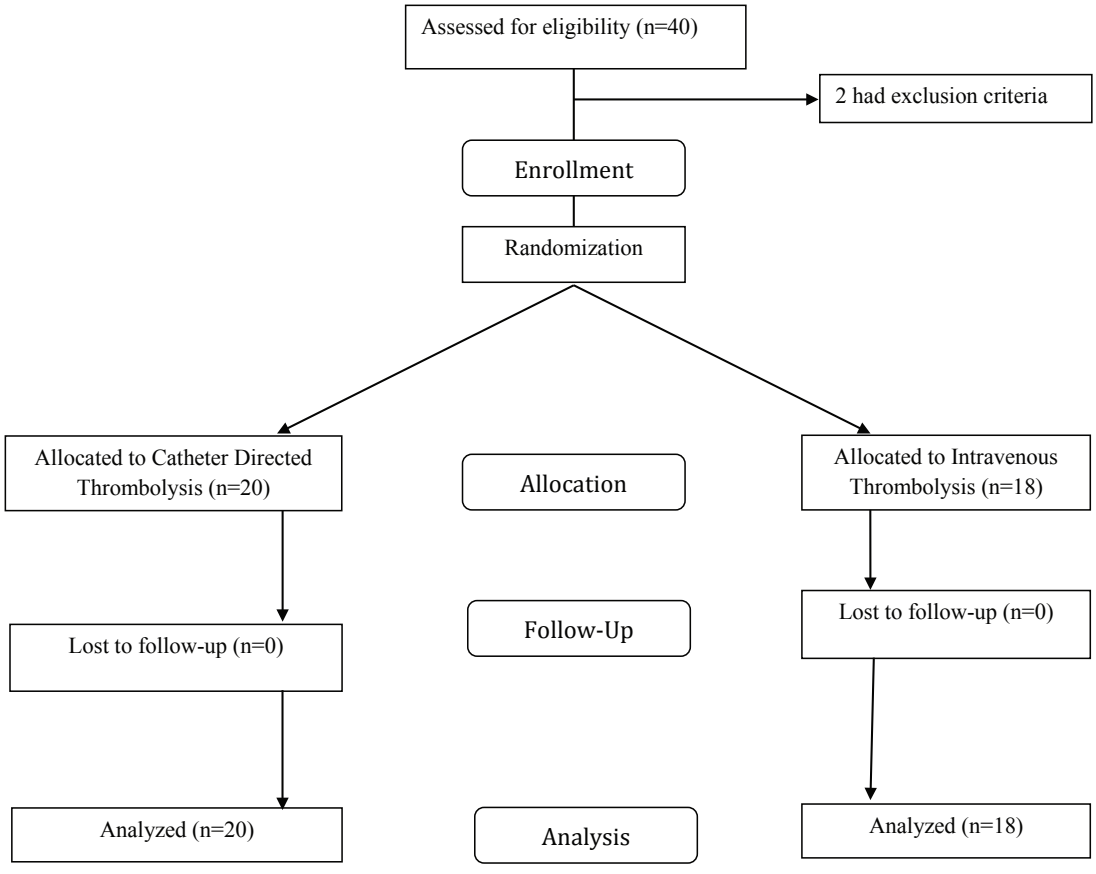

Fig. 1. CONSORT flow diagram of the study.

Table 2. Baseline characteristics of 38 patients with acute limb ischemia undergoing intravenous (n=18) or catheter directed thrombolysis (n=20) with alteplase.

	Catheter directed thrombolysis (n=40)	**Intravenous thrombolysis (n=38)**	***p* value**
Age (years)	55.52±16.05	88.55±9.98	0.442
Sex			
Men (%)	14 (36.84%)	9(23.96%)	0.944
Women (%)	11 (28.94%)	4 (10.52%)	0.932
Duration of symptoms (days)	5.45±3.95	6.38±2.99	0.419
Affected limb			
Upper (%)	2 (5.26%)	1 (2.63%)	0.608
Lower(%)	18 (47.36%)	17 (44.74%)	0.618
Cause			
Thrombosis(%)	17 (44.74%)	17 (44.74%)	0.332
Emboli (%)	3 (7.89%)	1 (2.63%)	0.350
Risk factors			
Hypertension (%)	10 (25%)	8 (22%)	0.998
DM[a] (%)	13 (35%)	12 (33.6%)	0.914
Smoking (%)	4 (20%)	4(22.2%)	0.867
IHD[b] (%)	7 (17%)	8 (22%)	0.934
Anticoagulation (%)	5 (15%)	6 (16.7%)	0.993
Rutherford grade			
I (n)	0 (0%)	0 (0%)	
IIa (n)	14 (36.84%)	12 (33.6%)	0.825
IIb (n)	6 (16.7%)	6 (16.7%)	
III (n)	0 (0%)	0 (0%)	
ABI[c]	0.0725±0.13	0.0533±0.08	0.360

[a]DM: Diabetes Mellitus;[b]IHD: Ischemic heart disease; [c]ABI: Ankle-brachial index.

Table 3. Outcome of 38 patients with acute limb ischemia undergoing intravenous (n=18) or catheter directed thrombolysis (n=20) with alteplase in 6-month follow-up.

	Catheter directed thrombolysis (n=20)	Intravenous thrombolysis (n=18)	*p* value
Amputation			
Forefoot (%)	0 (0%)	1 (2.6%)	0.096
Below knee (%)	0 (0%)	3 (16.66%)	
Ankle (%)	4 (20%)	2 (11.11%)	
Rutherford grade			
I (n)	10 (50%)	5 (27.7%)	0.088
IIa (n)	3 (15%)	7 (38.8%)	
IIb (n)	3 (15%)	0 (0%)	
III (n)	4 (20%)	6 (33.5%)	
Side effects (%)	4 (20%)	0 (0%)	0.107
ABI changes	0.0725±0.13	0.0533±0.08	0.360
Angiographic changes (%)	11 (55%)	1(5.55%)	<0.001
VAS[a] score	0.8±2.23	1.33±1.41	0.392

[a]VAS: Visual analogue scale

significant difference between two study groups regarding the frequency of side effects (p=0.017). Those who underwent CDT had significantly higher rate of angiographic improvement of thrombosis when compared to intravenous thrombolysis groups (p<0.001). Although the ABI increased in both study groups after 6 months, there was no significant difference between two study groups regarding the ABI (p=0.360). The VAS decreased significantly in both study groups after 6 months; however both study groups were comparable regarding the VAS score (p=0.316).

Discussion

Acute ischemia of lower extremities is among the causes of disability and in some circumstances mortality in developing and developed countries [7]. There are several guidelines for management of ALI such as the 2005 ACC/AHA guidelines on peripheral artery disease [16] and the 2012 American College of Chest Physician guidelines on antithrombotic therapy for peripheral artery disease [17]. These guidelines conclude that that CDT is effective and beneficial and is indicated in a subgroup of patients with ALI--patients in whom the signs do not dictate urgent time-critical intervention to avert immediate limb death. These recommendations were based on two randomized trials, the STILE [18] and TOPAS [19] trials, which compared thrombolysis and surgery.The application of endovascular method in treatment of the ALI has recently driven more attraction [20-23].

Tissue plasminogen activator (t-PA) is a drug with epithelial cell origin, so associated with less antigenicity. ABI and toe-pressure test have been both valuable and trusty in evaluation of extremity ischemia. In a study by Brothwayte and co-workers, bolus dose injection of t-PA has been reported as greatly valuable in acute arteriolar ischemia of extremities [24]. In a study by Nilson in Sweden, t-PA therapy has been reported as successful with 40% cases of acute arteriolar ischemia [25]. Pulse spry thrombolysis therapy in acute arteriolar ischemia has been introduced and reported as safe and effective [8]. Positive effects of high dose bolus therapy on obstructive ischemia of femoral artery, has been shown to be effective [26]. In the current study we compared that clinical and angiographic outcome of patients with ALI undergoing thrombolysis via intravenous route or CDT. We found that the clinical outcome as well as complication rate was comparable between two routs of t-PA administration. Most of the studies being performed till now have compared the outcome between surgery and CDT and data comparing the outcome between intravenous thrombolysis and CTD is scarce. Thus we performed that current study demonstrating that there is no difference between intravenous thrombolysis and CDT in ALI.

Thrombolysis has the benefit of being less invasive than surgery. The STILE [18] and TOPAS [19] trials reported that in patients who had received thrombolysis and later required surgical intervention, the magnitude and complexity of the procedure was often less than in those who had not received prior thrombolytic therapy. Thrombolysis is also a potentially attractive alternative to surgery because the culprit lesion can be identified and treated during the procedure with balloon angioplasty or stent placement.

A concern with thrombolysis is the risk of major hemorrhage [27]. Surgery has its own potential serious complications and therefore the specific risks for each patient need to be assessed [27]. In our audit, there was no major complication and adverse event recorded. In the Cochrane review, the stroke/intracerebral hemorrhage rate was 1.3%, while the major hemorrhage rate of was 8.8 [27]. None of patients in intravenous thrombolysis group in the current study experiences major or minor complications. Given the complication rate, many patients requiring thrombolysis could be appropriately managed on

general wards (bed cost approximately AUD $350 per day) if there were suitably trained staff. This would substantially reduce costs to approximately AUD $2,600 and AUD $3,000, respectively.

In conclusion, intravenous and catheter directed thrombolysis with t-PA is a safe and effective method in treatment of acute arteriolar ischemia of extremities. However there both intravenous thrombolysis and CDT are comparable regarding the clinical outcome.

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Conflict of interest: None declared.

References

1. Lurie F, Vaidya V, Comerota AJ. Clinical outcomes and cost-effectiveness of initial treatment strategies for nonembolic acute limb ischemia in real-life clinical settings. *J Vasc Surg*. 2015;**61**(1):138-46.
2. Malgor RD, Alalahdab F, Elraiyah TA, Rizvi AZ, Lane MA, Prokop LJ, et al. A systematic review of treatment of intermittent claudication in the lower extremities. *J Vasc Surg*. 2015;**61**(3 Suppl):54S-73S.
3. Ravari H, Rad MP, Bahadori A, Ajami O. Comparison of Conventional Angiographic Findings between Trauma Patients with or without Runoff. *Bull Emerg Trauma*. 2014;**2**(2):72-6.
4. von Allmen RS, Anjum A, Powell JT, Earnshaw JJ. Hospital trends of admissions and procedures for acute leg ischaemia in England, 2000-2011. *Ann R Coll Surg Engl*. 2015;**97**(1):59-62.
5. Baril DT, Ghosh K, Rosen AB. Trends in the incidence, treatment, and outcomes of acute lower extremity ischemia in the United States Medicare population. *J Vasc Surg*. 2014;**60**(3):669-77 e2.
6. Rutherford RB. Clinical staging of acute limb ischemia as the basis for choice of revascularization method: when and how to intervene. *Semin Vasc Surg*. 2009;**22**(1):5-9.
7. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. *N Engl J Med*. 2012;**366**(23):2198-206.
8. Acosta S, Kuoppala M. Update on intra-arterial thrombolysis in patients with lower limb ischemia. *J Cardiovasc Surg (Torino)*. 2015;**56**(2):317-24.
9. 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**(4):988-95.
10. Grip O, Kuoppala M, Acosta S, Wanhainen A, Akeson J, Bjorck M. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. *Br J Surg*. 2014;**101**(9):1105-12.
11. Khosla S, Jain P, Manda R, Razminia M, Guerrero M, Trivedi A, et al. Acute and long-term results after intra-arterial thrombolysis of occluded lower extremity bypass grafts using recombinant tissue plasminogen activator for acute limb-threatening ischemia. *Am J Ther*. 2003;**10**(1):3-6.
12. Wongwanit C, Hahtapornsawan S, Chinsakchai K, Sermsathanasawadi N, Hongku K, Ruangsetakit C, et al. Catheter-directed thrombolysis for acute limb ischemia caused by native artery occlusion: an experience of a university hospital. *J Med Assoc Thai*. 2013;**96**(6):661-8.
13. Pascoe H, Robertson D. Catheter-directed thrombolysis for acute limb ischaemia: An audit. *Australas Med J*. 2014;**7**(12):471-5.
14. Zhang F, Zhang H, Luo X, Liang G, Feng Y, Zhang WW. Catheter-directed thrombolysis-assisted angioplasty for chronic lower limb ischemia. *Ann Vasc Surg*. 2014;**28**(3):590-5.
15. Falkowski A, Poncyljusz W, Samad RA, Mokrzynski S. Safety and efficacy of ultra-high-dose, short-term thrombolysis with rt-PA for acute lower limb ischemia. *Eur J Vasc Endovasc Surg*. 2013;**46**(1):118-23.
16. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;**113**(11):e463-654.
17. Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;**141**(2 Suppl):e669S-90S.
18. Graor R, Comerota A, Douville Y, Turpie A, Froehlich J, Hosking J, et al. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower-extremity-the stile trial. *Annals of Surgery*. 1994;**220**(3):251-68.
19. 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**(16):1105-11.
20. Branco BC, Montero-Baker MF, Mills JL, Sr. The pros and cons of endovascular and open surgical treatments for patients with acute limb ischemia. *J Cardiovasc Surg (Torino)*. 2015;**56**(3):401-7.
21. Taha AG, Byrne RM, Avgerinos ED,

Marone LK, Makaroun MS, Chaer RA. Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia.*J Vasc Surg*. 2015;**61**(1):147-54.

22. Thukkani AK,Kinlay S. Endovascular intervention for peripheral artery disease.*Circ Res*. 2015;**116**(9):1599-613.

23. Troisi N,Ercolini L,Chisci E,Barbanti E,Peretti E,Setti M, et al. Urgent endovascular revascularization in acute on chronic critical limb ischemia.*J Cardiovasc Surg (Torino)*. 2014.

24. Braithwaite BD,Birch PA,Poskitt KR,Heather BP,Earnshaw JJ. Accelerated thrombolysis with high dose bolus t-PA extends the role of peripheral thrombolysis but may increase the risks.*Clin Radiol*. 1995;**50**(11):747-50.

25. Nilsson L,Albrechtsson U,Jonung T,Ribbe E,Thorvinger B,Thorne J, et al. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomised controlled study.*Eur J Vasc Surg*. 1992;**6**(2):189-93.

26. Tsetis DK,Kochiadakis GE,Hatzidakis AA,Skalidis EI,Chryssou EG,Tritou IN, et al. Transcatheter thrombolysis with high-dose bolus tissue plasminogen activator in iatrogenic arterial occlusion after femoral arterial catheterization.*Cardiovasc Intervent Radiol*. 2002;**25**(1):36-41.

27. Berridge DC,Kessel DO,Robertson I. Surgery versus thrombolysis for initial management of acute limb ischaemia.*Cochrane Database Syst Rev*. 2013;**6**:CD002784.