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Endovascular approach for acute limb ischemia without thrombolytic therapy

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Abstract

Background: Endovascular therapy for acute lower limb ischemia (ALLI) has developed and demonstrated safety and efficacy. The purpose of this study was to assess clinical outcomes in patients treated for ALLI with conventional endovascular or surgical revascularization.

Method: This study was a retrospective single-center review. Consecutive patients with ALLI treated with conventional endovascular revascularization (ER) without thrombolytic agent or surgical revascularization (SR) between 2008 and 2014 were investigated. The 1 year and 3 year amputation rate and mortality rate were assessed by time-to-event methods, including Kaplan–Meier estimation.

Result: A total of 64 limbs in 62 patients with ALLI due to thromboembolism or thrombosis of a native artery, bypass graft, or previous stented vessel were included. The majority of limbs (90.9%) presented with Rutherford clinical categories 1 to 2 ischemia. Technical success rate was 95.5% in ER and 92.9% in SR group ($p = 0.547$). Overall amputation rates were 9.1% in ER *versus* 9.5% in SR after 1 year ($p = 0.971$) and 9.1% in ER *versus* 11.9% in SR after 3 year ($p = 0.742$). Overall mortality rates were 15% in ER *versus* 7.1% in SR after 1 year ($p = 0.491$) and 15% in ER *versus* 11.2% in SR after 3 year ($p = 0.878$).

Conclusion: Endovascular or surgical revascularization of ALLI resulted in comparable outcomes in limb salvage and mortality rate at 1 year and 3 year. Conventional endovascular therapy without thrombolytic agent such as stenting, balloon angioplasty, or catheter-directed thrombosuction may be considered as a treatment option for ALLI.

Keywords: acute limb ischemia, endovascular therapy, revascularization

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Introduction

Treatment of acute lower limb ischemia (ALLI) by endovascular approach has developed since two large randomized controlled trials were published. Those studies demonstrated the comparable efficacy between open surgical revascularization and endovascular treatment.[1,2] Since then, endovascular therapy with catheter-directed thrombolysis (CDT) and/or percutaneous mechanical thrombectomy (PMT) have shown a safe and effective treatment option for ALLI.[3–5] Consequently, endovascular therapy has been an alternative to surgical intervention as an initial treatment option for ALLI. However, unresolved issues in the endovascular therapies have remained that some of the patients are not suited for thrombolysis agent concerning about risk of bleeding and/or novel devices for thrombolysis are not available in some cases. For restoring flow of occlusive arteries to salvage a threatened limb and to save a life, the conventional endovascular recanalization, including stent implantation or balloon angioplasty, combined with catheter-directed thrombus suction may be another endovascular treatment option.[6] There are few data that is comparable between surgical revascularization and conventional endovascular approach without thrombolysis in the setting of ALLI. This study was conducted to assess the effectiveness of conventional endovascular therapy, comparing surgical revascularization in terms of clinical efficacy with safety as an initial treatment option for ALLI.

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Methods

This study is a retrospective single-center review at Kishiwada Tokushukai Hospital approved by the Institutional Review Board (IRB) (16-05). All patients gave written informed consent to undergo the interventions listed.

Patients

The study included all patients with ALLI who underwent endovascular revascularization (ER) or surgical revascularization (SR) at Kishiwada Tokushukai Hospital between March 2008 and May 2014. All interventions were performed by interventional cardiologists or vascular surgeons. Procedural success, complication, limb salvage, and overall mortality were compared between the two groups. Patients with ALLI due to embolism or thrombosis of a native artery, bypass graft, or previous stent were included in this study. Blue toe syndrome, acute ischemia due to trauma, dissection or iatrogenic complications, and a case of using thrombolytic agent were excluded. All clinical, procedural, and demographic data were obtained through a review of the hospital's electronic records. ALLI was defined as the sudden onset or worsening within 14 days of ischemic manifestation and within the lower extremities due to embolism or thrombosis. Severity of ischemia was classified on presentation according to the Rutherford classification of acute limb ischemia.[7]

Procedures

The choice of the initial revascularization was at the primary clinician's discretion including the interventional cardiologist or vascular surgeon. There was no arrangement in which the primary clinician was either a cardiologist or surgeon to whom patients with ALLI were referred. However, the revascularization approach was standardized based on thrombus burden or occluded lesion length revealed by diagnostic imaging tests including echocardiogram, computed tomographic angiography, magnetic resonance angiography, or transcatheter angiogram. The method of recanalization in the ER group was balloon angioplasty, primary stenting, catheter-directed thrombus aspiration using 5Fr diagnostic catheter, guiding sheath, or commercially available aspiration catheters. Systemic or CDT therapy was not employed because these therapies for peripheral intervention were off-label in Japan. The SR group had thrombectomy performed by using Fogarty catheter and/or bypass grafting under general anesthesia. The timing of all procedures in both groups was completed within 24 h after establishing diagnosis of ALLI with a typical clinical manifestation and imaging test. All operative records and imaging were reviewed for technical details, acute result of restoring flow, and complications.

The technique of endovascular therapy for ALLI is similar to the common procedural steps of endovascular treatment for chronic occlusive arteries of a lower extremity. 5000-IU unfractionated heparin was administered intravenously after insertion of the sheath and by using a 0.014 or 0.035 inch wire, the occluded segment was crossed. After the guide wire passage, balloon-angioplasty catheter-directed thrombus aspiration was performed. The selection of aspiration devices was left to the operator's discretion. To cover the residual occluded segment, the stent was implanted and post dilatation using an under-sized balloon was performed using less than 6 atm. If there is a significant residual stenosis or distal embolization, ballooning and thrombus aspiration were repeated until restoration of flow was established.

Outcomes measurement

The technical success, procedural complications, and length of hospital stay were evaluated as an acute phase result. At 3 years post intervention, the amputation rate and mortality rate were assessed.

The definition of technical success in the ER procedure was defined as a restoration of straight line flow at the level of the ankle with at least one tibial vessel run-off at the time of final angiogram, whereas, in SR patients, angiogram was not available and technical success was defined by palpable pules with detection of a Doppler signal at the dorsal pedis artery or posterior tibial artery.

Statistical analysis

Patient demographics, comorbidities, severity of ischemia, and lesion characteristics were compared between the two groups by a chi-square test and *t*-test for categorical and interval scaled variables, respectively. Limb salvage and survival were assessed by time-to-event methods, including Kaplan–Meier estimation and competing risk-regression models. Tests assumed a significance level of 0.05. Analyses were performed using SPSS statistics (version 22; IBM, USA)

Result

A total of 64 limbs in 62 patients were included in this study. In total, 22 limbs in 20 patients underwent ER only and 42 limbs in 42 patients underwent SR. A combination therapy with ER and SR or cross-over treatment was not found in this series of patients.

Patient population

The baseline patient demographics and comorbidities are shown in Table 1. Patients in ER and SR groups were similar in terms of their baseline characteristics. In both groups, all patients with atrial fibrillation on the first presentation were not on anticoagulation therapy, poorly controlled prothrombin time-international normalized ratio, or cessation of anticoagulation drugs due to other bleeding causes.

Initial presentation and limb characteristics

Limb characteristics are shown in Table 2. Most limbs were classified on initial presentation as Rutherford class 1 to 2b (86.3% in ER groups *versus* 92.9% in SR groups). There were no significant differences in each class between the two groups ($p=0.369$). The location of the occluded segment of the artery in the lower limb extremity in each level was similar in the two groups. The native artery involvement is more prevalent in the SR group (92.9% in SR *versus* 68.2% in ER), whereas failed stent was seen more in the ER group (22.4% in ER *versus* 2.4% in SR).

Procedures

In both of the groups, all procedures were performed within 24 hours of arriving at our hospital and had not received pre-medication of systemic lysis therapy. In the ER groups, more than half of the limbs (16 of 22 limbs) were treated with stent implantation and included five in the iliac artery and 11 in the femoropopliteal artery. In total, 8 of the 16 stent implantation limbs required adjunctive catheter-directed thrombus aspiration due to distal embolism to the infrapopliteal arteries and succeeded in obtaining straight line flow to the ankle arteries. Four limbs were treated by only balloon angioplasty which included one in the iliac artery, one in the occluded previous stented iliac artery and two in the infrapopliteal artery. Two of the below-knee arteries had only catheter-directed thrombus aspiration performed. In the SR group, 37 limbs received thrombectomy alone – 18 in the iliac artery, 16 in the femoropopliteal artery, and three in the tibio-peroneal trunk – and five limbs received a combination with bypass graft surgery – four in iliac artery and one in femoropopliteal artery. The reason for the additional bypass surgery is due to an insufficient flow after the thrombectomy procedure. In both of the groups, all patients were treated with anticoagulation drugs after the procedures.

Table 1. Patient demographics.

	ER group ($n=20$)	SR group ($n=42$)	*p* value
Age. mean ± SD	73.3 ± 13.2	76.5 ± 11.6	0.354
Male (%)	10 (50.0)	24 (57.1)	0.597
Hypertension (%)	17 (85.0)	37 (88.1)	0.705
Dyslipidemia (%)	8 (40.0)	14 (33.3)	0.608
Diabetes (%)	8 (40.0)	7 (16.7)	0.060
Smoking (%)			
None	5 (25.0)	17 (40.5)	0.479
Previous	3 (15.0)	6 (14.3)	
Current	8 (40.0)	12 (28.6)	
CAD (%)	7 (35.0)	15 (35.7)	0.956
PAD (%)	14 (70.0)	20 (47.6)	0.098
CKD (%)	13 (65.0)	18 (42.9)	0.103
CVD (%)	6 (30.0)	13 (31.0)	0.939
Atrial fibrillation (%)	8 (40.0)	27 (64.3)	0.071

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; ER, endovascular revascularization; PAD, peripheral artery disease; SD, standard deviation; SR, surgical revascularization.

Technical success and complication

The technical success rate according to each definition in this study was 95.5% in the ER group and 92.9% in the SR group. One limb in the ER group failed to restore distal flow below the knee vessels by completion angiogram, which showed no vessel run-off, and three limbs in the SR groups failed to obtain palpable pulses or Doppler signals at ankle level. Of the four technical failures, one was treated with anticoagulation therapy, three limbs required an amputation, and three patients died. In the ER group, procedural

Table 2. Limb characteristics.

	ER group (*n* = 22)	SR group (*n* = 42)	*p* value
Rutherford class (%)			
1	5 (22.7)	8 (19.0)	0.369
2a	11 (50.0)	17 (40.5)	
2b	3 (13.7)	14 (33.3)	
3	3 (13.7)	3 (7.1)	
Location (%)			
Aortoiliac	7 (31.8)	23 (54.8)	0.156
Femoropopliteal	11 (50.0)	16 (38.1)	
Below the knee	4 (18.2)	3 (7.1)	
Vessel (%)			
Native artery	15 (68.2)	39 (92.9)	0.02
Graft	2 (9.1)	2 (4.8)	
Stent	5 (22.7)	1 (2.4)	

ER, endovascular revascularization; SR, surgical revascularization.

complication included access-site hematoma in two limbs, of which one required blood infusion and one pseudoaneurysm treated with manual compression under echo guidance. However, in the SR group, complications were one wound infection, one fasciotomy, one wound dehiscence, and one intracranial bleeding. The length of hospital stay was significantly shorter in the ER group compared with the SR group (11.9 ± 14.5 *versus* 23.7 ± 20.4 days; $p = 0.009$).

Limb loss and survival

The overall amputation rates were 9.1% in the ER group *versus* 9.5% in the SR group at 1 year ($p = 0.971$) and 9.1% in the ER group *versus* 11.9% in the SR group at 3 year ($p = 0.742$) (Figures 1 and 2). Seventy percent of all amputation limbs underwent the operation within 30-day after initial interventions. The overall mortality rates were comparable between ER and SR group at 1 year (15% *versus* 7.1%; $p = 0.491$) and at 3 year (15% *versus* 11.2%; $p = 0.878$) (Figures 3 and 4).

In the ER group, two patients (10%) died due to multi-organ failure related to reperfusion injury,

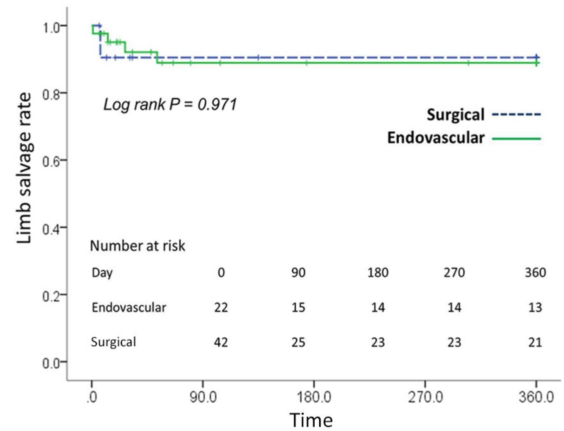

Figure 1. Limb salvage rate at 1 year.

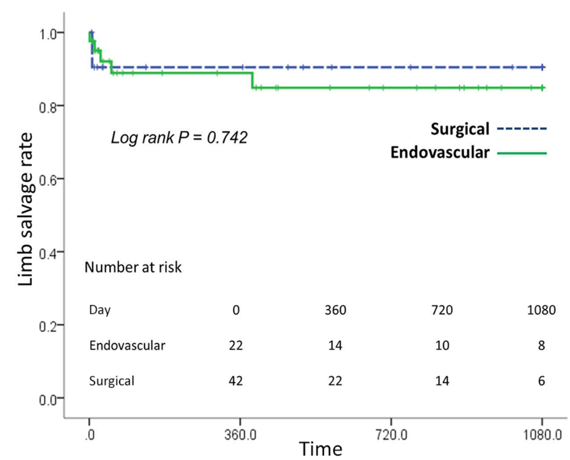

Figure 2. Limb salvage rate at 3 years.

one patient due to necrosis of ischemic limbs, and one due to pneumonia (5%). A major bleeding event was not seen in the ER group. Whereas, in the SR group, three patients died due to pneumonia (7.1%), one patient due to sepsis following wound infection of amputation (2.4%), and one due to intracranial hemorrhage (2.4%).

Discussion

The present study demonstrated that conventional endovascular recanalization including stent implantation, balloon angioplasty, percutaneous thrombus aspiration, or a combination of these techniques for ALLI can be performed without giving a thrombolytic agent. These conventional endovascular devices could achieve comparable outcomes with limb salvage and mortality rate at

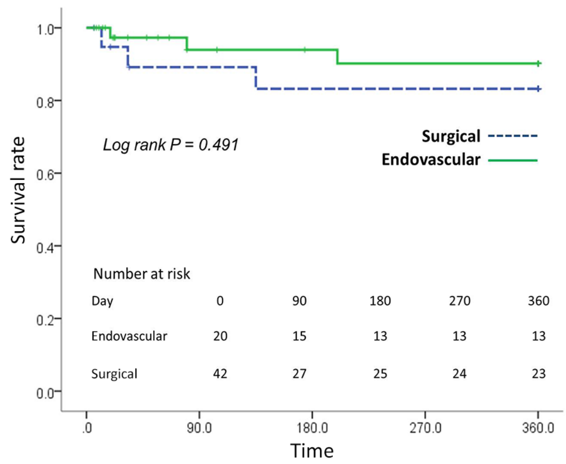

Figure 3. Survival rate at 1 year.

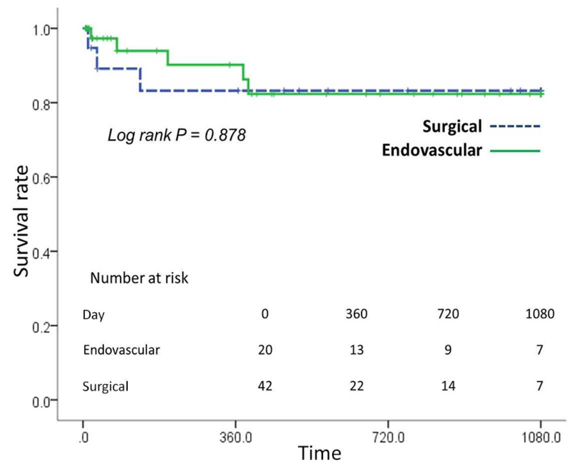

Figure 4. Survival rate at 3 years.

1 year and 3 years compared with open surgical recanalization. In the ER group there were no major bleeding events; however, access site minor hematoma was included in two limbs (9%) and no re-intervention or cross-over to surgical therapy was needed after initial ER.

The treatment strategy for ALLI has shifted toward non-SR since endovascular therapy demonstrated equal efficacy compared with open surgical thrombectomy. The development of these percutaneous devices and techniques contributed to make this paradigm shift.[8–11] However, the treatments for ALLI have remained a clinical dilemma in some patients who are not a candidate for open surgery and/or have a high-risk of bleeding complications caused by a thrombolytic agent.[12,13] Therefore, the standardized treatment strategy for ALLI has not been well-defined and there is no established guidelines for treatment strategy.[14] Among the various endovascular treatment options of ALLI, stent-assisted recanalization has not been considered for the treatment of acute limb ischemia. However, recent reports about primary stenting for ALLI have shown a good clinical efficacy with minimal occurrence of distal embolization.[15,16] In addition to this stent assisted strategy, percutaneous catheter thrombus aspiration for ALLI can be feasible with adjunct angioplasty and/or stenting and demonstrated favorable short- and mid-term outcome in its safety and efficacy.[17]

The amputation rate at 1 year (9.1%) in our study was relatively lower than that reported in the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial (15%).[2] Moreover, Byrne *et al.* reported outcomes of endovascular interventions for ALLI with CDT and/or PMT that showed an amputation rate at 1 year of 13.0% with no significant differences between the CDT and PMT groups. However, the systemic bleeding complications were seen in 5.2% and distal embolization or clot extension occurred in 9.7%, which required either adjunctive CDT or surgical conversion.[18] Endovascular therapy without thrombolysis offers several advantages compared with conventional CDT/PMT. First, this procedure is less likely to have a bleeding complication due to not having a thrombolytic agent and so could use a larger sheath for the implantation of the stent. Second, it might provide induced rapid recanalization once vascular access is obtained and the catheter is inserted. This rapid recanalization could be of good clinical benefit for improving symptoms and restoring flow to distal ischemic tissue. On the contrary, thrombolytic therapy may require some time to obtain completely restored flow. Kashyap *et al.* reported that, in endovascular therapy using thrombolytic agent for ALLI, more than 3 days of thrombolysis are associated with amputation due to a greater thrombus burden and/or chronic thrombus, which might be resistant to fibrinolytic therapy.[19] Rapid recanalization could facilitate a spontaneous dissolving of the thrombus and accelerate endogenous fibrinolytic action. In the setting of acute occlusion, the prompt recanalization of an ischemic limb is a critical factor for improved clinical outcomes. The endovascular technique, however, may have certain limitations. The management of distal embolization is still unresolved and might require further procedures including additional stent implantation, additive thrombus aspiration, or surgical intervention.[20] These adjunctive procedures might be more likely to be associated with complications and might be less cost-effective. Moreover, the restenosis induced by balloon angioplasty or stent implantation may become a concern in some patients.[21]

In the present study, both endovascular and open surgical intervention groups showed relatively low amputation and mortality rate compared with previous reports.[18,22,23] These better results could be due to prompt recanalization by either endovascular or surgical interventions. In our series, the initial diagnosis of ALLI was made within 24 hours and could obtain short a door to recanalization time. Just like an acute coronary syndrome, the similar concept of door to recanalization time is mandatory for all ALLI patients who present as Rutherford category 1 to 2b.[24,25]

There are several important limitations in our study. First, this study is a small population and non-randomized retrospective review. The selection of initial treatment options, whether endovascular or surgical intervention, was left to the first doctor's discretion and there is no fixed study protocol. Second, the definition of technical success between endovascular and surgical intervention groups was different. Nevertheless, either of the two groups could achieve a rapid improvement of symptoms and have a complete resolution of the ischemic condition of the distal foot. This short recanalization time might have resulted in a low amputation and mortality rate. Third, the target vessels included occlusion of a stent or bypass graft. This condition could be a different clinical status from the acute occlusion of the native artery. Patients who underwent any previous revascularizations with known peripheral artery disease might have had poor run-off and vascular bed of the distal foot. These patients might have had an impact on the results of the poorer outcomes. Finally, the relationship between amputation rate and Rutherford classification, or patency rate post recanalization, and preference of the treatment strategy in each Rutherford classification is important.[26] However we did not analyze this issue because of a very small number of patients and treated limbs.

Conclusion

ER or SR of ALLI resulted in comparable outcomes of both limb salvage rate and mortality rate. Conventional endovascular recanalization without using a thrombolytic agent may be considered as a first-line therapy in patients who are not candidate for thrombolysis or SR.

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Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg* 1994; 220: 251–268.
2. Ouriel K, Veith FJ and Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med* 1998; 338: 1105–1111.
3. Ouriel K, Shortell CK, DeWeese JA, *et al.* A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg* 1994; 19: 1021–1030.
4. Ouriel K. Endovascular techniques in the treatment of acute limb ischemia: thrombolytic agents, trials, and percutaneous mechanical thrombectomy techniques. *Semin Vasc Surg* 2003; 16: 270–279.
5. Ansel GM, Botti CF Jr and Silver MJ. Treatment of acute limb ischemia with a percutaneous mechanical thrombectomy-based endovascular approach: 5-year limb salvage and survival results from a single center series. *Catheter Cardiovasc Interv* 2008; 72: 325–330.
6. Rutherford RB, Baker JD, Ernst C, *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; 26: 517–538.
7. Kim C, Jeon W, Shin T, *et al.* Stent-assisted recanalisation of acute occlusive arteries in

patients with acute limb ischaemia. *Eur J Vasc Endovasc Surg* 2010; 39: 89–96.

8. Comerota AJ and Gravett MH. Do randomized trials of thrombolysis versus open revascularization still apply to current management: what has changed? *Semin Vasc Surg* 2009; 22: 41–46.
9. Kasirajan K, Haskal ZJ and Ouriel K. The use of mechanical thrombectomy devices in the management of acute peripheral arterial occlusive disease. *J Vasc Interv Radiol* 2001; 12: 405–411.
10. Nehler MR, Mueller RJ, McLafferty RB, *et al.* Outcome of catheter-directed thrombolysis for lower extremity arterial bypass occlusion. *J Vasc Surg* 2003; 37: 72–78.
11. Gupta R and Hennebry TA. Percutaneous isolated pharmaco-mechanical thrombolysis-thrombectomy system for the management of acute arterial limb ischemia: 30-day results from a single-center experience. *Catheter Cardiovasc Interv* 2012; 80: 636–643.
12. Raja J, Munneke G, Morgan R, *et al.* Stenting in acute lower limb arterial occlusions. *Cardiovasc Intervent Radiol* 2008; 31(Suppl. 2): S41–S44.
13. van den Berg JC. Thrombolysis for acute arterial occlusion. *J Vasc Surg* 2010; 52: 512–515.
14. Diehm N, Schillinger M, Minar E, *et al.* TASC II section E3 on the treatment of acute limb ischemia: commentary from European interventionists. *J Endovasc Ther* 2008; 15: 126–128.
15. Yilmaz S, Sindel T and Lüleci E. Primary stenting of embolic occlusions in iliac arteries. *J Endovasc Ther* 2003; 10: 629–635.
16. Berczi V, Thomas SM, Turner DR, *et al.* Stent implantation for acute iliac artery occlusions: initial experience. *J Vasc Interv Radiol* 2006; 17: 645–649.
17. Katsargyris A, Ritter W, Pedraza M, *et al.* Percutaneous endovascular thrombosuction for acute lower limb ischemia: a 5-year single center experience. *J Cardiovasc Surg (Torino)* 2015; 56: 375–381.
18. Byrne RM, Taha AG, Avgerinos E, *et al.* Contemporary outcomes of endovascular interventions for acute limb ischemia. *J Vasc Surg* 2014; 59: 988–995.
19. Kashyap VS, Gilani R, Bena JF, *et al.* Endovascular therapy for acute limb ischemia. *J Vasc Surg* 2011; 53: 340–346.
20. Zehnder T, Birrer M, Do DD, *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: 41–46.
21. Hirsch AT, Haskal ZJ, Hertzer NR, *et al.* 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; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. 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: e463–e654.
22. Taha AG, Byrne RM, Avgerinos ED, *et al.* Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia. *J Vasc Surg* 2015; 61: 147–154.
23. Baril DT, Ghosh K and 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: 669–677.
24. Walker TG. Acute limb ischemia. *Tech Vasc Interv Radiol* 2009; 12: 117–129.
25. Henke PK. Contemporary management of acute limb ischemia: factors associated with amputation and in-hospital mortality. *Semin Vasc Surg* 2009; 22: 34–40.
26. de Athayde Soares R, Matielo MF, Brochado Neto FC, *et al.* Analysis of the results of endovascular and open surgical treatment of acute limb ischemia. *J Vasc Surg* 2019; 69: 843–849.