Strategic of Revascularization for Critical Limb Ischemia Due to Infragenicular Lesions—Which Should Be Selected Firstly, Bypass Surgery or Endovascular Therapy?

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Background and Objectives: In patients with peripheral arterial diseases (PADs) due to infra-popliteal (below the knee; BTK) lesions, we often encounter situations requiring the immediate selection of either of two revascularization methods, namely bypass surgery or endovascular therapy (EVT). However, the question of whether endovascular or surgical revascularization should be performed initially for critical limb ischemia (CLI) patients with BTK lesions has not been clarified. To assess the efficacy and durability of EVT or bypass as a first approach, we evaluated the short- and mid-term outcomes of the first revascularizations achieved using EVT (EVT First Group; EVT-first) compared with bypass (Bypass First Group; Bypass-first). To verify the validity of each initial revascularization, we explored factors influencing overall survival (OS) rates using multivariate analyses.

Methods: A total of 169 consecutive BTK revascularization procedures (150 patients) for CLI conducted at our facility between November 2006 and July 2012 were analyzed. Patients undergoing revascularization were divided into two groups (EVT-first or Bypass-first), with 102 patients undergoing endovascular therapy first (EVT-first) and 51 undergoing bypass surgery first (Bypass-first). No statistically significant differences were noted between the two groups with respect to preoperative background including age, gender, and cardiovascular risk factors, which is non-ambulatory limb, aged less than 81 years, arterial disease (PAD), CAD, CHF, and a non-ambulatory limb. Patient follow-up ranged from 46–98 years; 65 men and 37 women) and 72.3 years (range, 43–93 years; 35 men and 13 women) in the EVT-first and Bypass-first groups, respectively. Patient follow-up ranged from 1 to 50 months (mean, 15 months). Patient follow-up ranged from 1 to 50 months (mean, 15 months). Respective technical and hemodynamic success rates were 96.2% and 66.7% for EVT-first and 100% and 94% for Bypass-first, respectively. Treatment was required an average of 1.5 times for EVT-first and 1.2 times for Bypass-first. Respective rates for other factors examined in the EVT-first and the Bypass-first groups were: major amputation rates 30 days post-procedure, 5.9%, and 3.9%; mortality rates 30 days post-procedure, 3.9%, and 0%; one-year AFS rates, 71.7%, and 79.5%; OS rates, 73.5% and 83.9%; and limb salvage rates, 88.8%, and 91.0%. Multivariate-analysis of all subjects in the two groups revealed that the OS rates were affected by four risk factors as follows: (1) age greater than 80 years, (2) CAD, (3) CHF, and (4) a non-ambulatory limb.

Conclusion: For patients with CLI due to BTK lesions and whose saphenous veins are in poor condition or are in poor general condition having two or more of the four severe risk factors, the EVT-First procedure is effective and provides durable results. Overall survival in patients with CLI due to BTK lesions is worse when patients have more than two severe risk factors, which is non-ambulatory limb, aged less than 81 years, with CAD or with CHF. (This article is a translation of Jpn J Vasc Surg 2014; 23: 766–773.)

Keywords: peripheral arterial diseases, critical limb ischemia, endovascular therapy, bypass surgery, below the knee lesions

Introduction

Selection of a revascularization method, endovascular therapy (EVT) or surgery, for the first treatment of peripheral arterial disease (PAD) patients with critical limb ischemia (CLI) is still controversial depending on the main lesion, and the selection may be biased to one with which an operator of revascularization is familiar. For the aortoiliac and femoropopliteal arterial areas, the therapeutic results of lower limb EVT including long-term outcomes have improved and become equivalent to those of bypass.
surgery,\(^1\)\(^-\)\(^4\) and application of EVT for the first treatment has been shown to be appropriate, although there are some exceptions. Regarding EVT for PAD with lesions mainly below the knee, the long-term patency rate is still low, and which of EVT or bypass surgery should be performed for the first treatment is the most controversial issue. CLI frequently extends over many regions, and lesions are present in the below-the-knee arteries in many cases.\(^5\) To ensure limb salvage, long-term supply of a large volume of blood to the defective tissue region is necessary,\(^6\) and below-the-knee-ankle joint bypass has been considered as the gold standard revascularization for CLI complicated by below-the-knee lesions.\(^7\)

However, CLI is often complicated by coronary arterial and cerebrovascular diseases and the general condition is poor in most cases,\(^8\) which frequently leads to hesitation to perform bypass surgery. Since the short-term outcome of EVT was comparable to bypass surgery on intention-to-treat analysis in the BASIL study,\(^9\) institutions selecting EVT for the first treatment may be increasing, but, in Japan, it may be too early to conclude that EVT is applicable for the first treatment of PAD mainly consisting of below-the-knee lesions based on the BASIL study because no dialysis patient was included and patients with only below-the-knee lesions accounted for only 20% in the BASIL study, which do not meet the conditions in Japan where about half of CLI patients are dialysis patients.\(^5\) There has been no study investigating which of EVT or bypass should be firstly performed on the condition that both treatments were performed by the same department in consideration of the conditions in Japan.

In this study, we divided all cases of revascularization of below-the-knee lesions performed at our institution into those treated with EVT (EVT First; E group) and below-the-knee-ankle joint bypass (Bypass First; B group) for the first treatment, and investigated the short- to mid-term outcomes to determine the effectiveness of EVT performed by vascular surgeons. At the same time, to investigate the type of patient for whom bypass surgery (Bypass First) is appropriate, factors influencing the survival rate of the CLI patients with below-the-knee lesions were investigated and a long-term survival group was identified by stratification with risk factors including all patients treated with revascularization in the analytical set.

Subjects and Methods

The subjects were all patients treated with revascularization for critical limb ischemia of the below-the-knee-ankle joint area (169 legs in 150 patients) between November 2006 and July 2012. Patients with a past medical history of revascularization of the same region on the same side performed at our or other institutions were excluded. The patients were divided into those treated with endovascular therapy (EVT First group, E group) (118 legs in 102 patients) and below-the-knee-ankle joint bypass (Bypass First group, B group) (51 legs in 48 patients) for the first treatment (Fig. 1). The primary endpoints were: (1) short- (1 year) and midterm (3 years) amputation-free survival rates, (2) survival rate, and (3) limb salvage rate, and the secondary endpoints were: (4) technical success rate, (5) 30-day mortality rate, and (6) 30-day amputation rate. In all patients, ankle brachial pressure index (ABPI) and skin perfusion pressure (SPP) were measured before treatment. Arteries of the ischemic leg were evaluated by contrast computed tomography (CT) or angiography before treatment, and when one straight line flow to the ankle joint was observed on the final contrast imaging after revascularization, the case was regarded as a technical success (including cases in which the only the peroneal artery was treated).

In all patients, the following preoperative conditions were investigated in medical records: the age, sex, concomitant diseases (hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), ischemic heart disease (coronary arterial disease (CAD)), cerebrovascular disease (CVD), maintenance dialysis for terminal renal failure (hemodialysis (HD)), and chronic heart failure (CHF)), preoperative Rutherford classification, availability of an autologous vein appropriate for bypass surgery, presence or absence of revascularization on the ipsilateral central side (iliac and femoropopliteal areas), and ADL (ambulatory/non-ambulatory condition) before the development of CLI. Patients with one of the following conditions were regarded as having chronic heart failure: a past medical history of heart failure, ingestion of an oral drug for heart failure, and an ejection fraction less than 40% on preoperative echocardiography. ABPI and SPP were measured to evaluate blood flow 2–4 weeks after treatment, and when SPP was 40 mmHg or higher, the treatment was regarded as a hemodynamic success. All
procedures, from the resection of necrotized tissue to major amputation, were performed at our department, and the patients were hospitalized throughout the period from wound bed preparation to free skin grafting and confirmation of engraftment. After wound healing, the patients were followed at the outpatient clinic every 3 months, as a rule, and physical examination (including palpation of graft pulse) and ABPI/SPP measurement were performed. When graft failure and relapse of CLI were suspected, such as relapse of pain at rest, ulcer, and necrosis and reductions of the arterial pulse, SPP to below 40 mmHg, and ABPI by 0.15 or more, examination by imaging, such as duplex ultrasonography, contrast CT, and direct angiography, was performed as needed, and additional revascularization was considered.

The saphenous vein was evaluated as follows in all patients: Contrast CT or lower limb venous echography was performed, and when the maximum minor axis in a supine position was 2.0 mm or greater on either test and a length sufficient for the planned bypass could be secured without a varix, the vein was regarded as acceptable for grafting (good or feasible graft), and a vein not meeting these conditions was regarded as unacceptable for grafting (poor graft) (Fig. 2).

Selection of EVT or bypass for the first treatment was decided by consultation between two surgeons of our department mainly based on the preoperative general and ambulatory conditions, availability of an acceptable autologous vein, and grade of tissue defect.

For between-group comparison of risk factors, Fisher’s exact test was performed, and continuous variables were compared using the t-test. Kaplan-Meier survival curves were prepared and compared between the two groups using the log-rank test. A p-value of less than 0.05 was regarded as significant in each test. For multivariate analysis of the survival rate, Cox proportional hazards models were used.

**Results**

The preoperative background is shown in Table 1. In the E/B groups, there were 65 males and 37 females/35 males and 13 females, respectively, and the mean age was 76.0/72.3 years old, respectively. No significant difference was noted in concomitant diseases between the two groups (hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), ischemic heart disease (coronary arterial disease (CAD)), cerebrovascular disease (CVD), maintenance dialysis for terminal renal failure (hemodialysis (HD)), and chronic heart failure (CHF)). As shown in Table 1, the rates of non-ambulatory patients (p <0.05), those with a poor graft (p <0.01), and those treated with simultaneous revascularization (p <0.01) were higher in the E group, whereas the rate of patients with R6 was higher in the B group.

In the B group, inflow revascularization was simultaneously performed in 11 legs (external iliac arterial stent: 4, superficial femoral artery (SFA) stent: 2, femoro-popliteal above knee (FPAK) bypass: 1, femoro-popliteal below knee (FPBK) bypass: 1, endarterectomy of the common femoral artery: 3). The central side of bypass anastomosis was the common femoral artery in 28 legs, superficial femoral artery in five, above-the-knee popliteal artery in one, and below-the-knee popliteal artery in 17. When crural arterial calcification was severe, the peripheral anastomosis site was decided by plain radiography and angiography. The peripheral anastomosis site was the anterior and posterior tibial arteries in 6 and 26 legs, respectively, peroneal artery in four, dorsal artery of the foot in 14, and lateral plantar artery in one. The vein used for grafting was the great and small saphenous veins in 49 and 1, respectively, and femoral vein in one. These were applied in situ in 16 legs, reversed in one, and non-reversed in 32 (single application in 28). Grafts were joined and applied as a spliced graft in four legs. An autologous vein with a sufficient length was not available for two legs, and a composite graft consisting of an artificial blood vessel and an autologous vein was used (the femoral vein was interposed in one, and a Miller Cuff prepared with the great saphenous vein was interposed in the other).

The treatment site in the E group was the anterior and posterior tibial arteries in 63 and 44 legs, respectively, peroneal artery in 33, dorsal artery of the foot in nine, and planter artery in 13. The mean length of treated lesion was 15.3 ± 9.3 cm.

The postoperative findings are shown in Table 2. The mean duration of follow-up was 15 (1–30) months. The technical success rates were 96.2 and 100% in the E and B groups, respectively (p = 0.32). The hemodynamic success rates were 66.7 and 94% (p <0.05), respectively, showing a significantly higher rate in the B group. Regarding the early outcome within 30 days after treatment, the surgical mortality rates were 3.9 and 0%, respectively, and the
major amputation rates were 5.9 and 3.9%, respectively, showing no significant difference between the two groups.

Amputation-free survival over the course is shown in Fig. 1. The 1-year and amputation-free survival rates were 76.7 and 79.5% in the E and B groups, respectively, and the 3-year rates were 41.6 and 65.4%, respectively, showing no significant difference between the two groups (p = 0.22). The limb salvage rates are shown in Fig. 2. The 1-year rates were 88.8 and 91.0% in the E and B groups, respectively, and the 3-year rates were 83.2 and 80.1%, respectively, showing no significant difference between the two groups (p = 0.63). The survival rates are shown in Fig. 3. The 1-year rates were 73.5 and 83.9% in the E and B groups, respectively, and the 3-year rates were 55.3 and 57.6%, respectively, showing no significant difference between the two groups (p = 0.54).

In the E group, additional bypass surgery was performed in 19 legs (16%) due to unsuccessful hemodynamic outcomes (Table 2). In the B group, the anastomotic structure of the anastomosed region was treated with balloon dilatation during the follow-up period in five legs (10%). Thus, the mean frequency of revascularization applied per leg was 1.5 (1–7) in the E group and 1.2 (1–2) in the B group (p < 0.05). In the legs treated with additional bypass surgery in the E group, the 2-year limb salvage rate was 100%, and both the 2-year survival and amputation-free survival rates were 41.6%.

Factors influencing the survival rate were investigated including all patients in analysis. On multivariate analysis, the age (81 years old or older), non-ambulatory condition, and presence or absence of CAD and CHF were significant factors (Table 3). Since the risk ratios of these four factors were mostly equivalent, the patients were stratified with the number of these factors, and the survival rate was investigated. The 2-year survival rates of patients with none, 1, 2, 3, and 4 of the 4 risk factors were 100, 66.8, 44.3, 47.5, and 0%, respectively, showing that the outcome was poor when two or more risk factors were present (Fig. 4).
Strategy of Revascularization for Critical Limb Ischemia

Discussion

EVT is simple and applicable under local anesthesia. It can be rapidly performed in emergency cases and repeatedly applied. Thus, it is considered very useful for CLI.\(^{10}\) No patient died of surgery in the Bypass First group, suggesting that the application of bypass for the first treatment was avoided in patients with a poor general condition for whom long-term survival sufficient to receive benefit from bypass surgery could not be expected. The outcome of the EVT First group surpassed the target values of the optimal performance goal reported by Conte,\(^ {11}\) suggesting that EVT is also useful for below-the-knee lesions when it is effectively applied. A favorable autologous vein for grafting was available in only 30% in the EVT First group, clarifying that only EVT may be applicable for revascularization in many patients.

For revascularization of Rutherford 5/6 CLI accompanied by necrosis, long-term retention of blood flow to the defective region is necessary,\(^ {4}\) and it is difficult to complete treatment by a single application of EVT in the course of wound healing. It has been reported that restenosis occurred 3 months after infrapopliteal arterial EVT in more than 70% when only balloon dilatation was applied,\(^ {12,13}\) clarifying that restenosis is the weakest point of EVT. EVT was required a maximum of seven times in a case, and the mean frequency of treatment was significantly lower in the Bypass First group, suggesting that early conversion to bypass is desirable for cases in which the final tissue defect is large and inevitably requires repeated EVT. The treatment was converted to bypass surgery to the foot in 16% in the EVT First group. Physicians performing revascularization should always consider bypass surgery to the foot as the second procedure for cases in which revascularization cannot be completed by the first EVT. Unlike the results of BASIL by treatment group,\(^ {14}\) no decrease in the limb salvage rate due to previous EVT was noted. Since bypass surgery was performed at our department, its application without a delay may have prevented a decrease in the salvage rate. Therefore, we do not recommend easily adopting EVT for the first treatment of CLI with below-the-knee lesions despite our achievement.

The types of case for which bypass and EVT are appropriate for the first treatment, respectively, are major issues for physicians performing revascularization. To judge whether or not a patient with CLI can receive benefit from bypass, such as long-term patency, it is necessary to predict

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**Table 3** Multivariate analysis for overall survival in both groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Multivariate</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
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<td>Gender (male vs. female)</td>
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<td>Diabetes</td>
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<td>0.23–1.45</td>
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<td>Coronary arterial disease</td>
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<td>1.11–4.21</td>
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<td>Cerebrovascular disease</td>
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<td>Chronic heart failure</td>
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<td>2.32</td>
<td>1.15–4.74</td>
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<tr>
<td>Non-ambulatory limb</td>
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<td>2.57</td>
<td>1.20–5.78</td>
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<td>Rutherford 5/6</td>
<td></td>
<td>1.80</td>
<td>0.62–2.59</td>
<td>0.157</td>
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</table>

HR: hazard ratio; CI: confidence interval; EVT: endovascular therapy

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**Fig. 3** Overall survival of two groups (EVT First group versus Bypass First group). EVT: endovascular therapy

**Fig. 4** Risk stratification of overall survival (OS) based on multivariable logistic analysis. Patients were assigned to groups based on the number of multivariable risk factors, named severe risk factors as follows; Age over 80 year-old, chronic heart failure, coronary arterial disease, and non-ambulatory limb. OS was lower in the higher-risk groups (2-year rates by number of factors: 100% for 0; 66.8% for 1; 44.3% for 2; 47.5% for 3; and 0% for 4 factors, respectively).

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\(^{1)}\) Conte, et al., 2008

\(^{2)}\) Conte, et al., 2009

\(^{3)}\) Conte, et al., 2006

\(^{4)}\) Conte, et al., 2007

\(^{5)}\) Conte, et al., 2006

\(^{6)}\) Conte, et al., 2007

\(^{7)}\) Conte, et al., 2008

\(^{8)}\) Conte, et al., 2009

\(^{9)}\) Conte, et al., 2006

\(^{10)}\) Conte, et al., 2007

\(^{11)}\) Conte, et al., 2008

\(^{12)}\) Conte, et al., 2009

\(^{13)}\) Conte, et al., 2006

\(^{14)}\) Conte, et al., 2007
the survival time of the patient. In response to the results of BASIL, it is described in the 2011 ACC/AHA guidelines that revascularization by bypass surgery should be applied to ‘patients with an utilisable saphenous vein and 2-year or longer vital prognosis’. The criterion, ‘patients with 2-year or longer vital prognosis’, is very vague and not concrete for physicians performing revascularization in actual clinical practice. Although it is difficult to judge for the first revascularization, they have to identify risk factors determining survival of the patient and predict whether or not the patient is likely to survive for 2 years based on the risk factors on the first examination.

On multivariate analysis, serious risk factors: ischemic heart disease, chronic heart failure, an advanced age of 81 years old or older, non-ambulatory condition, and significantly decreased survival rate. Since the risk ratios of these were almost equivalent on multivariate analysis, we stratified the patients with the number of these risk factors. As shown in Fig. 4, the 2-year survival rate was higher than 50% in patients with 0 or one risk factor, but it decreased to below 50% in patients with two or more risk factors. Therefore, it is clear before treatment that long-term survival cannot be expected for these patients, and bypass surgery should be avoided for them. We propose that the strategy: selection of EVT for the first treatment for patients with two or more of the four risk factors, is relatively simple for physicians performing revascularization to select a procedure. Iida et al. reported that the following eight factors are independent risk factors to predict AFS of patients with CLI induced by a single below-the-knee lesion: (1) BMI below 18.5, (2) a serum albumin level below 3.0 g/dL, (3) non-ambulatory condition, (4) terminal renal failure, (5) EF below 50%, (6) Rutherford 6, (7) a CRP level of 3.0 mg/dL or higher, and (8) concomitant lesion below the ankle joint. Although the investigation item was different from ours (AFS vs. survival rate), dialysis was not included in the risk factors, and this remains to be investigated in the future.

There are limitations of this study. The number of patients was small and the duration of follow-up was short, weakening the findings. Secondly, patients already diagnosed with ischemic heart disease before treatment were included in the group with ischemic heart disease as an independent risk factor, and not all patients were examined by coronary arterial angiography or an exercise load test before lower limb revascularization treatment. Therefore, it cannot be ruled out that some patients with ischemic heart disease were included in the group without ischemic heart disease. Thirdly, evaluation was insufficient because blood test data and anatomical factors on angiography were missing. Moreover, the presence of a large selection bias cannot be ruled out because this was a retrospective study performed involving only a single institution. It is necessary to verify the findings in a prospective multicenter study.

Bypass and EVT for below-the-knee lesions are complementary to each other, and vascular surgeons have to become proficient in both procedures. Since the usefulness of EVT for various cases has been reported, it is somewhat careless to deny the effect of EVT on CLI. Although bypass surgery to the foot is the gold standard, its benefit may be lost unless it is applied to appropriate patients. The application of EVT within a range not interfering with bypass surgery to the foot or its decision is difficult for physicians other than vascular surgeons. The introduction of novel devices, such as Drug Coating Balloon, is expected for infrapopliteal arterial EVT.13 If a novel device improves the restenosis rate after infrapopliteal arterial EVT, the first treatment of CLI with below-the-knee lesions may be markedly shifted to EVT. Vascular surgeons have to improve their technical skills of bypass surgery and understand its advantage, and, at the same time, they should learn the advantage of below-the-knee EVT and widely utilize it.

**Conclusion**

EVT for below-the-knee lesions is useful for patients for whom de novo bypass surgery is inappropriate. Independent risk factors of death after a long time for below-the-knee CLI patients were an advanced age, concomitant ischemic heart disease, concomitant chronic heart failure, and non-ambulatory condition.

**Disclosure Statement**

There is no conflict of interest regarding the author (Takahiro Ohmine) and co-authors.

**References**