Wound Healing and Wound Location in Critical Limb Ischemia Following Endovascular Treatment

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Background: The differences in wound healing according to wound location remain unclear.

Methods and Results: Between April 2007 and October 2011, 138 patients (166 limbs) with critical limb ischemia with tissue loss were treated with endovascular treatment. On these limbs, 177 individual wounds were identified on the foot and were evaluated for wound healing rates and time to healing according to their locations. Wound locations were divided into 3 groups: group T (Toe wounds, n=112), group H (Heel wounds, n=25), and group E (Extensive wounds extending onto the fore- or mid-foot along with dorsum or plantar surfaces, n=40). The mean follow-up period was 23±19 months. At 3, 6, 9, and 12 months, wound healing rates were 51%, 64%, 75%, and 75%, respectively, in group T; 12%, 36%, 36%, and 52%, respectively, in group H; and 0%, 5%, 8%, and 13%, respectively, in group E. The median time to healing was 64 days (interquartile range 25–156 days) in group T, 168 days (interquartile range 123–316 days) in group H, and 267 days (interquartile range 177–316 days) in group E (P=0.038).

Conclusions: Extensive wounds extending onto the fore- or mid-foot along with dorsum or plantar surfaces were the most difficult type of wound to heal. (Circ J 2014; 78: 1746–1753)

Key Words: Critical limb ischemia; Time to wound healing; Wound healing rate; Wound location

Endovascular treatment (EVT) has recently been considered as an acceptable treatment for critical limb ischemia (CLI), in addition to surgical revascularization, particularly in patients with many comorbidities. Previous studies have reported that the major amputation rate for CLI after EVT was 10.5–25%. To avoid major amputation, “wound healing” is a very important endpoint, although many earlier reports have focused largely on vessel patency, limb salvage, and mortality rates, with insufficient evaluation as to whether wounds were completely healed. Although some data are available on wound healing rates and time to healing after surgical revascularization or EVT, these reports examined wound healing rates according to limb rather than individual wounds. Sometimes, several wounds exist on 1 limb; thus, each wound should be evaluated separately. Furthermore, the locations of wounds are only occasionally evaluated as an important factor influencing the healing rate. It has been reported that heel ulcers and gangrene are difficult to treat and often lead to major amputation. However, in clinical practice, difficulty is experienced in treating wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces. The aim of this study was thus to evaluate the healing of each wound according to its location in CLI following EVT.

Methods

Patients
We performed EVT to treat 895 patients (1,395 limbs) with peripheral artery disease; this was the primary treatment used in our institute from April 2007 to October 2011. Of these, 154 patients (182 limbs) had non-healing ulcers or gangrene classified as Rutherford 5 or 6 and were treated by EVT. A total of 198 separate wounds were identified in these limbs. Ten of these wounds were excluded because of their small number (3 being located only on the shin, 5 located only on the ankle, and 2 small wounds located only on the surface of the dorsum of the foot). Furthermore, 9 of the limbs (5.2%) receiving additional surgical revascularization (6 distal bypass and 3 femoropopliteal bypass) were excluded; therefore, eventually, 138 patients, 166 limbs, and 177 individual wounds were included. Although we discussed the indications of bypass with vascular surgeons, a number of patients were inoperable because of the high surgical risk and severe diffuse calcification of the distal artery. The study protocol was developed in accordance with the Declaration of Helsinki, with all patients providing written informed consent prior to enrollment.

The 177 individual wounds were divided into 3 groups ac-
cording to their location (Figure 1). Group T (toe) comprised wounds localized only to the toes, group H (heel) comprised wounds localized to the heel, and group E (extensive) comprised extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces. Wound healing rates and time to healing were retrospectively analyzed.

**Patient Evaluation and Intervention Procedure**

On admission, an interventional cardiologist and plastic surgeon checked the location and extent of tissue loss, and images of all wounds were captured to compare the course of healing. The patient’s lower limb arteries (femoral, popliteal, dorsalis, and posterior tibial artery) were palpated, and the hemodynamic status was evaluated using the ankle brachial index (ABI), skin perfusion pressure (SPP), and duplex ultrasound. SPP was measured on the dorsal and plantar sides of the foot. Flow in the lower limb artery was evaluated routinely before EVT using duplex ultrasound and digital subtraction angiography (DSA). The indications for EVT were decided after discussions with vascular surgeons.

A retrograde approach was generally used for treatment of iliac lesions. A 6-Fr sheath was inserted into the ipsilateral common femoral artery and a 0.014-inch or 0.018-inch wire was advanced into the lesion under intravascular ultrasound (IVUS) guidance. After pre-dilatation using an optimal size of balloon, primary stenting using a self-expandable stent was performed. The correct balloon and stent diameter was determined by IVUS. For treating femoropopliteal lesions, the majority of cases were treated by an antegrade approach through the contralateral common femoral artery. A 6-Fr sheath was used and a 0.014-inch wire was advanced into the lesion. Balloon angioplasty using a balloon with a diameter 1–2 mm less than the reference diameter was performed for 120–180 s. If the patients had a residual pressure gradient of >10 mmHg, residual diameter stenosis of >30%, and/or flow-limiting dissection after balloon angioplasty, a self-expandable stent was implanted. For treating infrapopliteal lesions, generally a 4-Fr sheath was inserted into the ipsilateral common femoral artery for an antegrade approach. A 0.014-inch wire was then advanced into the lesion and only balloon angioplasty was performed. Patients always received 5,000 U heparin after sheath insertion. Dual antiplatelet therapy of aspirin (100 mg/day) plus ticlopidine (200 mg/day), or clopidogrel (75 mg/day) was administered to all patients before the procedures and continued for at least a month.

**Follow-up and Wound Care**

The mean follow-up period was 23±19 months. Patients were followed up at our outpatient foot care clinic after EVT until their wound was completely healed. If patients did not attend the clinic, we called them to ask about the status of the wounds and made a further appointment at the foot care clinic on a different day. However, 11 patients (7%) were lost to follow up because of transferring to other hospitals or losing contact. We took pictures of the wounds each time, with the time of wound healing being recorded. Wound healing was based on the TIME classification (Tissue, Infection or Inflammation, Moisture imbalance, and Edge of wound). After wound healing, the patients were monitored by clinical assessment every 3 months. Our management included cleaning of the wounds, application of ointment, wound debridement, use of vacuum-assisted closure therapy (VAC; Kinetic Concepts, San Antonio, TX, USA),22,23 and education of patients and families with regard to daily care of wounds. Enzymatic ointments were applied if necessary, as per the plastic surgeon’s discretion. In addition, off-loading techniques were employed using customized shoes for the purpose of depressurization. Infectious wounds were treated by using appropriate antibiotics, and if infection was not resolved sufficiently, myelitis or subcutaneous abscesses was investigated using magnetic resonance imaging or duplex ultrasound. If necessary, incisional drainage and osteotomy were added or an auto skin graft and free flap reconstruction were performed by a plastic surgeon. We evaluated ABI or SPP every 3 months for all patients, and duplex ultrasound was performed when ABI or SPP values suggested an abnormality and delay in wound healing. However, we do not necessarily perform an angiography if wound healing is favorable, even though ABI, SPP and duplex values suggest restenosis. After angiographical restenosis was evident, we performed repeat intervention for only the wounds with delayed healing. Repeat intervention was performed until wound healing was achieved. If this intervention failed, the vascular surgeon was requested to perform surgical revascularization.
Table 1. Baseline Characteristics of the 138 Critical Limb Ischemia Patients

<table>
<thead>
<tr>
<th></th>
<th>Group T (n=84)</th>
<th>Group H (n=17)</th>
<th>Group E (n=37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>73±10</td>
<td>73±8</td>
<td>71±13</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>54 (64%)</td>
<td>14 (82%)</td>
<td>20 (54%)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>22±4</td>
<td>20±3</td>
<td>20±3</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Risk factors/comorbidities**

- Hypertension: 69 (82%) vs. 14 (82%) vs. 29 (78%); 0.88
- Dyslipidemia: 28 (33%) vs. 5 (29%) vs. 14 (38%); 0.81
- Diabetes mellitus: 60 (71%) vs. 14 (82%) vs. 29 (78%); 0.53
- Insulin use: 21 (25%) vs. 4 (24%) vs. 13 (35%); 0.48
- Dependence on hemodialysis: 32 (38%) vs. 6 (35%) vs. 23 (62%); 0.036
- Coronary artery disease: 27 (32%) vs. 8 (47%) vs. 16 (43%); 0.33
- Cerebrovascular disease: 23 (27%) vs. 4 (24%) vs. 11 (30%); 0.89
- **EF**
  - 57±12 vs. 57±13 vs. 56±13; 0.91
- **Low EF <40%**
  - 9 (11%) vs. 2 (12%) vs. 5 (14%); 0.92
- **Non-ambulatory status**
  - Wheelchair: 22 (26%) vs. 8 (47%) vs. 12 (32%); 0.12
  - Bedridden: 3 (4%) vs. 0 (0%) vs. 4 (11%); 0.15
- **Laboratory data**
  - Albumin g/dl: 3.3±0.5 vs. 3.0±0.5 vs. 2.8±0.7; <0.001
  - C-reactive protein mg/dl: 2.0±1.7 vs. 2.6±1.6 vs. 5.2±2.1; <0.001
  - White blood cell /μl: 7,300±2,100 vs. 6,900±3,000 vs. 9,400±4,500; 0.001
  - Creatinine mg/dl: 3.3±2.5 vs. 3.3±2.1 vs. 4.6±3.5; 0.18
  - Hemoglobin A1c %: 6.8±1.7 vs. 6.8±1.4 vs. 6.6±1.4; 0.73
- **Medications**
  - Cilostazol: 58 (69%) vs. 12 (71%) vs. 17 (46%); 0.04

Group T, toe wounds; Group H, heel wounds; Group E, extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces; EF, Ejection fraction.

Table 2. Lesion Characteristics and Endovascular Procedures of 177 Individual Wounds

<table>
<thead>
<tr>
<th></th>
<th>Group T (n=112)</th>
<th>Group H (n=25)</th>
<th>Group E (n=40)</th>
<th>P value</th>
</tr>
</thead>
</table>
| **Location of target lesion**
  - Aortoiliac         | 0 (0%)          | 0 (0%)         | 0 (0%)         | 0.16    |
  - Femoropopliteal    | 3 (2.7%)        | 2 (8%)         | 0 (0%)         |         |
  - Infrapopliteal     | 68 (60.6%)      | 12 (48%)       | 21 (52.5%)     | 0.47    |
  - Aortoiliac+Femoropopliteal | 2 (1.8%) | 1 (4%)         | 0 (0%)         | 0.47    |
  - Aortoiliac+Infrapopliteal | 5 (4.5%) | 2 (8%)         | 2 (5%)         | 0.77    |
  - Femoropopliteal+Infrapopliteal | 28 (25%) | 5 (20%)       | 14 (35%)       | 0.34    |
  - Aortoiliac+Femoropopliteal+Infrapopliteal | 6 (5.4%) | 3 (12%)       | 3 (7.5%)       | 0.48    |
| **Proportion of infrapopliteal**
  - Chronic total occlusion (length >200 mm) | 48 (43%) | 11 (44%) | 30 (75%) | 0.03 |
| **Lesion calcification**
  *Defined as a significant calcified wall, assessed by angiography.*
  - Lesion calcification* | 39 (35%) | 13 (52%) | 25 (63%) | 0.007 |
| **Infection**
  - Infection | 38 (34%) | 12 (48%) | 33 (83%) | <0.001 |
| **Gangrene**
  - Gangrene | 45 (40%) | 17 (68%) | 33 (83%) | 0.001 |
| **Treatment outcomes**
  - One straight line to the foot | 102 (91%) | 23 (92%) | 26 (65%) | <0.001 |
  - Direct blood flow to the wounds | 82 (73%) | 19 (76%) | 20 (50%) | <0.001 |
  - ABI before EVT | 0.67±0.23 | 0.51±0.15 | 0.56±0.15 | 0.06 |
  - ABI after EVT | 0.89±0.16 | 0.81±0.13 | 0.87±0.12 | 0.45 |
  - SPP before EVT mmHg | 22±11 | 19±9 | 20±9 | 0.10 |
  - SPP after EVT mmHg | 53±23 | 52±22 | 53±19 | 0.15 |
  - Repeat EVT | 29 (26%) | 9 (36%) | 12 (30%) | 0.61 |

ABI, Ankle brachial index; EVT, endovascular treatment. Group T, toe wounds; Group H, heel wounds; Group E, extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces; SPP, Skin perfusion pressure.

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Endpoints
The primary endpoint of this study was the wound healing rate and the secondary endpoint was time to wound healing.

Definitions
Ischemic tissue loss due to CLI was defined according to the Trans Atlantic Inter-Society Consensus (TASC) guideline as tissue loss associated with an ankle pressure of <70 mmHg or a toe pressure of <50 mmHg. If these measurements could not be obtained due to intractable rest pain or a non-compressible artery due to severe calcification, SPP was measured at the dorsum and sole of the foot. An SPP of <40 mmHg was defined as ischemic tissue loss or rest pain. Technical success was defined as achievement of at least 1 straight line to the foot with <30% residual stenosis in the target lesion without any obvious flow-limiting lesions. One straight line included collateral flow from the peroneal artery to the distal tibial artery. Direct blood flow to the wound was defined as achieve-
ment of adequate blood flow to the wound evaluated by DSA after EVT in addition to the 1 straight line to the foot, irrespective of the use of the angiosome concept. We defined time to healing as the time needed to achieve complete epithelialization of the ischemic lesions, with all wound care becoming unnecessary including wound cleaning and application of ointment. An infectious wound was defined by the use of any antibiotic during the course of a disease, excluding prophylactic purposes. Toe or transmetatarsal amputations were considered minor amputations, whereas major amputation included all above-ankle amputations. Wounds were left open after minor amputation, and wound treatment to achieve the growth of granulation was performed. Thus, time to healing after minor amputation was also defined as complete epithelialization of the ischemic lesions, with no further need of wound care, including wound cleaning and ointment application. Coronary artery disease was defined as documented angina pectoris, myocardial infarction, or a history of coronary artery revascularization, and cerebrovascular disease as a history of stroke, transient ischemic attacks, carotid artery revascularization, or intracranial hemorrhage. Non-ambulatory status was defined as being wheelchair-bound or in a bedridden state.

Statistical Analysis
The analysis was on an intention-to-treat basis. Continuous variables with normal distributions were expressed as mean±standard deviation, whereas variables without normal distribution were expressed as median and interquartile range (namely, wound healing time). Categorical variables were shown as percentages. Comparisons of more than 2 groups were tested by using 1-way analysis of variance or the Chi-squared test, whereas multiple comparisons were performed by using Tukey’s honestly significant difference test. Univariate analysis was performed to identify factors that predicted wound healing, and Cox proportional hazard analysis was used to identify the independent predictors of wound healing. Kaplan-Meier analysis and the log-rank test were used to compare groups for wound healing rates. A 2-sided P value of <0.05 was considered statistically significant. All analyses were performed by using SPSS software (version 19; IBM Corporation, Somers, NY, USA).

Results

Patient Characteristics
This study included 138 patients (88 males, mean age 71±10 years), 166 limbs, and 177 individual wounds treated by only EVT. Group T included 112 wounds, group H included 25 wounds, and group E included 40 wounds. There were no significant differences between the 3 groups except for albumin (Alb), C-reactive protein (CRP) levels, white blood cell (WBC), rates of hemodialysis, and cilostazol administration. As shown in Table 1, Alb was lower in group E than in the other 2 groups (group T, 3.3±0.5 g/dl; group H 3.0±0.5 g/dl; group E 2.8±0.7 g/dl; P<0.001), the corresponding CRP and WBC values were higher in group E than in the other 2 groups (CRP: group T 2.0±1.7 mg/dl, group H 2.6±1.6 mg/dl, group E 5.2±2.1 mg/dl; P<0.001; WBC: group T 7,300±2,100 /μl, group H 6,900±3,000 /μl, group E 9,400±4,500 /μl; P=0.001). Rates of hemodialysis were higher in group E than in the other 2 groups (38%, 35%, and 62%, respectively, P=0.036). Cilostazol administration rates were 69%, 71%, and 46%, respectively (P=0.04).

Lesion Characteristics and Endovascular Procedures
There were no significant differences in the location of the target lesions in groups T, H, and E (Table 2). The majority of patients had infrapopliteal lesions (group T 95%, group H 88%, and group E 100%, respectively). The corresponding percentages for chronic total occlusion (CTO) lesions longer than 200 mm for each group (T, H, E) were 43%, 44%, and 75%, respectively (P=0.03). The lesion calcification was significantly severe in group E (group T 35%, group H 52%, and group E 63%, respectively, P=0.007). The rates of 1 straight line to the foot for groups T, H and E were 91%, 92%, and 65%, respectively, (P<0.001), and the rates of direct blood flow to the wound were 73%, 76%, and 50%, respectively (P<0.001).
Wound Healing and Wound Location

### Table 3. Multivariate Cox Proportional Hazard Analysis for Wound Healing After Endovascular Therapy for Critical Limb Ischemia

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces</td>
<td>0.17</td>
<td>0.07–0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dependence on hemodialysis</td>
<td>0.33</td>
<td>0.21–0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heel wounds</td>
<td>0.39</td>
<td>0.22–0.71</td>
<td>0.002</td>
</tr>
<tr>
<td>Infectious wounds</td>
<td>0.65</td>
<td>0.42–0.99</td>
<td>0.046</td>
</tr>
<tr>
<td>Direct blood flow to the wounds</td>
<td>1.90</td>
<td>1.12–3.24</td>
<td>0.018</td>
</tr>
</tbody>
</table>

### Discussion

Occasionally, there are several wounds on limbs of patients with CLI, and each of their healing courses are different. In a typical case, 1 wound could be healed but the other wound could not, meaning that as a result, the patient must undergo major amputation or die. In such a case, wound healing could not be obtained for the limb, however, one wound would be successfully healed. Therefore, it is important to investigate the factors that influenced wound healing between these 2 wounds. The important thing is that wound healing should be assessed by “each wound” and not by each limb. The same is true for CLI patients with both legs’ tissue loss.

This study revealed that the wound healing rate of extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces were the lowest. The biggest factor of wound non-healing in extensive wounds was poor achievement rate of direct blood flow to the wounds. We achieved 50% direct blood flow to the wound in group E, but this rate was statistically significantly lower than that in the other 2 groups. In our opinion, this result can be derived from the fact that group E had more severe target lesion characteristics. The incidence rates of CTO lesions >200 mm and lesion calcification were statistically significantly higher in group E. In the BASIL study that compared balloon angioplasty with bypass surgery, it revealed favorable results for bypass surgery in patients with CLI; however, the BASIL study was conducted with the exception of unsuitable patients for bypass surgery.

In contrast, the present study included all CLI patients with non-healing ulceration or gangrene, irrespective of whether revascularization succeeded. Of these, there were numerous inoperable cases because of the high risk of surgery and severe diffuse calcification of the distal artery. These patients had no choice but to be treated by catheter intervention, although the effects were limited. In fact, this is the actual scenario in our clinical settings, and we cannot ignore these patients in day-to-day clinical practice; therefore, we must evaluate wound healing rates, including those for wounds that are difficult to treat.

A large discrepancy was observed between direct blood flow rates and wound healing rates in group H and group E, implying that some wounds in group H and group E did not heal successfully despite achievement of direct blood flow to the wounds. On the contrary, the wound healing rate was higher than the direct blood flow rate in group T. A reasonable interpretation of these discrepancies is that success of revascularization is not the only factor that predicts wound healing. Although there are few published studies investigating predictors of not only limb salvage or death, but also of “wound healing,” Iida et al. reported that a body mass index (BMI) of <18.5 (HR, 0.54; P=0.03) and wound infection (HR, 0.60; P=0.04) were predictors of unhealed wounds. Furthermore, Kawarada et al. reported that DM, infectious wounds, and pedal arch...
classification were independent predictors of wound non-healing. In this study, multivariate Cox proportional hazard analysis revealed that extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces, heel wounds, infectious wounds, and dependence on HD were independent predictors of non-healing wounds. These findings suggest that evaluation of wound locations is meaningful for the prediction of wound healing.

Ulceration or gangrene located at the heel is considered difficult to treat, and it has been recommended to carry out primary amputation in selected individuals with heel necrosis. Soderstrom et al. showed that ischemic tissue lesions located on the mid- and hind-foot had significantly prolonged ulcer healing times (HR 0.4, P=0.044). In contrast, Berceli et al. on the mid- and hind-foot had significantly prolonged ulcer healing for major lower extremity amputation (9.8% vs. 9.3%, P=0.87). The complete healing rates were similar (90.5% vs. 86.5%, P=0.26), with comparable rates showing that complete healing rates for forefoot and heel lesions were similar (90.5% vs. 86.5%, P=0.26), with comparable rates for major lower extremity amputation (9.8% vs. 9.3%, P=0.87).

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Dosluoglu et al. reported that 24-month limb salvage and patency rates were similar between patients with heel ulcers or gangrene and those with lesions on other parts of the foot. Our findings are in agreement with those of Soderstrom et al., and they indicate that the rate of healing of heel wounds was lower than that of toe wounds, and that it took a considerably longer time to heal. We consider that heel wounds, which tend to be larger than toe wounds, get compressed easily while walking and sleeping, leading to a further delay in wound healing. Furthermore, the rate of infection and gangrene was higher in group H than in group T. These factors might influence each other and might cause a delay of healing of heel wounds.

Minor amputations were performed for 35 wounds in group T (31%) and 12 wounds (30%) in group E; however, none were performed in group H. Some reports suggested the use of minor amputation for the treatment of large ulcers or gangrene. After optimal minor amputations, we could achieve wound healing more easily and also shorten the time of healing for large wounds such as wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces. Minor amputations were performed for all healed wounds in group E in this study. In contrast, Bollinger and Thordarson found that partial calcanectomy was a good alternative to below-knee amputation. Although we could not perform minor amputations for heel wounds, it might be possible that a partial calcanectomy for heel wounds refractory to conservative therapy might improve the rate of wound healing and reduce the healing time.

In the clinical setting, we generally divide wounds into 2 groups using the Rutherford classification, that is, into Rutherford 5 or Rutherford 6. However, the Rutherford classification is ambiguous and sometimes it is difficult to clearly categorize wounds into 2 groups because there are various types of wounds and sometimes multiple wounds on 1 limb. In the present study, we divided wounds into 3 groups according to their locations, and revealed statistically different results of wound healing rates, although there were differences in baseline characteristics. Multivariate analysis revealed that extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces and heel wounds were independent predictors of wound non-healing. Thus, a different classification system that includes detailed information of wound characteristics might be needed. Azuma et al. reported wound healing rates in patients with CLI after bypass surgery using a similar categorization (Rutherford 5, Rutherford 6 with heel ulcer or gangrene, Rutherford 6 without heel lesion). In our study, we divided wounds more specifically into 3 types, with respect to wound locations, and included only patients treated by EVT alone. Thus, this is a meaningful study in the evaluation of the clinical course of patients with CLI treated by EVT alone. In addition, although wound care is very important, usually there is no discussion regarding the type of treatment administered. To improve wound healing rates in patients with CLI, establishment of effective treatment strategies and standardization of wound treatment is necessary.

Group E patients had a poor baseline background (DM: 78%, HD: 62%; infection: 83%, gangrene: 83%) and an extremely poor wound healing rate (only 13%) in this study. In addition, these patients had a high rate of major amputation (47.5%) and death (64.9%) before achieving complete wound healing. EVT has limitations in the treatment of such patients, and bypass surgery should be considered if their general condition is fair and there are sufficient distal arteries to connect bypass. Extensive wounds always develop from smaller wounds such as toe wounds; therefore, it is essential to diagnose CLI patients with tissue loss at an earlier stage and perform revascularization and provide appropriate wound care as soon as possible to prevent wound growth. Furthermore, for these extensive wounds from patients with poor background characteristics such as dependence on HD or wound infection, it might be necessary to consider primary amputation, if we cannot achieve successful revascularization or if there are no signs of wound healing following successful revascularization.

Study Limitations
This study had several limitations. First, it was a non-randomized, retrospective analysis at a single center, with a relatively small sample size. Second, evaluation of the severity of each wound was insufficient. The Texas University classification and Wegner’s classification have been established for evaluation of the diabetic foot. These classifications include assessment of ulcer size, wound appearance, clinical evidence of infection, ischemia, and neuropathy. The size and depth of wounds were not considered in this study. Third, we could not completely follow the patency rates of the treated vessels. Finally, the strategy of infrapopliteal angioplasty was limited to only balloon angioplasty as other options such as bare-metal stents, drug-eluting stents, drug-coated balloons, and laser atherectomy were not available in Japan. In this regard, a reduction of target lesion revascularization has been reported with the use of drug-eluting stents or laser atherectomy.

Conclusions
Extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces had the lowest healing rates and the longest time to healing compared with other types of wounds. It is difficult to achieve direct blood flow to these extensive wounds because of their severe target lesion. In addition, patients who belonged to group E were apparently in a poor condition in terms of wound healing due to low albuminemia, high CRP, and high WBC. These factors were all related to hemodialysis, so not only wound location but also the patient background, especially if they are being treated with hemodialysis, have a great impact on wound healing. Heel wounds also exhibited a poor healing rate and took a considerably longer time to heal compared with toe wounds. Multivariate analysis revealed that wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces and heel wounds were an independent adverse predictor of wound healing, as factor of wound locations as well as hemodialysis and wound infection. Apart from successful revascularization, various factors including patient background and wound characteristics are associated with wound healing; therefore, we should treat not
only “target lesions” but also the “wounds.” The Rutherford classification is not sufficient to determine the severity of wounds in patients with CLI.

References