Ambulatory Status Over Time after Revascularization in Patients with Chronic Limb-Threatening Ischemia

Akio Kodama¹, Mitsuyoshi Takahara², Osamu Iida³, Yoshimitsu Soga⁴, Hiroto Terashi⁵, Daizo Kawasaki⁶, Yuichi Izumi⁷, Shinsuke Mii⁸, Kimihiro Komori¹ and Nobuyoshi Azuma⁹ on behalf of the SPINACH investigators.

¹Division of Vascular Surgery, Department of Surgery, Nagoya University School of Medicine, Nagoya, Japan
²Department of Diabetes Care Medicine, and Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
³Cardiovascular Center, Kansai Rosai Hospital, Hyogo, Japan
⁴Department of Cardiology, Kokura Memorial Hospital, Fukuoka, Japan
⁵Department of Plastic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
⁶Cardiovascular Center, Morinomiya Hospital, Osaka, Japan
⁷Nayoro City General Hospital, Hokkaido, Japan
⁸Department of Vascular Surgery, Saiseikai Yahata General Hospital, Fukuoka, Japan
⁹Department of Vascular Surgery, Asahikawa Medical University, Hokkaido, Japan

Aim: Maintaining functional status through revascularization is a major goal in patients with chronic limb-threatening ischemia (CLTI). Nevertheless, there is a lack of clarity on the impact of revascularization on mobility over time. This study examined ambulatory status over time after revascularization and predictors of ambulation loss in CLTI patients.

Methods: We used a clinical database established by the Surgical reconstruction versus Peripheral INtervention in pAtients with critical limb isCHemia study, a prospective, multicentre, observational study including patients with CLTI. The primary endpoint was mobility over time.

Results: Of the 381 patients, the ambulatory proportion at baseline was 71%. The proportion gradually decreased, finally reaching 40% at 36 months. In non-ambulatory patients at revascularisation, approximately 20-40% of patients achieved ambulation. Multivariate analysis confirmed that age, impaired mobility before CLTI onset and at revascularization, renal failure on dialysis, and WIfI clinical stage 4 were positively associated with ambulation loss at either specific or all time points, whereas male sex and surgical reconstruction were inversely associated with the outcomes at specific time points.

Conclusion: Mobility in the overall population gradually decreased, whereas the number of deceased patients increased. Advanced age, impaired mobility before CLTI onset and at revascularization, renal failure on dialysis, and WIfI stage 4 were associated with ambulation loss at almost all points after revascularization.

Clinical trial registration: UMIN000007050.

Key words: Chronic limb-threatening ischemia, Revascularization, Ambulatory, Functional status, Ambulatory status

Introduction

Chronic limb-threatening ischemia (CLTI) is the most severe form of peripheral arterial disease (PAD) and is characterised by ischaemic rest pain and tissue loss⁴. The CLTI population is generally frail and has impaired activities of daily living (ADL) and limited lower limb functionality due to ongoing ischaemic...
pain and wounds. Revascularization is needed to improve ischaemic symptoms and avoid major amputation\textsuperscript{1}). The functional status of CLTI patients decreases after major amputation; therefore, one of the major goals in treating CLTI patients is to salvage ischaemic limbs and preserve baseline functional status\textsuperscript{1, 2}). Moreover, CLTI is significantly associated with high mid- and long-term mortality\textsuperscript{3}). Therefore, we should consider not only a patient’s functional status but also their life expectancy in decision-making regarding appropriate treatment\textsuperscript{3, 4}).

Many previous studies have evaluated and used ambulation capability as a surrogate for functional status. Preoperative ambulatory status has been reported to be a predictor of major clinical outcomes, including amputation-free survival and mortality\textsuperscript{3, 5}). Although several studies have attempted to evaluate patient functional outcomes after revascularization, many of them were single-centre studies, investigated a small number of CLTI patients, and were limited by their relatively restricted scope in assessing functional outcomes because of their retrospective nature\textsuperscript{6}). Therefore, the impact of revascularization on ambulatory status remains poorly understood in actual clinical settings.

Although previous studies have revealed several predictors of the ambulatory status and functional outcomes of patients following revascularization, such as amputation and preoperative non-ambulatory status, only a few studies have investigated the factors related to affected limb severity and investigated surviving patients\textsuperscript{7, 8}).

Aim

The aim of the current study was to evaluate ambulatory status over time after revascularization for CLTI and to investigate its associated factors, including not only patient characteristics but also ischaemic limb severity, at each time point in CLTI patients who underwent surgical and endovascular revascularization.

Methods

We extracted data from a clinical database established by the Surgical reconstruction versus Peripheral INtervention in pAtients with critical limb isCHemia (SPINACH) study, a prospective, multicentre, observational study that registered patients who had CLTI due to atherosclerotic arterial disease in 23 centres (12 vascular surgery departments and 11 interventional cardiology departments) in Japan. The details of the SPINACH study are described elsewhere\textsuperscript{9, 10}). The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each centre. Written informed consent was obtained. The current study analysed 381 CLTI patients who underwent revascularization due to either ischaemic rest pain with Wound, Ischemia, and foot Infection [WIfI] grade 3 ischemia or tissue loss with WIfI grade 2/3 ischemia. Patients who were non-ambulatory before the current CLTI onset with a long-term wheelchair requirement or bedridden status, for example, because of neurogenic deficits (paraplegia, stroke, and so on), who had already undergone major amputation at registration, and who had been diagnosed with dementia, were excluded from the current analysis.

Definitions

As mentioned previously, the WIfI classes of the study participants were retrospectively determined using photographs of pedal wounds and medical records, including laboratory examinations at the time of registration\textsuperscript{11}). The initial judgement was made at each participating centre and was subsequently reviewed by an independent plastic surgeon. Disagreements were discussed and resolved in a subsequent committee meeting attended by a plastic surgeon, a vascular surgeon and an interventional cardiologist. Skin perfusion pressures (SPPs) of 31-40 mmHg and \( \leq 30 \) mmHg were considered WIfI grade 2 and 3 ischemia, respectively. The ambulatory status immediately before revascularization for the current CLTI and at each time point after revascularization was classified into the following categories: (1) ambulatory without aid (i.e., independently ambulatory), (2) ambulatory with aid (i.e., ambulatory using crutches/cane/walker), (3) wheelchair without aid (i.e., operates a wheelchair without aid), (4) wheelchair with aid (i.e., operates a wheelchair assisted by another person), (5) bedridden, and (6) deceased. The data on ambulatory status before the current CLTI onset were obtained from medical records or self-reports. Renal failure was defined as an estimated glomerular filtration rate <30 ml/min/1.73 m\(^2\) or dependence on dialysis. During the three-year follow-up period, ambulatory status was scheduled to be assessed at 3, 12, 24, and 36 months, with a tolerated deviation of \( \pm 1 \) month.

Outcome Measures

The outcome measure in the current study was ambulation, i.e., survival with ambulation regardless of aid. Ambulation loss indicated a wheelchair-bound, bedridden, or deceased status.
respectively. WIfI clinical stage 1, 2, 3, and 4 accounted for 0%, 18%, 31%, and 51%, respectively. Forty percent of the population underwent surgical reconstruction, and the rest underwent only endovascular therapy. In the patients undergoing endovascular treatment (EVT) alone, 102 patients (44%) underwent stent implantation (19 patients [8%] drug-eluting stent implantation), and 167 (73% of only endovascular therapy patients) underwent infrapopliteal revascularization. In the patients undergoing surgical reconstruction, distal anastomoses were performed on crural or pedal arteries in 113 patients (75% of surgical reconstruction patients).

Fig. 1 illustrates the changes in mobility during the three years after revascularization. The estimated proportion of ambulation in the overall population [95% confidence interval] was 71% [66% to 75%] at baseline, and thereafter gradually decreased (P < 0.05 versus baseline), finally reaching 40% [35% to 45%] at 36 months. The estimated mortality rates at 12, 24, 36 months were 17% [13% to 20%], 29% [24% to 33%], and 43% [38% to 48%], respectively (Fig. 1A).

On the other hand, in patients without ambulation at revascularization, approximately 40% of patients achieved ambulation after revascularization, and the proportion of patients achieving ambulation was

### Statistical Analysis

Data are presented as the mean and standard deviation (SD) for continuous variables or as percentages for discrete variables, if not otherwise mentioned. A *P* value of < 0.05 was considered statistically significant, and 95% confidence intervals are reported when appropriate. The proportions of the outcome measures at specific time points were compared with those at baseline using the McNemar test. The associations of baseline characteristics with either ambulation loss or independent ambulation loss were investigated with binomial logistic regression models. We also supplementarily investigated the association between limb status and ambulation at each time point. Missing data were treated with the use of multiple imputation (10 times) by the chained equations method. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

### Results

The baseline characteristics of the study population are summarized in Table 1. The mean age was 72 ± 9 years, and the prevalence of diabetes mellitus and renal failure was 75% and 58%, respectively. WIfI clinical stage 1, 2, 3, and 4 accounted for 0%, 18%, 31%, and 51%, respectively. Forty percent of the population underwent surgical reconstruction, and the rest underwent only endovascular therapy. In the patients undergoing endovascular treatment (EVT) alone, 102 patients (44%) underwent stent implantation (19 patients [8%] drug-eluting stent implantation), and 167 (73% of only endovascular therapy patients) underwent infrapopliteal revascularization. In the patients undergoing surgical reconstruction, distal anastomoses were performed on crural or pedal arteries in 113 patients (75% of surgical reconstruction patients).

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observed only in 20–40%) that the multivariate regression models might be subject to overfitting. Future studies with a larger number of this subgroup population will be needed to validate the current findings.

The association of limb status after revascularization and ambulation loss were also investigated (Supplementary Fig. 2 and Supplementary Table 3). Patients with major amputation and those with tissue loss were more likely to have ambulation loss. ()

Discussion

In this study, we demonstrated short- and mid-term changes in mobility after revascularization, which were stratified by ambulation status at revascularization. Moreover, we revealed some predictors of ambulation loss, including not only patient characteristics but also affected limb severity, by using the WIfI stage. In the current study, we applied only preoperative variables in the logistic regression model to clarify the risk stratification of ambulation loss after revascularization in actual clinical settings. With respect to mobility over time in the overall cohort, it gradually decreased until 3 years, and the proportion of deceased patients increased. Approximately 20–40% of patients without ambulation at revascularization recovered their functional capacity after revascularization until 3 years. Multivariate analysis confirmed that renal failure on dialysis was associated with ambulatory loss after revascularization throughout the study period. WIfI clinical stage 4 was also associated with this outcome in the short-term (within a year) after revascularization.

In clinical decision-making, to preserve functional status after revascularization, physicians...
Table 2. Associations of baseline characteristics with ambulation loss

| Characteristic                                                                 | Crude odds ratio | Adjusted odds ratio |
|-------------------------------------------------------------------------------|------------------|---------------------|
| **Age (per 10 years)**                                                        |                  |                     |
| At 3 months                                                                   | 1.3 [1.0 to 1.7]  | (P = .029)*         |
| At 12 months                                                                  | 1.3 [1.0 to 1.6]  | (P = .084)          |
| At 24 months                                                                  | 1.3 [1.0 to 1.7]  | (P = .028)*         |
| At 36 months                                                                  | 1.0 [0.8 to 1.3]  | (P = .88)           |
| **Male sex (vs. female sex)**                                                  |                  |                     |
| At 3 months                                                                   | 0.6 [0.4 to 1.0]  | (P = .444)*         |
| At 12 months                                                                  | 0.5 [0.3 to 0.9]  | (P = .101)          |
| At 24 months                                                                  | 0.8 [0.5 to 1.3]  | (P = .44)           |
| At 36 months                                                                  | 1.2 [0.8 to 2.0]  | (P = .39)           |
| **Ambulatory with aid before CLI onset (vs. ambulatory without aid)**         |                  |                     |
| At 3 months                                                                   | 2.2 [1.3 to 3.6]  | (P = .002)*         |
| At 12 months                                                                  | 3.1 [1.8 to 5.3]  | (P < .001)*         |
| At 24 months                                                                  | 3.1 [1.7 to 5.5]  | (P < .001)*         |
| At 36 months                                                                  | 2.1 [1.0 to 4.2]  | (P = .040)*         |
| **Ambulatory with aid at revascularization (vs. ambulatory without aid)**    |                  |                     |
| At 3 months                                                                   | 1.2 [0.6 to 2.3]  | (P = .65)           |
| At 12 months                                                                  | 1.8 [1.0 to 3.3]  | (P = .045)*         |
| At 24 months                                                                  | 1.8 [1.0 to 3.2]  | (P = .048)*         |
| At 36 months                                                                  | 1.3 [0.7 to 2.6]  | (P = .43)           |
| **Non-ambulatory at revascularization (vs. ambulatory without aid)**         |                  |                     |
| At 3 months                                                                   | 5.6 [3.1 to 10.2] | (P < .001)*         |
| At 12 months                                                                  | 4.7 [2.8 to 7.8]  | (P < .001)*         |
| At 24 months                                                                  | 4.2 [2.3 to 7.4]  | (P < .001)*         |
| At 36 months                                                                  | 3.6 [1.7 to 7.7]  | (P = .002)*         |
| **Current smoking**                                                           |                  |                     |
| At 3 months                                                                   | 0.4 [0.2 to 0.8]  | (P = .009)*         |
| At 12 months                                                                  | 0.4 [0.2 to 0.9]  | (P = .022)*         |
| At 24 months                                                                  | 0.5 [0.2 to 0.9]  | (P = .025)*         |
| At 36 months                                                                  | 0.7 [0.4 to 1.2]  | (P = .21)           |
| **Diabetes mellitus**                                                         |                  |                     |
| At 3 months                                                                   | 1.5 [0.9 to 2.7]  | (P = .15)           |
| At 12 months                                                                  | 1.2 [0.7 to 2.0]  | (P = .47)           |
| At 24 months                                                                  | 1.4 [0.9 to 2.3]  | (P = .15)           |
| At 36 months                                                                  | 1.7 [1.1 to 2.8]  | (P = .029)*         |
| **Renal failure without dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)**              |                  |                     |
| At 3 months                                                                   | 0.6 [0.1 to 2.7]  | (P = .52)           |
| At 12 months                                                                  | 1.6 [0.5 to 4.8]  | (P = .41)           |
| At 24 months                                                                  | 1.0 [0.4 to 2.9]  | (P = .95)           |
| At 36 months                                                                  | 1.2 [0.4 to 3.3]  | (P = .72)           |
| **Renal failure on dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)**                   |                  |                     |
| At 3 months                                                                   | 2.5 [1.6 to 4.2]  | (P < .001)*         |
| At 12 months                                                                  | 3.2 [1.9 to 5.3]  | (P < .001)*         |
| At 24 months                                                                  | 3.1 [1.9 to 5.1]  | (P < .001)*         |
| At 36 months                                                                  | 3.3 [1.9 to 5.7]  | (P < .001)*         |
should consider life expectancy because the CLTI population has a generally poor survival rate. Although multiple risk stratification tools to estimate life expectancy have been developed and applied to the CLTI population, the recently published guidelines state that no specific model can be recommended. Indeed, we cannot predict mortality in each patient in an actual clinical setting. Therefore, we analysed ambulatory status over time in all CLTI patients, which included not only surviving but also deceased patients. This was a deliberate choice by the participants of the SPINACH study to combine mortality and ambulatory status, which is different from other analyses. Obviously this influences the outcome rates which should be kept in mind. Several studies reported that the rates of maintenance of ambulation at 1 and 3 years were 70-90% and 70-80%, respectively. These outcomes seemed to be much better than our results. However, these studies retrospectively assessed only surviving patients at each time point; therefore, the proportion of ambulatory patients was higher than that in studies including deceased patients.

Data were derived from a univariate logistic regression model, whereas adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the tables were entered as explanatory variables. Asterisks indicate $P < 0.05$.

| (Cont. Table 2) | Crude odds ratio | Adjusted odds ratio |
|-----------------|------------------|---------------------|
| **Heart failure** |                  |                     |
| At 3 months     | 1.5 [0.8 to 2.8] ($P = 0.21$) | 1.0 [0.5 to 2.2] ($P = 0.90$) |
| At 12 months    | 1.5 [0.8 to 2.7] ($P = 0.19$) | 1.0 [0.5 to 2.1] ($P = 0.96$) |
| At 24 months    | 1.6 [0.8 to 3.2] ($P = 0.17$) | 1.0 [0.5 to 2.4] ($P = 0.91$) |
| At 36 months    | 1.9 [1.0 to 3.7] ($P = 0.048$)$^*$ | 1.4 [0.7 to 2.9] ($P = 0.39$) |
| **Haemoglobin (per 1 g/dl)** |                  |                     |
| At 3 months     | 0.9 [0.8 to 1.0] ($P = 0.026$)$^*$ | 1.0 [0.9 to 1.2] ($P = 0.81$) |
| At 12 months    | 0.9 [0.8 to 1.0] ($P = 0.343$)$^*$ | 1.1 [0.9 to 1.3] ($P = 0.30$) |
| At 24 months    | 0.8 [0.7 to 0.9] ($P = 0.002$)$^*$ | 1.0 [0.8 to 1.1] ($P = 0.52$) |
| At 36 months    | 0.8 [0.7 to 0.9] ($P = 0.006$)$^*$ | 1.0 [0.8 to 1.1] ($P = 0.56$) |
| **WIfI clinical stage 4 (vs. WIfI clinical stage 2/3)** |                  |                     |
| At 3 months     | 2.0 [1.3 to 3.1] ($P = 0.003$)$^*$ | 2.1 [1.2 to 3.7] ($P = 0.010$)$^*$ |
| At 12 months    | 2.1 [1.4 to 3.2] ($P = 0.001$)$^*$ | 2.9 [1.6 to 5.0] ($P < 0.001$)$^*$ |
| At 24 months    | 1.4 [0.9 to 2.2] ($P = 0.15$) | 1.6 [0.9 to 2.8] ($P = 0.085$) |
| At 36 months    | 1.3 [0.8 to 2.1] ($P = 0.21$) | 1.2 [0.7 to 1.9] ($P = 0.54$) |
| **Surgical reconstruction (vs. EVT alone)** |                  |                     |
| At 3 months     | 0.9 [0.6 to 1.4] ($P = 0.65$) | 0.9 [0.5 to 1.5] ($P = 0.59$) |
| At 12 months    | 0.7 [0.4 to 1.0] ($P = 0.067$) | 0.6 [0.3 to 1.0] ($P = 0.038$)$^*$ |
| At 24 months    | 0.5 [0.3 to 0.8] ($P = 0.007$)$^*$ | 0.5 [0.3 to 0.8] ($P = 0.006$)$^*$ |
| At 36 months    | 0.8 [0.5 to 1.4] ($P = 0.42$) | 0.8 [0.5 to 1.4] ($P = 0.46$) |

Data are odds ratios for ambulation loss (regardless of aid) at 3, 12, 24, and 36 months [95% confidence intervals] ($P$ values). Crude odds ratios were derived from the univariate logistic regression model, whereas adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the tables were entered as explanatory variables. Asterisks indicate $P < 0.05$.
mid-term period and tried to identify predictors considering preoperative variables, including limb severity, in real-world settings. A recently published meta-analysis of the natural history of untreated CLTI reported that both all-cause mortality and major amputation rate at 12 months were 22%\(^{10}\). Several studies demonstrated that major amputation has been reported to be associated with reduced mobility\(^{8, 17}\). Furthermore, despite initial successful prosthetic rehabilitation, prosthetic use deteriorates over time\(^{18}\). Indeed, our results did not show promise in terms of mobility after revascularization at mid-term follow-up, but the impact of revascularisation on mobility in CLTI patients needs to be clarified in the near future.

There are multiple factors that contribute to functional status, including age, severity of comorbidities, physiologic reserves, severity of affected limb, dementia, and so on. In short, functional capacity is significantly affected by patient and limb backgrounds. Therefore, it is difficult to select an appropriate treatment on the basis of preoperative risk factors for ambulatory loss. Several studies have reported that preoperative impaired mobility negatively affects the improvement of functional outcomes\(^{8, 13, 19}\). Vogel et al. reported that poor baseline mobility was significantly associated with a worsening functional status over time\(^{19}\). Flu et al. reported that non-ambulatory patients had an increase in the occurrence of adverse events and poor long-term survival rates and did not receive a benefit from revascularization after six years in terms of functional status improvement\(^{19}\). The study in poor-risk CLTI patients who required assistance for daily life by Iida et al. showed no improvement in ADL scores after revascularization\(^{20}\). The current study also revealed that non-ambulatory status at revascularization was one of the independent predictors of ambulatory loss. However, approximately 30-50% of patients with a preprocedural non-ambulatory status achieved improved mobility within 6 months after revascularization. We should distinguish these patients despite their impaired mobility at revascularization in clinical decision-making.

We found that renal failure on dialysis was also associated with ambulation loss at almost all time points after revascularization. One possible explanation is that patients with renal failure on dialysis were unlikely to recover even after revascularization because renal failure on dialysis has been associated with frailty in several studies\(^{21}\). Another possible explanation is the high mortality in CLTI patients with renal failure on dialysis\(^{5}\). The current analysis included deceased patients at each time point after revascularization. Indeed, renal failure on dialysis was one variable in the predictive model of mortality derived from the SPINACH cohort\(^4\).

The presence of ischaemic lesions at presentation was shown to affect short-term functionality and postoperative morbidity in a previous univariate analysis\(^{20}\). However, whether the severity of pedal necrosis or infection affects functional outcome after revascularization is unknown. The WIfI classification system has been reported to be associated with limb prognosis, including wound healing of ischaemic ulcer prognoses\(^{23}\). We used the WIfI clinical stage as a surrogate for the severity of ischaemic wounds. Hata et al reported WIfI stage 4 as one of the independent predictors of wound healing after EVT\(^{24}\). A possible explanation would be delayed rehabilitation due to severe ischaemic wounds and prolonged wound healing time. These factors might contribute to the need for long hospitalization times. Hospitalization itself has been reported to be associated with substantial and sustained declines in ADL\(^{19}\).

In the current study, surgical reconstruction was inversely associated with (independent) ambulation loss during the short term after revascularization. Vogel et al. demonstrated that EVT was associated with a less favourable functional status than after surgical reconstruction\(^{19}\). This result might be explained by the fact that, in the SPINACH cohort, the wound healing rates at 1, 3, and 6 months after surgical reconstruction were better than those after EVT in the secondary propensity score matched population, as was previously published by our group\(^{11}\). Furthermore, several studies have shown superior wound healing with bypass surgery\(^{25}\). Indeed, tissue loss at 3, 12, and 36 months after revascularization was associated with ambulation loss (Supplementary Table 2). Another possible explanation for this is that there might be a selection bias when the treatment strategy was determined by a team of vascular specialists. In general, surgical reconstruction is more invasive than angioplasty. Therefore, patients who underwent surgical treatment might be less frail than patients who underwent angioplasty. However, the cause-and-effect relationship (whether bypass surgery reduces the risk of amputation loss) is unknown in the present study. An intervention trial is needed to clarify whether surgical treatment could reduce the risk of ambulation loss. The BEST-CLI, BASIL-2, and BASIL-3 studies could show the superiority between angioplasty and bypass surgery in terms of functional status\(^{26-28}\).

This study has several limitations. First, this study was an observational study; therefore, revascularization strategies were chosen by clinicians, and hence, some relevant bias may be present. Second,
the WIfI classification of each patient could be a potential bias, although data were prospectively collected and reviewed by an independent plastic surgeon. Furthermore, the ischemic grade was determined based on the SPP value especially when assessing ischemic limbs with severely calcified noncompressible arteries. The boundary values of SPP for the WIfI ischaemic grade have not been clarified at the moment, therefore, it could also be a potential bias. Third, the rehabilitation programme was different at each institution. Rehabilitation after revascularization has a strong impact on the recovery of functional status. CLTI cohorts are generally frail and need rehabilitation to maintain mobility. Fourth, the causes of ambulation loss related to ambulatory loss, including the postoperative factors such as ischaemic pain status were not clarified. These factors might influence ambulatory status. Finally, this study did not analyse cause and effect relationship. Although this study has several limitations, we believe that it offers useful information to clinicians regarding clinical decision-making for the management of CLTI patients.

Conclusion

In the current study, we investigated mobility over time in CLTI patients who underwent revascularization and identified some predictors of ambulation loss. The estimated proportion of ambulation in the overall population gradually decreased, whereas the number of deceased patients increased. However, in patients without ambulation at revascularization, approximately 20-40% of patients achieved ambulation during 36 months after revascularization. Advanced age, impaired mobility before CLTI onset and at revascularization, renal failure on dialysis, and WIfI stage 4 were strongly associated with ambulation loss during the follow-up period. Consideration of patient and limb characteristics and preoperative functional status are necessary for clinicians to decide a treatment strategy considering patient-oriented outcomes. Further studies are needed to clarify mobility over time after revascularization and the differences between EVT and surgical bypass with uniform rehabilitation programmes and wound management with multicentre, prospective, randomized control trials.

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Conflicts of Interest

There are no conflicts of interests associated with this manuscript.

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Supplementary Fig. 1. Change in mobility status

Panels A to C illustrate the proportions of the respective mobility statuses in the overall population (A), in a wheelchair regardless of aid, or bedridden) at baseline (B), and in patients who were ambulatory without aid (i.e., independently ambulatory) at baseline (C). Error bars indicate 95% confidence intervals for the proportion of patients who were ambulatory without aid (i.e., independently ambulatory), and asterisks represent *P*<.05 versus the baseline value regarding the proportion of patients who were ambulatory without aid.
Supplementary Table 1. Associations of baseline characteristics with independent ambulation loss

|                                | Crude odds ratio | Adjusted odds ratio |
|--------------------------------|------------------|---------------------|
| **Age (per 10 years)**         |                  |                     |
| At 3 months                    | 1.2 [1.0 to 1.6] | P<.051              |
| At 12 months                   | 1.4 [1.0 to 1.8] | P<.001*             |
| At 24 months                   | 1.3 [1.0 to 1.6] | P<.001*             |
| At 36 months                   | 1.2 [0.8 to 1.6] | P<.001*             |
| **Male sex (vs. female sex)**   |                  |                     |
| At 3 months                    | 0.6 [0.4 to 1.0] | P<.001*             |
| At 12 months                   | 0.4 [0.2 to 0.7] | P<.001*             |
| At 24 months                   | 0.7 [0.4 to 1.1] | P<.001*             |
| At 36 months                   | 1.1 [0.7 to 1.8] | P<.001*             |
| **Ambulatory with aid before CLI onset (vs. ambulatory without aid)** |                  |                     |
| At 3 months                    | 5.4 [3.0 to 9.8] | P<.001*             |
| At 12 months                   | 3.8 [2.0 to 7.5] | P<.001*             |
| At 24 months                   | 3.5 [1.8 to 6.9] | P<.001*             |
| At 36 months                   | 3.1 [1.4 to 6.6] | P<.001*             |
| **Ambulatory with aid at revascularization (vs. ambulatory without aid)** |                  |                     |
| At 3 months                    | 5.8 [3.1 to 10.8] | P<.001*             |
| At 12 months                   | 2.7 [1.5 to 4.9] | P<.001*             |
| At 24 months                   | 2.4 [1.3 to 4.5] | P<.001*             |
| At 36 months                   | 2.1 [1.1 to 3.8] | P<.001*             |
| **Non-ambulatory at revascularization (vs. ambulatory without aid)** |                  |                     |
| At 3 months                    | 9.5 [5.3 to 16.9] | P<.001*             |
| At 12 months                   | 5.3 [3.0 to 9.2] | P<.001*             |
| At 24 months                   | 7.2 [3.5 to 14.6] | P<.001*             |
| At 36 months                   | 4.8 [2.2 to 10.5] | P<.001*             |
| **Current smoking**            |                  |                     |
| At 3 months                    | 0.6 [0.3 to 1.0] | P<.001*             |
| At 12 months                   | 0.6 [0.3 to 1.1] | P<.001*             |
| At 24 months                   | 0.5 [0.3 to 1.0] | P<.001*             |
| At 36 months                   | 0.6 [0.3 to 1.1] | P<.001*             |
| **Diabetes mellitus**          |                  |                     |
| At 3 months                    | 1.5 [0.9 to 2.4] | P<.001*             |
| At 12 months                   | 0.8 [0.5 to 1.5] | P<.001*             |
| At 24 months                   | 1.8 [1.1 to 2.9] | P<.001*             |
| At 36 months                   | 1.8 [1.1 to 3.2] | P<.001*             |
| **Renal failure without dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)** |                  |                     |
| At 3 months                    | 2.1 [0.8 to 5.6] | P<.001*             |
| At 12 months                   | 2.3 [0.8 to 6.6] | P<.001*             |
| At 24 months                   | 1.7 [0.5 to 5.6] | P<.001*             |
| At 36 months                   | 2.1 [0.7 to 6.8] | P<.001*             |
| **Renal failure on dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)** |                  |                     |
| At 3 months                    | 2.1 [1.3 to 3.2] | P<.001*             |
| At 12 months                   | 2.5 [1.5 to 4.2] | P<.001*             |
| At 24 months                   | 3.3 [2.1 to 5.2] | P<.001*             |
| At 36 months                   | 3.1 [1.8 to 5.2] | P<.001*             |
(Cont. Supplementary Table 1)

|                          | Crude odds ratio | Adjusted odds ratio |
|--------------------------|------------------|---------------------|
| **Heart failure**        |                  |                     |
| At 3 months              | 2.1 [1.1 to 4.1] (P=.032)* | 1.5 [0.6 to 3.4] (P=.36) |
| At 12 months             | 1.5 [0.9 to 2.7] (P=.14) | 1.1 [0.6 to 2.3] (P=.71) |
| At 24 months             | 1.5 [0.8 to 2.9] (P=.18) | 0.9 [0.4 to 2.0] (P=.79) |
| At 36 months             | 1.8 [0.9 to 3.6] (P=.094) | 1.1 [0.5 to 2.4] (P=.82) |
| **Haemoglobin (per 1 g/dl)** |                  |                     |
| At 3 months              | 0.9 [0.8 to 1.0] (P=.024)* | 1.1 [0.9 to 1.2] (P=.39) |
| At 12 months             | 0.9 [0.8 to 1.0] (P=.020)* | 1.0 [0.9 to 1.2] (P=.65) |
| At 24 months             | 0.8 [0.7 to 0.9] (P=.001)* | 1.0 [0.8 to 1.1] (P=.73) |
| At 36 months             | 0.8 [0.7 to 0.9] (P=.001)* | 0.9 [0.8 to 1.1] (P=.27) |
| **WIfI clinical stage 4 (vs. WIfI clinical stage 2/3)** |                  |                     |
| At 3 months              | 1.9 [1.2 to 3.0] (P=.003)* | 1.9 [1.1 to 3.3] (P=.032)* |
| At 12 months             | 1.5 [0.9 to 2.3] (P=.10) | 1.7 [1.0 to 3.2] (P=.069) |
| At 24 months             | 1.5 [1.0 to 2.3] (P=.058) | 1.5 [0.9 to 2.6] (P=.10) |
| At 36 months             | 1.3 [0.9 to 2.1] (P=.21) | 1.2 [0.7 to 2.1] (P=.44) |
| **Surgical reconstruction (vs. EVT alone)** |                  |                     |
| At 3 months              | 1.1 [0.7 to 1.7] (P=.74) | 1.0 [0.6 to 1.7] (P=.89) |
| At 12 months             | 0.6 [0.4 to 1.0] (P=.041)* | 0.5 [0.3 to 1.0] (P=.037)* |
| At 24 months             | 0.6 [0.4 to 0.9] (P=.024)* | 0.5 [0.2 to 0.9] (P=.022)* |
| At 36 months             | 0.6 [0.4 to 1.0] (P=.054) | 0.5 [0.3 to 1.0] (P=.041)* |

Data are odds ratios for independent ambulation loss at 3, 12, 24, and 36 months [95% confidence intervals] (P values). Crude odds ratios were derived from the univariate logistic regression model, whereas adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the tables were entered as explanatory variables. Asterisks indicate P<.05.
**Supplementary Table 2.** Associations of baseline characteristics with ambulation loss in patients who were non-ambulatory at revascularization

|                                | Crude odds ratio | Adjusted odds ratio |
|--------------------------------|------------------|---------------------|
| **Age (per 10 years)**         |                  |                     |
| At 3 months                    | 1.2 [0.8 to 1.8] | (P=.44)             |
| At 12 months                   | 1.1 [0.7 to 1.6] | (P=.79)             |
| At 24 months                   | 1.3 [0.7 to 2.4] | (P=.43)             |
| At 36 months                   | 0.9 [0.5 to 1.7] | (P=.72)             |
| **Male sex (vs. female sex)**   |                  |                     |
| At 3 months                    | 0.9 [0.4 to 2.0] | (P=.76)             |
| At 12 months                   | 0.6 [0.2 to 1.4] | (P=.20)             |
| At 24 months                   | 0.8 [0.3 to 2.1] | (P=.67)             |
| At 36 months                   | 1.2 [0.3 to 4.7] | (P=.80)             |
| **Ambulatory with aid before CLI onset (vs. ambulatory without aid)** |                  |                     |
| At 3 months                    | 2.9 [1.2 to 7.1] | (P=.018)*           |
| At 12 months                   | 4.1 [1.5 to 11.2]| (P=.007)*           |
| At 24 months                   | 4.5 [1.1 to 18.0]| (P=.034)*           |
| At 36 months                   | 3.3 [0.9 to 11.7]| (P=.067)            |
| **Current smoking**            |                  |                     |
| At 3 months                    | 0.8 [0.2 to 3.9] | (P=.80)             |
| At 12 months                   | 0.5 [0.1 to 2.4] | (P=.40)             |
| At 24 months                   | 0.8 [0.1 to 4.2] | (P=.77)             |
| At 36 months                   |                   | (not converged)      |
| **Diabetes mellitus**          |                  |                     |
| At 3 months                    | 1.2 [0.4 to 3.7] | (P=.74)             |
| At 12 months                   | 0.9 [0.3 to 2.6] | (P=.83)             |
| At 24 months                   | 1.0 [0.3 to 3.4] | (P=.97)             |
| At 36 months                   | 1.3 [0.4 to 5.0] | (P=.66)             |
| **Renal failure without dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)** |                  |                     |
| At 3 months                    |                   | (not converged)      |
| At 12 months                   | 0.5 [<0.1 to 5.8]| (P=.56)             |
| At 24 months                   | 0.5 [<0.1 to 8.9]| (P=.66)             |
| At 36 months                   | 1.0 [<0.1 to 12.9]| (P=.97)             |
| **Renal failure on dialysis (vs eGFR ≥ 30 ml/min/1.73 m²)** |                  |                     |
| At 3 months                    | 1.6 [0.6 to 4.0] | (P=.30)             |
| At 12 months                   | 2.4 [1.0 to 5.6] | (P=.042)*           |
| At 24 months                   | 2.3 [0.7 to 7.1] | (P=.15)             |
| At 36 months                   | 3.4 [1.1 to 10.9]| (P=.041)*           |
| **Heart failure**              |                  |                     |
| At 3 months                    | 1.1 [0.4 to 2.8] | (P=.85)             |
| At 12 months                   | 1.4 [0.5 to 3.8] | (P=.48)             |
| At 24 months                   | 1.4 [0.5 to 4.3] | (P=.54)             |
| At 36 months                   | 2.4 [0.6 to 10.2]| (P=.24)             |
| **Hb (per 1 g/dl)**            |                  |                     |
| At 3 months                    | 0.9 [0.8 to 1.2] | (P=.63)             |
| At 12 months                   | 1.0 [0.8 to 1.2] | (P=.73)             |
| At 24 months                   | 1.0 [0.8 to 1.3] | (P=.94)             |
| At 36 months                   | 1.0 [0.8 to 1.4] | (P=.75)             |
(Cont. Supplementary Table 2)

|                                | Crude odds ratio | Adjusted odds ratio |
|--------------------------------|------------------|---------------------|
| **WIfI clinical stage 4 (vs. WIfI clinical stage 2/3)** |                  |                     |
| At 3 months                    | 2.0 [0.9 to 4.5] (\textit{P} = .095) | 3.2 [1.1 to 9.1] (\textit{P} = .027)* |
| At 12 months                   | 2.6 [1.1 to 6.1] (\textit{P} = .023)* | 7.6 [1.7 to 33.2] (\textit{P} = .009)* |
| At 24 months                   | 1.5 [0.6 to 4.0] (\textit{P} = .41) | 3.8 [0.8 to 18.7] (\textit{P} = .092) |
| At 36 months                   | 1.9 [0.7 to 4.9] (\textit{P} = .19) | 5.0 [1.2 to 20.9] (\textit{P} = .029)* |
| **Surgical reconstruction (vs. EVT alone)** |                  |                     |
| At 3 months                    | 0.8 [0.3 to 1.7] (\textit{P} = .49) | 0.9 [0.4 to 2.2] (\textit{P} = .81) |
| At 12 months                   | 0.5 [0.2 to 1.2] (\textit{P} = .14) | 0.6 [0.2 to 1.8] (\textit{P} = .34) |
| At 24 months                   | 0.4 [0.2 to 1.0] (\textit{P} = .51) | 0.5 [0.1 to 1.5] (\textit{P} = .20) |
| At 36 months                   | 0.5 [0.2 to 1.7] (\textit{P} = .28) | 0.7 [0.2 to 2.6] (\textit{P} = .53) |

Data are odds ratios for ambulation loss (regardless of aid) at 3, 12, 24, and 36 months [95% confidence intervals] (\textit{P} values). Crude odds ratios were derived from the univariate logistic regression model, whereas adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the tables were entered as explanatory variables. Asterisks indicate \( P < .05 \).
Supplementary Fig. 2. Limb status and ambulation

Panels A illustrate the proportions of the respective limb statuses in the overall population. Error bars indicate 95% confidence intervals for the proportion of patients without amputation or tissue loss, and asterisks represent $P < .05$ versus the baseline value regarding the proportion of patients without amputation or tissue loss. Panels B to F illustrate the proportions of respective mobility statuses in patients alive with major amputation (regardless of tissue loss) at each time point (B), in those alive with minor amputation and tissue loss at each time point (C), in those alive with minor amputation and no tissue loss at each time point (D), in those alive with no amputation and tissue loss at each time point (E), and in those alive with no amputation and no tissue loss at each time point (F). Note that in Panel B, patients alive with major amputation were not distinguished by the presence of tissue loss, simply because of their small number. Error bars in Panels B to F indicate 95% confidence intervals for the proportion of patients who were ambulatory regardless of aid.

Supplementary Table 3. Associations of limb status at a specific time point with ambulation loss at the same time point

|                      | At 3 months | At 12 months | At 24 months | At 36 months |
|----------------------|-------------|--------------|--------------|--------------|
| Tissue loss          |             |              |              |              |
| Amputation (vs. none)| 2.5 [1.5 to 4.1] ($P < .001$) * | 2.9 [1.5 to 5.6] ($P = .001$) * | 2.6 [1.0 to 7.3] ($P = .060$) | 3.0 [1.0 to 8.7] ($P = .044$) * |
| Minor amputation     | 2.2 [1.3 to 3.7] ($P = .004$) * | 2.2 [1.1 to 4.1] ($P = .020$) * | 1.2 [0.6 to 2.5] ($P = .64$) | 1.6 [0.7 to 3.8] ($P = .26$) |
| Major amputation     | (Not converged) | 15.8 [2.4 to 104] ($P = .007$) * | (Not converged) | 16.3 [2.9 to 90.8] ($P = .002$) * |

Data are multivariate odds ratios for ambulation loss (regardless of aid) at 3, 12, 24, and 36 months [95% confidence intervals] ($P$ values), which were derived from the multivariate logistic regression model in which tissue loss and amputation at the index time point were entered as explanatory variables. Asterisks indicate $P < .05$. 