

The Association of Preoperative Characteristics with Reintervention Risk in Patients Undergoing Revascularization for Chronic Limb-Threatening Ischemia

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Aim: To investigate the associations between preoperative characteristics and the risk of reintervention in patients undergoing revascularization for chronic limb-threatening ischemia (CLTI) in a contemporary real-world setting.

Methods: We retrospectively analyzed data from a clinical database formed by the Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia (SPINACH) study, which was a multicenter, prospective, observational study. The study population was composed of 520 CLTI patients with the wound, ischemia, and foot infection (WIFI) classes I-3 with resting pain or classes I-2/3 with ulcers/gangrene. Of the 520 patients, 192 had surgical reconstruction planned, whereas 328 had endovascular therapy (EVT) alone planned at the time of registration. The current analysis was conducted to explore the associations between preoperative characteristics and the risk of reintervention.

Results: A total of 452 participants (87%) completed the 3-year follow-up regarding reintervention. The competing risk analysis estimated that the three-year cumulative incidence rates for reintervention and reintervention-free deaths were 44.0% and 28.7%, respectively. No preoperative characteristics had a significant interaction effect with EVT versus surgical reconstruction. The risk analysis identified the following independent risk factors for reintervention: 1) EVT instead of bypass reconstruction, 2) renal dysfunction, 3) history of revascularization after CLTI onset (i.e., requirement of redo revascularization for CLTI), and 4) bilateral CLTI. Patients with more than one of these risk factors had an increased risk of reintervention.

Conclusions: The current study identified preoperative characteristics associated with an increased risk of reintervention. No preoperative characteristics had any significant interactions with EVT or surgical reconstruction.

Key words: Chronic limb-threatening ischemia, Surgical reconstruction, Endovascular therapy, Reintervention

Introduction

Endovascular therapy (EVT) has been widely applied as a revascularization strategy in patients with

chronic limb-threatening ischemia (CLTI)^{1,2}. Its safety and effectiveness are acknowledged in current guidelines, and it plays an increasingly important role in the management of CLTI³⁻⁵. However, due to the subop-

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timal durability of the associated devices, EVT has yet to provide clinical results that are equivalent to those of surgical reconstruction⁶⁻⁸⁾ The importance of surgical therapy has been consistently highlighted in the latest guidelines particularly because patients frequently require reintervention after EVT⁵⁾. In fact, the Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia (SPINACH) study recently found that CLTI patients undergoing EVT had a higher risk of reintervention than a matched population undergoing surgical reconstruction, although no significant differences were observed with regard to major amputation or all-cause mortality⁷⁾.

Reintervention for patients with CLTI increases medical costs and is undesirable from a health economics standpoint. Therefore, it is important to preoperatively predict which patients will need reintervention in real-world clinical settings. Although the EVT group had a higher reintervention risk than the surgical reconstruction groups in the matched analysis, there might be subgroups of patients in the EVT group for whom the reintervention risk was not higher (or even lower) than that of the patients in the surgical reconstruction group. Furthermore, some patients with certain preoperative characteristics might have a higher reintervention risk regardless of the selected treatment strategy. However, these issues needed to be addressed using a database with patients undergoing EVT and those undergoing surgical reconstruction in today's real-world clinical settings. The aim of the current study was to investigate the associations between preoperative characteristics and the reintervention risk after revascularization for CLTI using the data from the SPINACH study.

Methods

We analyzed clinical data from the SPINACH study. The SPINACH study was a prospective, multicenter, observational study that enrolled patients who had CLTI due to atherosclerotic arterial disease, either with or without supra-inguinal disease, in Japan. The details were described previously⁷⁾. In brief, CLTI patients who underwent planned revascularization (either surgical reconstruction or EVT) were registered in advance of the procedure. The preoperative data were collected prospectively before patients underwent revascularization rather than retrospectively. Patients who were scheduled to undergo primary major amputation were excluded. The treatment strategy was determined by a team of vascular specialists that included vascular surgeons and practicing interventional cardiologists. The selection of the treatment

strategy was left to the discretion of the treating physicians at each center. Note that each hospital could select surgical and endovascular treatments. The patients were followed up for up to three years. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each center that registered patients. A written informed consent was obtained from the patients.

The study population was composed of 520 CLTI patients with wound, ischemia, and foot infection (WIFI) classes I-3 with resting pain or classes I-2/3 with ulcers/gangrene⁹⁾. The WIFI I classification was based on the ankle pressure, ankle-brachial index, skin perfusion pressure (SPP), and transcutaneous oxygen tension. SPPs of 31–40 and ≤ 30 mmHg were considered WIFI I-2 and I-3, respectively⁷⁾. As previously reported, 192 of the 520 patients had surgical reconstructions planned, whereas 328 had EVT planned.

The current subanalysis was retrospectively conducted to explore the associations between preoperative characteristics and the risk of reintervention, which was defined as any reintervention during the study period. The indications for reintervention after EVT were clinical symptoms, including delayed, worsened, and recurrent wounds and ischemic pain. In other words, reintervention was not conducted in asymptomatic patients even if they presented restenotic or reocclusive lesions. Furthermore, in patients treated with surgical reconstruction, especially with bypass surgery, the indications for reintervention were not clinical symptoms. Instead, the need for reintervention was determined by the results of a surveillance program, which consisted of a clinical follow-up and repeated scanning. Reintervention was indicated by patency loss, regardless of the presence of symptoms. In the current study, the follow-up assessments were scheduled at 1, 3, 6, 12, 24, and 36 months, with a tolerance of ± 1 month. Major amputation was included in the reintervention events rather than being censored. This was simply because the clinical purpose of revascularization (including reintervention) was limb salvage (i.e., avoidance of amputation). When the blood supply to the index limb is insufficient for limb salvage after the initial revascularization, either major amputation or reintervention will be selected. Major amputation will be selected when it cannot be avoided by performing reintervention. Therefore, we treated major amputation not as a competing risk against reintervention but as the same outcome indicating that the initial revascularization was unsuccessful.

Definitions

Impaired mobility was categorized as none (self-ambulatory), requiring equipment, and requiring a personal aid. Non-adherence to cardiovascular risk management was defined as defaulting on clinical appointments for cardiovascular risk management, e.g., antidiabetic, antihypertensive, or antihyperlipidemic treatments. Body mass index (BMI) was calculated as (body weight [kg])/(height [m])². Smoking was categorized as never, past, and current smoking. Diabetes mellitus was determined when the fasting plasma glucose levels were ≥ 126 mg/dl, the casual plasma glucose levels were ≥ 200 mg/dl, the hemoglobin A1c levels were $\geq 6.5\%$, the plasma glucose levels 2 hours after a 75 g oral glucose tolerance test were ≥ 200 mg/dl, or patients were treated for diabetes¹⁰. Renal function was categorized as an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m², an eGFR of 30–60 ml/min/1.73 m², an eGFR < 30 ml/min/1.73 m², and end-stage renal disease on a regular dialysis. The latter two categories together were considered chronic renal failure (including dialysis). A history of claudication indicated a prior history of intermittent claudication before CLTI onset. The severity of tissue loss was assessed using the Rutherford classification, University of Texas (UT) classification, and WIfI classification¹¹. A history of revascularization after CLTI onset indicated that patients had already undergone revascularization for the current CLTI, but the revascularization was unsuccessful at relieving the CLTI and repeated revascularization for the CLTI was required at the time of registration. The severity of arterial lesions was assessed using the Trans-Atlantic Inter-Society Consensus (TASC) II classification for the aorto-iliac and femoro-popliteal segments¹² and the TASC classification for the infra-popliteal lesions¹³. A pedal artery lesion was defined as a lesion that had a stenosis that was $>75\%$ of the diameter on diagnostic angiography and was hemodynamically significant at the pedal arch. The assessment was based on angiography. Initial technical success was evaluated from the anatomical (angiographic) and hemodynamic aspects⁷. Anatomical success was defined as at least one straight line reaching the foot for EVT and as a patent bypass graft perfusing blood directly to the foot for surgical reconstruction. Hemodynamic success referred to an increase in the ABI of more than 0.1 or an increase in the SPP of more than 10 mmHg⁷. Any reintervention indicated major and minor interventions in the index procedure. Major reinterventions included a new bypass graft, jump, interposition graft revision or the use of thrombectomy or thrombolysis in stents upon loss of primary-

assisted patency. Minor reinterventions were defined as endovascular procedures (percutaneous transluminal angioplasty, atherectomy, and stenting) without thrombectomy or thrombolysis and minor surgical revisions (patch angioplasty)¹⁴.

Statistical Analyses

The statistical analysis was performed per patient. The data are presented as the means \pm standard deviations for continuous variables and as percentages for categorical variables, unless otherwise indicated. A *P*-value < 0.05 was considered statistically significant. The associations between preoperative characteristics and the risk of reintervention was investigated using a competing risk analysis, in which death was treated as the competing risk event. We performed a regression analysis using the semiparametric proportional hazards model proposed by Fine and Gray¹⁵ with the R packages *cmprsk* and *crstep*. To address missing data, we adopted the multiple imputation method ($n=20$). In the multivariate analysis, we adopted information-criterion-based variable selection using the Akaike information criterion in each imputed data set. The final model included the variables that were selected in at least 80% ($n=16$) of the imputed data sets. Hazard ratios are reported with their 95% confidence intervals. The discriminatory power of the risk factor clustering was assessed by the area under the time-dependent receiver operating characteristic (ROC) curve, based on the method proposed by Heagerty¹⁶, except for the estimation of the proportion of event-exposed cases and event-free cases, which was derived from the cumulative incidence function instead of the Kaplan–Meier method. The 95% confidence interval of the time-dependent ROC curve was obtained by 10,000 bootstraps. By contrast, Fine and Gray's competing risk analysis addressed the risk of reintervention that first occurred after initial revascularization, and the number of total (i.e., first and subsequent) reinterventions during follow-ups were analyzed using the Poisson regression model. All statistical analyses were performed with R version 3.1.0 (R Development Core Team, Vienna, Austria).

Results

The baseline characteristics of the study population are summarized in **Table 1**. The patients were 73 ± 10 years old; 67% were male, 53% were on dialysis, and 87% had ischemic tissue loss. The study flow chart is shown in **Fig. 1**.

Among the patients who had EVT planned at registration ($n=328$), one patient died before revascularization, two patients did not undergo revasculariza-

Table 1. Baseline characteristics of the study population

<i>N</i>	520
Age (years)	73 ± 10
Male sex	350 (67%)
Impaired mobility	
None (self-ambulatory)	195 (38%)
Requiring equipment	191 (37%)
Requiring a personal aid	134 (26%)
History of non-adherence to cardiovascular risk management	129 (25%)
Body mass index (kg/m ²)	21.9 ± 3.5
Hemoglobin (g/dl)	11.0 ± 1.9
Albumin (g/dl)	3.4 ± 0.6
Cholinesterase (U/l)	220 ± 74
Smoking	
Never	209 (40%)
Past	231 (44%)
Current	80 (15%)
Diabetes mellitus	386 (74%)
Renal function	
eGFR ≥ 60 ml/min/1.73 m ²	116 (22%)
eGFR 30-60 ml/min/1.73 m ²	97 (19%)
eGFR < 30 ml/min/1.73 m ²	30 (6%)
End-stage renal disease on dialysis	277 (53%)
Heart failure	
Left ventricular ejection fraction (%)	97 (19%)
History of claudication	61 ± 13
Rutherford classification	274 (53%)
Category 4	67 (13%)
Category 5	359 (69%)
Category 6	94 (18%)
University of Texas classification	
Class 0	67 (13%)
Class 1	212 (41%)
Class 2	97 (19%)
Class 3	144 (28%)
WIfI classification: Wound	
W-0	67 (13%)
W-1	159 (31%)
W-2	210 (40%)
W-3	84 (16%)
WIfI classification: I-3	
I-2	85 (16%)
I-3	435 (84%)
WIfI classification: Foot infection	
fl-0	300 (58%)
fl-1	110 (21%)
fl-2	97 (19%)
fl-3	13 (2%)
History of minor amputation	46 (9%)
History of revascularization after CLTI onset	41 (8%)
Bilateral CLTI	71 (14%)
Contralateral major amputation	21 (4%)

Data are expressed as the means ± standard deviations or numbers (percentages). Data were unavailable for albumin levels in 12 patients (2.3%), cholinesterase levels in 59 patients (11.3%), left ventricular ejection fraction in 17 patients (3.3%), and history of claudication in 1 patient (0.2%). For the University of Texas (UT) classification and the Wound, Ischemia and foot Infection (WIfI) classification, see references nos. 9 and 11.

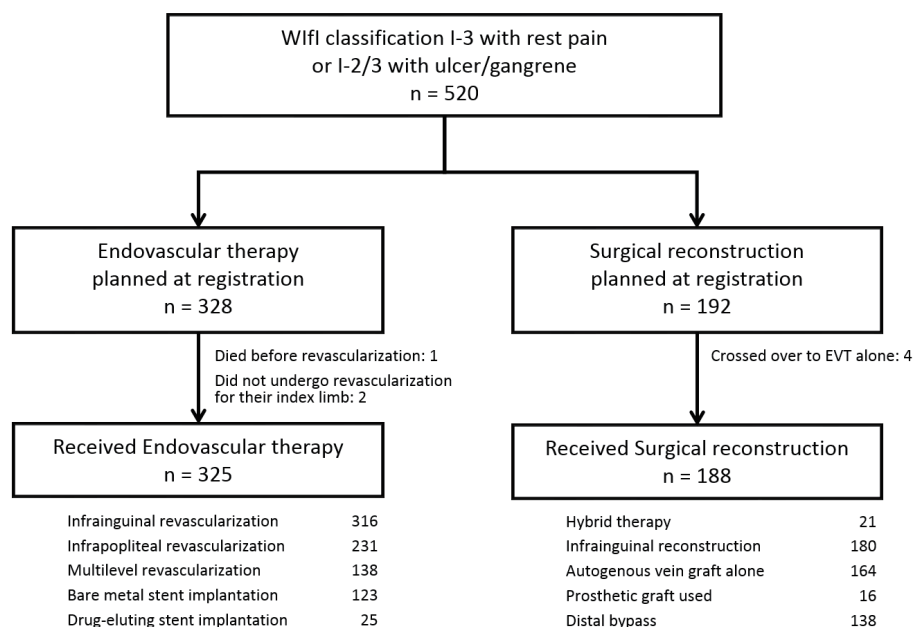


Fig. 1. Study flow chart

tion for their index limb, and the remaining 325 patients underwent EVT alone. No patients in the EVT group switched to the surgical reconstruction group. Of the 325 patients who underwent EVT alone, 316 patients (97%) underwent infra-inguinal revascularization, and 231 patients (71%) underwent infra-popliteal revascularization. Multilevel revascularization accounted for 42% of the procedures (138/325). Stents were implanted in 148 patients (46%), of whom 25 (8%) underwent drug-eluting stent implantation. Information on postoperative medication was collected from all patients except one who died during the perioperative period. Dual antiplatelet therapy was administered to 123 of the 324 patients (38%), whereas anticoagulants, statins, and cilostazol were administered to 18% (59/324), 29% (93/324), and 38% (123/324) of the patients, respectively. In the patients undergoing EVT alone, there was no significant association of the revascularization procedures or postoperative medications with the subsequent reintervention risk (Table 2).

Among the patients who had surgical reconstruction planned at registration ($n=192$), four patients crossed over to the EVT group, whereas the remaining 188 underwent surgical reconstruction, with 37 (20%) undergoing hybrid treatments (21 iliac EVT plus infra-inguinal bypass \pm endoarterectomy, 6 femoropopliteal EVT plus distal bypass, and 10 others). All 188 patients in the surgical reconstruction group underwent infra-inguinal reconstruction. Infra-inguinal bypass surgery was performed in 180 patients

(96%), of whom 16 had prosthetic grafts and 164 had autogenous vein grafts. Distal anastomoses were performed to the crural or pedal arteries in 138 patients. Multilevel reconstruction accounted for 66% of the procedures (125/188). Information on postoperative medications was collected from all patients except one who died during the perioperative period. Antiplatelet therapy was administered to 136 of the 187 patients (73%), whereas anticoagulants, statins, and cilostazol were administered to 26% (48/187), 31% (58/187), and 60% (60/187) of the patients, respectively. In the patients who underwent surgical reconstruction, there was no significant association of the revascularization procedures or postoperative medications with the subsequent reintervention risk (Table 2).

Data on the initial technical success (angiographic, hemodynamic, or both) were available for 506 of the 517 patients who underwent revascularization (98%). Data on the angiographic and hemodynamic initial technical success were obtained for 497 and 439 patients, respectively. As shown in Table 3, the initial technical success, especially the hemodynamic success, was significantly associated with the subsequent reintervention risk, without any significant interaction effect of (i.e., no significant intergroup difference between) EVT versus surgical reconstruction.

Of the 520 patients, 452 (87%) completed the 3-year follow-up regarding reintervention and death. Reintervention was performed in 221 patients, of whom 87 died after reintervention during the follow-up period; 138 reintervention-free patients died. The

Table 2. Revascularization performed and postoperative medication

	Prevalence	Adjusted hazard ratio for reintervention risk
EVT alone		
Revascularization procedure		
Bare metal stent	123/325 (38%)	1.02 [0.67-1.56] (P = .92)
Drug-eluting stent	25/325 (8%)	0.83 [0.43-1.62] (P = .59)
Infra-inguinal revascularization	316/325 (97%)	3.69 [0.45-30.1] (P = .22)
Infra-popliteal revascularization	231/325 (71%)	1.25 [0.80-1.94] (P = .32)
Multilevel revascularization	138/325 (42%)	1.30 [0.86-1.94] (P = .21)
Medication		
Dual antiplatelet therapy	123/324 (38%)	1.37 [0.91-2.05] (P = .13)
Anticoagulant	59/324 (18%)	1.10 [0.71-1.72] (P = .66)
Statin	93/324 (29%)	0.88 [0.62-1.25] (P = .46)
Cilostazol	123/324 (38%)	1.10 [0.75-1.62] (P = .62)
Surgical reconstruction		
Revascularization procedure		
Hybrid revascularization	37/188 (20%)	1.28 [0.63-2.58] (P = .49)
Reconstruction other than infra-inguinal bypass	8/188 (4%)	0.34 [0.04-3.11] (P = .34)
Infra-inguinal bypass with artificial graft	16/188 (9%)	0.87 [0.34-2.23] (P = .77)
Distal bypass	138/188 (73%)	1.03 [0.54-1.96] (P = .93)
Multilevel reconstruction	125/188 (66%)	0.63 [0.36-1.10] (P = .10)
Medication		
Antiplatelet therapy	136/187 (73%)	1.66 [0.88-3.12] (P = .12)
Anticoagulant use	48/187 (26%)	1.27 [0.72-2.24] (P = .40)
Statin use	58/187 (31%)	1.53 [0.93-2.51] (P = .093)
Cilostazol use	60/187 (32%)	1.12 [0.66-1.90] (P = .66)

Data are expressed as numbers (percentages) for the prevalence and estimates [95% confidence intervals] (*P* values) for the hazard ratios. The adjusted hazard ratios were obtained separately from the competing risk analysis in patients in whom EVT alone was performed as planned and in those in whom surgical reconstruction was performed as planned.

Table 3. Initial technical success and reintervention risk

	Prevalence	Interaction of EVT versus surgical reconstruction (fold difference)	Unadjusted hazard ratio for reintervention risk	Adjusted hazard ratio for reintervention risk
Anatomical	467/497 (94%)	1.69 [0.45-6.32]	0.48 [0.27-0.84]*	0.61 [0.32-1.16]
Hemodynamic	366/439 (83%)	1.03 [0.45-2.34]	0.50 [0.35-0.71]*	0.54 [0.38-0.78]*

Data are expressed as numbers (percentages) for the prevalence and estimates [95% confidence intervals] for the interaction effect and hazard ratios. Asterisks indicate *P* < 0.05. N/I, not included. Anatomical success was defined as at least one straight line reaching the foot for EVT and as a patent bypass graft perfusing blood directly to the foot for surgical reconstruction, while hemodynamic success referred to an increase in the ABI of more than 0.1 or an increase in the SPP of more than 10 mmHg⁷.

competing risk analysis estimated that the one-year cumulative incidence rates of reintervention and reintervention-free death were 36.3% (95% confidence interval: 32.1% to 40.5%) and 14.0% (11.1% to 17.1%), respectively, whereas the corresponding three-year rates were 44.0% (39.6% to 48.3%) and 28.7% (24.6% to 32.9%), respectively. In the EVT group, 313 reinterventions, including first and subsequent ones, were observed during a 582.9-person-year fol-

low-up; 153 patients underwent reinterventions, of whom 26 underwent major amputation. Of the 153 first reintervention, 132 were observed during the first year, whereas 222 of the 313 total reinterventions (i.e., first plus subsequent ones) were observed during the first year. In the surgical reconstruction group, 137 reinterventions, including first and subsequent ones, were observed during 400.7-person-year follow-up; 68 patients underwent reinterventions, of whom 18

Table 4. Cumulative incidence reintervention rate and total number of incident reinterventions during follow-up

	Follow-up	Cumulative reintervention incidence rate	Total number of incident reinterventions
EVT group	1 year	41% [35%-46%]	0.82 [0.72-0.93] /person-year
	2 years	47% [42%-53%]	1.25 [1.11-1.40] /person·2 years
	3 years	48% [43%-54%]	1.61 [1.44-1.80] /person·3 years
Surgical reconstruction group	1 year	29% [22%-35%]	0.56 [0.46-0.69] /person-year
	2 years	35% [28%-42%]	0.84 [0.70-1.00] /person·2 years
	3 years	37% [30%-44%]	1.03 [0.87-1.21] /person·3 years

Data are estimates [95% confidence intervals] for cumulative incidence rate of first reintervention at 1, 2, and 3 years, derived from the competing risk analysis, and for the total number of incident reintervention (including both first and subsequent ones) during 1-, 2-, and 3-year follow-up, derived from the Poisson regression model.

underwent major amputation. Of the 68 first reintervention, 54 were observed during the first year, whereas 92 of the 137 total reinterventions (i.e., first plus subsequent ones) were observed during the first year. The estimated cumulative incidence rate of reintervention and number of total incident reinterventions per time unit in the two groups are summarized in [Table 4](#).

We first performed an interaction analysis to investigate whether the impact of preoperative characteristics on the reintervention risk differed between EVT and surgical reconstruction. As shown in [Table 5](#), no preoperative characteristics had a significant interaction effect with EVT versus surgical reconstruction, indicating that all preoperative characteristics had a similar impact on the reintervention risk for both types of treatment and that the reintervention risk of the treatment strategies did not significantly vary according to the preoperative characteristics. The subsequent risk analysis identified the following as independent risk factors for reintervention: 1) EVT instead of surgical reconstruction, 2) an eGFR of 30–60 ml/min/1.73 m² and chronic renal failure (eGFR <30 ml/min/1.73 m² and on dialysis), 3) a history of revascularization after CLTI onset (i.e., need for repeated revascularization for CLTI), and 4) bilateral CLTI ([Table 5](#)). When we performed a complete case analysis after listwise deletion, all the factors except an eGFR of 30–60 ml/min/1.73 m² were significant, and Wifl classification was identified as an additional independent risk factor ([Table 6](#)). Moreover, when those who had a history of revascularization after CLTI onset were excluded from the study population, 1) EVT versus surgical reconstruction, 2) chronic renal failure (including dialysis), and 3) bilateral CLTI were again identified as independent risk factors for reintervention, whereas there was no independent association of an eGFR of 30–60 ml/min/1.73 m² or Wifl classification with the reinter-

vention risk ([Table 7](#)). These identified risk factors for the first reintervention were also associated with the number of total incident reinterventions (including first and subsequent ones) per time unit ([Table 8](#)). Patients with multiple risk factors had an elevated reintervention risk ([Fig. 2](#)). The areas under the time-dependent ROC curve of the risk factor clusters for the first reintervention (95% confidence interval) were 0.65 (0.60–0.69) at 1 year, 0.63 (0.58–0.67) at 2 years, and 0.62 (0.57–0.67) at 3 years, respectively.

Discussion

The current study revealed the associations between preoperative characteristics and the reintervention risk in patients undergoing revascularization for CLTI. No preoperative characteristics had a significant interaction effect on the association of EVT versus surgical reconstruction with the reintervention risk. The risk analysis identified the following independent risk factors for reintervention: 1) EVT instead of surgical reconstruction, 2) renal dysfunction, 3) a history of revascularization after CLTI onset (need for repeated revascularization for CLTI), and 4) bilateral CLTI. Patients with multiple risk factors had an elevated risk of reintervention.

Although previous studies assessed the reintervention risk after EVT and surgical reconstruction, most analyzed data from retrospective databases examined peripheral artery disease (PAD) patients, including non-CLTI patients (i.e., claudicants), or limited the study population to those undergoing EVT alone (or those undergoing surgical reconstruction alone). A few prospective studies have compared surgical reconstruction versus endovascular intervention in patients with CLTI. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial is a well-recognized prospective study¹⁷⁾ that is undoubtedly an important and informative study in the field of CLTI. Although

Table 5. Associations between baseline characteristics and reintervention risk

	Interaction of EVT versus surgical reconstruction (fold difference)	Unadjusted hazard ratio for reintervention	Adjusted hazard ratio for reintervention
EVT (versus surgical reconstruction)	---	1.52 [1.15-2.01]*	1.71 [1.26-2.31]*
Age (per 10 years)	1.18 [0.90-1.56]	0.89 [0.78-1.01]	0.88 [0.77-1.01]
Male sex	1.09 [0.60-1.98]	0.93 [0.71-1.23]	N/I
Impaired mobility	0.82 [0.55-1.21]	1.04 [0.88-1.24]	N/I
History of non-adherence to cardiovascular risk management	0.93 [0.49-1.78]	1.12 [0.84-1.49]	N/I
BMI (per 5 kg/m ²)	0.95 [0.64-1.42]	1.02 [0.85-1.22]	N/I
Hemoglobin (per 1 g/dl)	0.96 [0.81-1.13]	0.92 [0.85-1.00]*	0.96 [0.88-1.04]
Albumin (per 1 g/dl)	1.02 [0.61-1.72]	1.01 [0.79-1.28]	N/I
Cholinesterase (per 100 U/l)	0.83 [0.55-1.24]	0.95 [0.78-1.16]	N/I
Smoking			
Past smoking	1.25 [0.67-2.34]	1.09 [0.82-1.45]	N/I
Current smoking	1.22 [0.50-2.98]	0.91 [0.61-1.37]	N/I
Diabetes mellitus	1.54 [0.80-2.94]	1.14 [0.83-1.56]	N/I
Renal function			
eGFR 30-60 ml/min/1.73 m ²	0.59 [0.23-1.41]	1.61 [1.02-2.54]*	1.64 [1.02-2.64]*
eGFR <30 ml/min/1.73 m ² / on dialysis	0.92 [0.43-1.96]	1.94 [1.35-2.78]*	1.91 [1.31-2.77]*
Heart failure	1.06 [0.52-2.14]	1.42 [1.04-1.95]*	1.22 [0.88-1.69]
Left ventricular ejection fraction (per 10%)	0.99 [0.81-1.22]	0.94 [0.85-1.03]	N/I
History of claudication	0.76 [0.42-1.37]	1.07 [0.82-1.39]	N/I
Rutherford classification	0.77 [0.47-1.25]	1.01 [0.81-1.27]	N/I
University of Texas classification	0.89 [0.68-1.15]	1.00 [0.88-1.13]	N/I
WIfI classification: Wound	0.80 [0.58-1.09]	1.01 [0.88-1.16]	N/I
WIfI classification: Ischemia	1.17 [0.43-3.15]	1.02 [0.71-1.47]	N/I
WIfI classification: Foot infection	1.16 [0.83-1.63]	1.11 [0.95-1.30]	1.18 [0.99-1.41]
History of minor amputation	0.43 [0.15-1.24]	0.90 [0.53-1.51]	N/I
History of revascularization after CLTI onset	0.68 [0.26-1.73]	1.65 [1.05-2.57]*	1.74 [1.11-2.74]*
Bilateral CLTI	0.89 [0.42-1.87]	2.01 [1.42-2.85]*	1.83 [1.27-2.63]*
Contralateral major amputation	0.74 [0.08-6.97]	0.54 [0.22-1.33]	0.44 [0.18-1.13]
TASC II aorto-iliac classification	0.89 [0.70-1.13]	0.95 [0.85-1.07]	N/I
TASC II femoro-popliteal classification	1.03 [0.86-1.23]	0.95 [0.87-1.03]	N/I
TASC II infra-popliteal classification	1.30 [0.97-1.73]	1.01 [0.87-1.18]	N/I
Pedal artery lesion	1.51 [0.72-3.19]	1.33 [0.90-1.95]	N/I

Hazard ratios are presented together with the 95% confidence intervals. Asterisks indicate $P < 0.05$. N/I, not included. A pedal artery lesion was defined as a lesion with a stenosis that was $>75\%$ of the diameter on diagnostic angiography and that was hemodynamically significant at the pedal arch.

the BASIL study generated a survival prediction model to facilitate clinical decision making, a risk analysis focusing on reintervention risk was not reported. More recently, the Registry of First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) study reported that younger age, lack of runoff vessels, previous vascular intervention, and lack of statin administration were risk factors for major amputation and/or reintervention, whereas EVT was not significantly associated with the risk of reintervention¹⁸. Their findings were somewhat different from ours. One possible explanation might be that they performed the risk analysis using a Cox model, without

treating death as a competing risk. A CLTI population has a high risk of mortality, and death events might affect the results. Another explanation might be the differences in the study populations. For example, patients classified as Rutherford category 4 (ischemic pain without tissue loss) accounted for more than 20% of their study population, which was a higher proportion than among our patients.

The current study showed that EVT was associated with a higher reintervention risk than surgical reconstruction in a CLTI population. The number of patients with PAD has globally increased in recent decades, presumably because of global trends in popu-

Table 6. Sensitivity analysis for associations between baseline characteristics and reintervention risk (complete case analysis)

	Interaction of EVT versus surgical reconstruction (fold difference)	Unadjusted hazard ratio for reintervention	Adjusted hazard ratio for reintervention
EVT (versus surgical reconstruction)	---	1.52 [1.15-2.01]*	1.83 [1.25-2.68]*
Age (per 10 years)	1.18 [0.90-1.56]	0.89 [0.78-1.01]	N/I
Male sex	1.09 [0.60-1.98]	0.93 [0.71-1.23]	N/I
Impaired mobility	0.82 [0.55-1.21]	1.04 [0.88-1.24]	N/I
History of non-adherence to cardiovascular risk management	0.93 [0.49-1.78]	1.12 [0.84-1.49]	N/I
BMI (per 5 kg/m ²)	0.95 [0.64-1.42]	1.02 [0.85-1.22]	N/I
Hemoglobin (per 1 g/dl)	0.96 [0.81-1.13]	0.92 [0.85-1.00]*	0.95 [0.87-1.05]
Albumin (per 1 g/dl)	1.02 [0.60-1.73]	1.01 [0.79-1.28]	N/I
Cholinesterase (per 100 U/l)	0.85 [0.55-1.32]	0.91 [0.73-1.13]	N/I
Smoking			
Past smoking	1.25 [0.67-2.34]	1.09 [0.82-1.45]	N/I
Current smoking	1.22 [0.50-2.98]	0.91 [0.61-1.37]	N/I
Diabetes mellitus	1.54 [0.80-2.94]	1.14 [0.83-1.56]	N/I
Renal function			
eGFR 30-60 ml/min/1.73 m ²	0.59 [0.23-1.51]	1.61 [1.02-2.54]*	1.48 [0.86-2.56]
eGFR <30 ml/min/1.73 m ² / on dialysis	0.92 [0.43-1.96]	1.94 [1.35-2.78]*	1.63 [1.06-2.52]*
Heart failure	1.06 [0.52-2.14]	1.42 [1.04-1.95]*	1.37 [0.95-1.98]
Left ventricular ejection fraction (per 10%)	0.98 [0.80-1.21]	0.94 [0.85-1.03]	N/I
History of claudication	0.77 [0.43-1.38]	1.06 [0.81-1.38]	N/I
Rutherford classification	0.77 [0.47-1.25]	1.01 [0.81-1.27]	N/I
University of Texas classification	0.89 [0.68-1.15]	1.00 [0.88-1.13]	N/I
WIfI classification: Wound	0.80 [0.58-1.09]	1.01 [0.88-1.16]	N/I
WIfI classification: Ischemia	1.17 [0.43-3.15]	1.02 [0.71-1.47]	N/I
WIfI classification: Foot infection	1.16 [0.83-1.63]	1.11 [0.95-1.30]	1.26 [1.04-1.53]*
History of minor amputation	0.43 [0.15-1.24]	0.90 [0.53-1.51]	N/I
History of revascularization after CLTI onset	0.68 [0.26-1.73]	1.65 [1.05-2.57]*	2.19 [1.21-3.97]*
Bilateral CLTI	0.89 [0.42-1.87]	2.01 [1.42-2.85]*	2.01 [1.31-3.09]*
Contralateral major amputation	0.74 [0.08-6.97]	0.54 [0.22-1.33]	0.39 [0.12-1.21]
TASC II aorto-iliac classification	0.88 [0.70-1.12]	0.95 [0.85-1.07]	N/I
TASC II femoro-popliteal classification	1.04 [0.87-1.24]	0.95 [0.88-1.03]	N/I
TASC II infra-popliteal classification	1.27 [0.94-1.71]	1.01 [0.87-1.17]	N/I
Pedal artery lesion	1.60 [0.66-3.83]	1.49 [1.01-2.20]*	1.41 [0.93-2.14]

Hazard ratios are presented together with the 95% confidence intervals. Asterisks indicate $P < 0.05$. N/I, not included.

lation aging, the incidence of diabetes, and the increase in chronic renal failure¹⁹). Importantly, these risk factors commonly lead to distal vessel disease^{20, 21}). Hence, PAD with infra-inguinal and, especially, infra-popliteal lesions have been increasing in prevalence in the clinical setting. These lesions are often challenging to address during revascularization procedures. Courtesy of the development of EVT devices and techniques, increasing numbers of PAD patients have been endovascularly treated in the clinical setting^{1, 2}). Despite the widespread use of the endovascular approach, EVT is not yet equivalent to surgical reconstruction in terms of durability. Plain balloon angioplasty, which is still the standard endovascular proce-

cedure for infra-inguinal lesions, has a high rate of recoil, restenosis, and reintervention²²⁻²⁴). It is, therefore, reasonable to find that EVT itself increases the risk of reintervention in this analysis. Unexpectedly, anatomical severity, as evaluated by the TASC classification, was not significantly associated with the reintervention risk in the current study. There is a possibility that the TASC classification is not well suited for the evaluation of the reintervention risk in practice. However, poor initial technical success was significantly associated with a high reintervention risk, suggesting that patients with refractory anatomy were at a high risk for reintervention. A more sophisticated classification of the relevant anatomical features,

Table 7. Associations between baseline characteristics and reintervention risk after excluding patients who previously underwent revascularization

	Interaction of EVT versus surgical reconstruction (fold difference)	Unadjusted hazard ratio for reintervention	Adjusted hazard ratio for reintervention
EVT (versus surgical reconstruction)	---	1.68 [1.24-2.28]*	1.78 [1.28-2.46]*
Age (per 10 years)	1.11 [0.83-1.48]	0.89 [0.79-1.02]	0.89 [0.77-1.02]
Male sex	1.03 [0.52-2.01]	1.01 [0.76-1.36]	N/I
Impaired mobility	0.77 [0.49-1.20]	1.03 [0.85-1.23]	N/I
History of non-adherence to cardiovascular risk management	1.02 [0.50-2.06]	1.20 [0.89-1.63]	N/I
BMI (per 5 kg/m ²)	1.02 [0.65-1.59]	1.06 [0.87-1.29]	N/I
Hemoglobin (per 1 g/dl)	0.93 [0.79-1.11]	0.95 [0.88-1.03]	N/I
Albumin (per 1 g/dl)	0.91 [0.51-1.62]	1.02 [0.79-1.32]	N/I
Cholinesterase (per 100 U/l)	0.87 [0.57-1.33]	0.93 [0.76-1.15]	N/I
Smoking			
Past smoking	1.37 [0.69-2.72]	1.08 [0.80-1.47]	N/I
Current smoking	1.04 [0.42-2.59]	1.00 [0.66-1.50]	N/I
Diabetes mellitus	1.59 [0.80-3.18]	1.04 [0.75-1.44]	N/I
Renal function			
eGFR 30-60 ml/min/1.73 m ²	0.70 [0.26-1.87]	1.40 [0.88-2.25]	1.40 [0.86-2.29]
eGFR < 30 ml/min/1.73 m ² / on dialysis	1.12 [0.51-2.46]	1.75 [1.21-2.54]*	1.70 [1.16-2.49]*
Heart failure	1.14 [0.52-2.48]	1.40 [1.00-1.95]*	1.28 [0.92-1.79]
Left ventricular ejection fraction (per 10%)	0.97 [0.78-1.22]	0.95 [0.85-1.05]	N/I
History of claudication	0.99 [0.53-1.85]	1.02 [0.77-1.35]	N/I
Rutherford classification	0.79 [0.47-1.33]	1.03 [0.81-1.30]	N/I
University of Texas classification	0.88 [0.67-1.17]	0.99 [0.87-1.12]	N/I
Wifl classification: Wound	0.76 [0.54-1.07]	1.00 [0.86-1.16]	N/I
Wifl classification: Ischemia	1.35 [0.49-3.70]	0.99 [0.68-1.46]	N/I
Wifl classification: Foot infection	1.22 [0.84-1.76]	1.09 [0.92-1.29]	1.20 [0.99-1.46]
History of minor amputation	0.65 [0.17-2.52]	0.63 [0.33-1.22]	0.59 [0.30-1.15]
Bilateral CLTI	0.96 [0.42-2.17]	1.94 [1.33-2.82]*	1.82 [1.23-2.69]*
Contralateral major amputation	0.72 [0.08-6.81]	0.59 [0.24-1.47]	0.50 [0.20-1.26]
TASC II aorto-iliac classification	0.85 [0.67-1.09]	0.98 [0.86-1.10]	N/I
TASC II femoro-popliteal classification	1.03 [0.84-1.26]	0.94 [0.86-1.03]	N/I
TASC infra-popliteal classification	1.33 [1.00-1.78]	0.99 [0.85-1.15]	N/I
Pedal artery lesion	1.56 [0.72-3.42]	1.28 [0.86-1.90]	N/I

Hazard ratios are presented together with the 95% confidence intervals. Asterisks indicate $P < 0.05$. N/I, not included.

Table 8. Associations between baseline characteristics and total number of incident reinterventions during 1-, 2- and 3-year follow-up

	During 1 year	During 2 years	During 3 years
EVT (versus surgical reconstruction)	1.36 [1.06-1.75]*	1.44 [1.15-1.79]*	1.54 [1.24-1.90]*
Renal function			
eGFR 30-60 ml/min/1.73 m ²	1.71 [1.14-2.56]*	1.48 [1.04-2.11]*	1.35 [0.96-1.90]
eGFR < 30 ml/min/1.73 m ² / on dialysis	2.20 [1.56-3.10]*	2.29 [1.70-3.07]*	2.42 [1.84-3.20]*
History of revascularization after CLTI onset	1.38 [0.96-1.97]	1.47 [1.07-2.02]*	1.46 [1.08-1.99]*
Bilateral CLTI	2.65 [2.07-3.40]*	2.46 [1.98-3.07]*	2.40 [1.94-2.96]*

Data are increased risk (fold difference) of total reintervention incidence during 1-, 2-, and 3-year follow-up [95% confidence interval], derived from the multivariate Poisson regression model in which all the explanatory variables listed in the table were entered. Asterisks indicate $P < 0.05$.

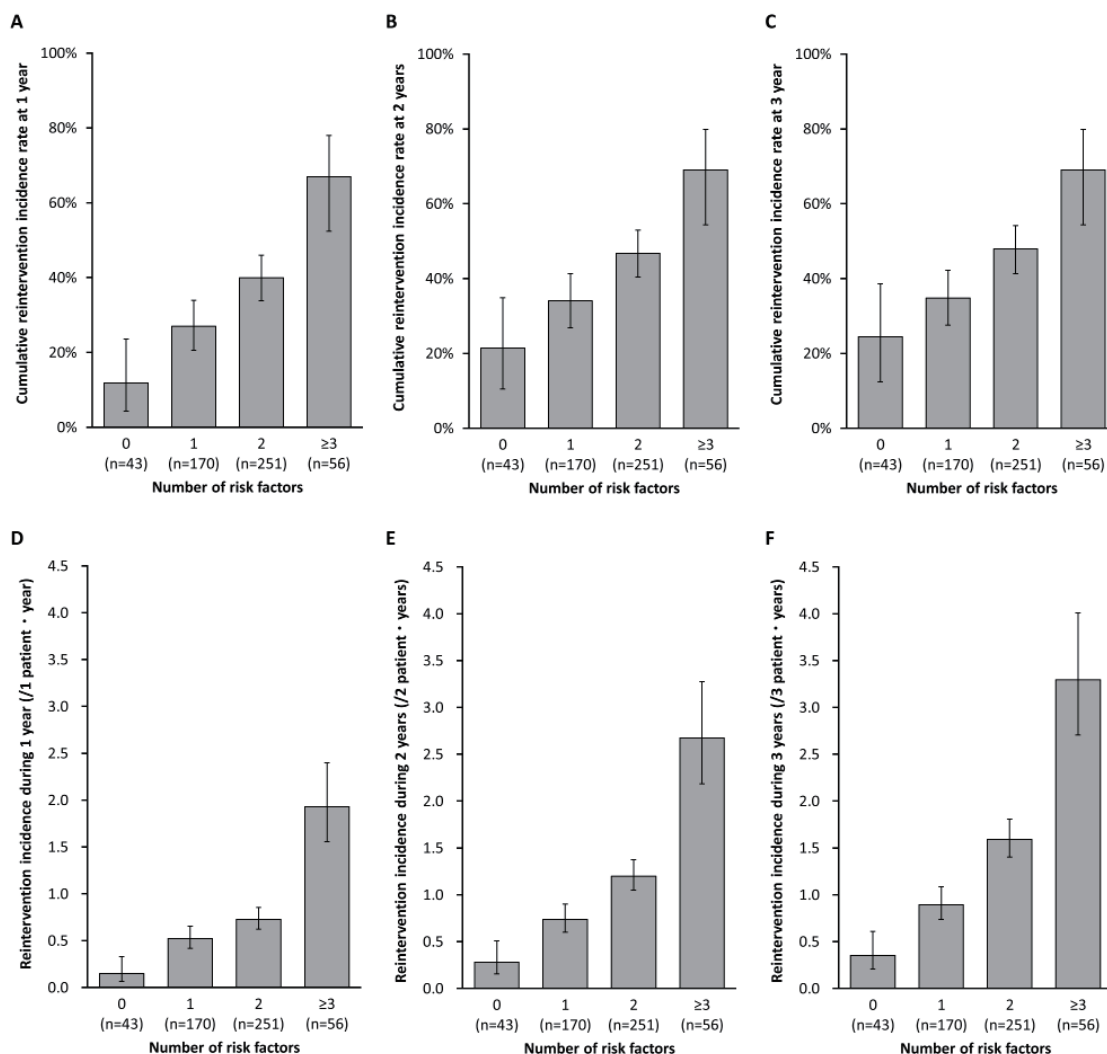


Fig. 2. Risk factor clustering and reintervention risk

Panel A, B, and C show the cumulative incidence rate of first reintervention at 1, 2, and 3 years, respectively, derived from the competing risk analysis, whereas panel C, D, and E show the total number of reinterventions (including the first and subsequent ones) during 1-, 2-, and 3-year follow-up, respectively, derived from the Poisson regression model. The risk factors were as follows: 1) EVT instead of bypass reconstruction, 2) an eGFR of 30–60 ml/min/1.73 m² and chronic renal failure (eGFR < 30 ml/min/1.73 m² and on dialysis), 3) a history of revascularization after CLTI onset, and 4) bilateral CLTI. Error bars represent the 95% confidence intervals.

which can allow for the stratification of patients according to their reintervention risk, is clinically necessary.

Renal dysfunction was found to be another risk factor for reintervention. Chronic renal failure is a major risk factor for the progression and exacerbation of PAD¹²). It has also been reported that patients with chronic renal failure present more severe symptoms than those without it²⁵). In general, arterial lesions are located in more distal vessels and are accompanied by more severe calcification in patients with concurrent chronic renal failure than in those without it²⁰). In addition to distally located lesions, vascular calcification has also been reported to be a negative factor

affecting short- and long-term outcomes in both treatment strategies, which might explain the elevated risk of reintervention in patients with renal dysfunction. In this analysis, an eGFR of 30–60 ml/min/1.73 m² was associated with as high an intervention risk as was chronic renal failure (eGFR < 30 ml/min/1.73 m² and on dialysis). It has been widely understood that atherosclerotic changes in peripheral arteries have been developing among patients even on the earlier stages of kidney dysfunction. One of the mechanisms may be an increased oxidative stress, which can cause endothelial dysfunction through the inhibition of nitric oxide bioavailability²⁶). Such a dysfunction may lead to an increasing risk of reintervention in patients with

an eGFR of 30–60 ml/min/1.73 m².

A history of revascularization after CLTI onset (need for repeated revascularization for CLTI) was also associated with an increased risk of reintervention. A subanalysis of the BASIL trial revealed poor results of surgical bypass after the failure of EVT²⁷⁾. In addition, this study shows that a relevant medical history was associated with a poor response to initial treatment. In such patients, the affected leg may have anatomically severe disease that may increase the risk of reintervention. Several subanalyses of medical interventions reveal that patients who had previously undergone vascular revascularization had significantly elevated risks of reintervention and major amputation, which is consistent with the findings of this study^{28, 29)}. Given these findings, a history of revascularization indicates patients with severe limb ischemia with a future risk for reintervention. Our study also identified bilateral CLTI as a risk factor for reintervention, which can be simply explained by the doubled potential for reintervention.

We found that high-risk Wifl classifications and severe wounds (Rutherford grade 6) were not associated with reintervention in the overall study population, which was a somewhat unexpected result. One possible explanation is that reintervention is a soft, rather than a hard, endpoint. In clinical practice, the indication for reintervention is determined not only by the wound severity or the clinical course of wound healing but also by the patient's general condition. Patients with severe wounds are likely to have poor general conditions and to be at high risk for mortality. Reintervention may be avoided in such patients. Some of these patients may die before reintervention can be performed. By contrast, patients with less severe wounds are less likely to suffer from a poor general condition and are more likely to undergo aggressive reintervention, not only for limb salvage but also sometimes to avoid minor amputations and relieve claudication. Consequently, the incidence of reintervention is not different between patients with severe wounds and those with nonsevere wounds in the overall study population. When performing the complete case analysis after listwise deletion, the Wifl classification was additionally identified as an independent risk factor. Although the risk of selection bias due to the listwise deletion should be kept in mind, this finding may indicate some clinically important findings. Wound infection is a well-known risk factor associated with major amputation and delayed wound healing in CLTI populations. Infected wounds generally need longer times for wound healing, during which the risk of restenosis increases, which in turn disturbs the wound healing process.

In terms of medical interventions, no postoperative medications were significantly associated with the reintervention risk in the current study population. Medications can change during the follow-up period, and the change may influence the association with the risk of reintervention. Statins and direct oral anticoagulants potentially reduce the risk of reintervention and major amputation, although those trials studied patients with PAD rather than focused on patients with CLTI²⁸⁾. Further investigation is warranted to assess the efficacy of these drugs in a CLTI population.

The limitations of the current study are as follows: First, the eligibility criteria for reintervention were left to the treating physicians' discretion in each clinical practice. Furthermore, the patient's general condition during the follow-up period may have also influenced the indication for reintervention, but its impact remains unclear. Second, neither drug-eluting balloons nor atherectomy devices were available for EVT when the SPINACH study was conducted. The use of these devices may have affected the current results. However, patients with CLTI often have complex lesions for which a treatment with drug-coated balloons or other proprietary products is generally not suitable. We therefore believe that the current findings are still relevant to the current real-world clinical setting. Third, the current study was conducted in Japan, and whether the findings will also be true in other countries remains unknown. The characteristics of patients with CLTI who undergo revascularization differ between Japan and other countries. For example, a Japanese CLTI population included a larger number of patients on dialysis. Furthermore, the medical insurance system in Japan and other countries is different. The system will influence the judgment of whether to perform reintervention or not. Fourth, detailed data on reasons for reintervention were not collected. Generally, the indication for reintervention differs between EVT and surgical reconstruction in clinical practice. However, the prevalence of renal failure is rapidly increasing worldwide. We expect that the number of patients with CLTI with renal failure will also increase. Studies including patients with CLTI with renal failure, especially those undergoing surgical and endovascular reconstruction, are scarce, and we believe that our study provides clinically relevant information. Finally, although we analyzed data from a prospective multicenter database in which patients undergoing surgical reconstruction or EVT performed in a real-world setting were included, of whom 87% completed a 3-year follow-up, the remaining 13% of patients were lost to follow-up, and some data were also missing for the patients who completed

the follow-up period. We attempted to statistically minimize the impact of those facts on the outcomes, but bias cannot be completely removed from our study.

Conclusions

In conclusion, the current study reveals the associations between preoperative characteristics and the reintervention risk in patients undergoing revascularization for CLTI. From the viewpoint of health economics, it is important to preoperatively stratify patients according to reintervention risk. The current findings will be useful for decision making regarding the selection of the appropriate revascularization procedure and predicting the postoperative course in a real-world clinical setting.

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Disclosures

There are no conflicts of interest regarding this manuscript.

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