The aim of the current study was to describe the clinical profile, frequency of in-hospital complications, and predictors of adverse events in patients undergoing endovascular therapy (EVT) for acute limb ischemia (ALI), and to compare them with those of patients undergoing EVT for chronic symptomatic peripheral artery disease (PAD).

Methods: The current study compared 2,398 cases of EVT for ALI with 74,171 cases of EVT for chronic symptomatic PAD performed between January 2015 and December 2018 in Japan. We first compared the clinical profiles of ALI patients with those of PAD patients. We then evaluated the proportion of in-hospital complications and investigated their risk factors in the ALI patients. The association of clinical characteristics with the risk of in-hospital complications was analyzed via logistic regression modeling.

Results: Patients with ALI were older and had a higher prevalence of female sex, impaired mobility, and history of cerebrovascular disease, but a lower prevalence of cardiovascular risk factors and history of coronary artery disease. The proportion of in-hospital EVT-related complications in ALI was 6.1% and was significantly higher compared with those in chronic symptomatic PAD patients (2.0%, \( P<0.001 \)). Bedridden status (adjusted odds ratio [aOR], 1.74 [1.14 to 2.66]; \( P=0.010 \)), history of coronary artery disease (aOR, 1.80 [1.21 to 2.68]; \( P=0.004 \)), and a suprapopliteal lesion (aOR, 1.70 [1.05 to 2.74]; \( P=0.030 \)) were identified as independent risk factors for in-hospital complications.

Conclusion: The current study demonstrated that ALI patients with significant comorbidities show a higher proportion of in-hospital complications after EVT.

Key words: Acute limb ischemia, Endovascular therapy, Peripheral artery disease, In-hospital outcomes

Introduction

In the recent years, endovascular therapy (EVT) for lower extremity ischemia has become more widespread and accessible due to technological advances and an accumulation of experience in endovascular field. The latest clinical practice guidelines have shifted toward an endovascular-first approach as a revascularization strategy in patients with chronic symptomatic peripheral arterial disease.
However, application of EVT in acute limb ischemia (ALI) has been scarcely studied. ALI is caused by an abrupt decrease in arterial perfusion of the limb, and remains the most life- and limb-threatening condition. Surgical revascularization, which includes surgical thrombectomy, bypass, and arterial repair, has long been considered the first-line treatment, albeit the procedural risk being high for patients with comorbidities. Extensive research validating the outcomes of EVT for ALI in the contemporary era of EVT is lacking since ALI is a rarely encountered condition with an incidence of just 1.5 cases per 10,000 persons per year4, 5).

Aim
The aim of the current study was to describe 1) the clinical profile, 2) frequency of in-hospital complications, and 3) predictors of adverse events in patients undergoing EVT for ALI and to compare them with those of patients undergoing EVT for chronic symptomatic PAD using a nationwide procedure-based registry in Japan. Such research would aid in providing a better understanding of the current status of EVT for patients with ALI.

Methods
The current study analyzed data from a national Japanese registry of EVT (J-EVT) between January 2015 and December 2018. The J-EVT, organized by the Japanese Association of Cardiovascular Intervention and Therapeutics, is the nationwide multicenter registry of EVT in Japan. The association obliges interventionalists and their cardiovascular centers to register all EVT cases in the J-EVT for board certification and application renewal. The registered data include the clinical diagnosis, treated vessel territories, and baseline patient characteristics (age, sex, smoking, hypertension, dyslipidemia, diabetes mellitus, end-stage renal disease on dialysis, coronary artery disease [CAD], and cerebrovascular disease). The data analysis was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Clinical Research Promotion Network Japan.

Study Population
Between 2015 and 2018, 2,398 cases of EVT for ALI were registered. We first compared the patients’ clinical profiles with those of 74,171 cases of EVT for chronic symptomatic PAD registered during the same period (namely, patients undergoing aortoiliac, femoropopliteal, and/or below-the-knee EVT for critical limb ischemia and aortoiliac and/or femoropopliteal EVT for intermittent claudication). We then evaluated the proportion of in-hospital complications and investigated the associated risk factors in the 2,398 cases of EVT for ALI.

Procedures
The EVT strategy was at each operator’s discretion. In general, after insertion of a 6-Fr or 7-Fr sheath, an intra-arterial bolus of 5,000 IU of heparin was injected and supplemented, as required, to maintain an active clotting time of >200 seconds. A 0.035-, 0.018-, or 0.014-inch guidewire was used to cross the thrombotic lesion. After successful wire crossing, direct catheter-based thrombectomy was performed using a conventional aspiration catheter, followed by balloon angioplasty. If the thrombus occlusion did not improve or severe residual stenosis remained, thrombolysis or stenting was additionally performed at the discretion of each operator.

Variable Definitions
ALI was defined as sudden onset or acute deterioration of clinical symptoms of lower limb ischemia within the last 14 days4). Chronic symptomatic PAD included critical limb ischemia and intermittent claudication. Critical limb ischemia was determined when patients had lower extremity rest pain or unhealed ulcers/gangrenes due to chronic severe ischemia, whereas intermittent claudication was determined as muscle discomfort in the lower limb produced by exercise and relieved by rest within 10 minutes due to chronic limb ischemia6).

Patients’ clinical profiles were defined as follows. Smoking was defined as any history of smoking within the past year. Diabetes mellitus was considered present when fasting plasma glucose levels were ≥ 126 mg/dL, casual plasma glucose levels were ≥ 200 mg/dL, hemoglobin A1c levels were ≥ 6.5%, plasma glucose levels 2 hours after a 75-g oral glucose tolerance test were ≥ 200 mg/dL, or patients were treated with antidiabetic medication6). Hypertension was considered present when systolic blood pressure was ≥ 140 mmHg, diastolic blood pressure was ≥ 90 mmHg,
or patients were treated with antihypertensive medication. Dyslipidemia was considered present when fasting triglyceride levels were ≥ 150 mg/dL, fasting high-density lipoprotein cholesterol levels were < 40 mg/dL, fasting low-density lipoprotein cholesterol levels calculated from the Friedewald equation were ≥ 140 mg/dL, non-high-density lipoprotein cholesterol levels were ≥ 170 mg/dL, or patients were treated with lipid-lowering medication. End-stage renal disease on dialysis included both hemodialysis and peritoneal dialysis.

In-hospital complications included in-hospital mortality within 30 days after EVT, urgent surgery, bleeding requiring transfusion, distal embolism, blood vessel rupture, acute occlusion, and contrast-induced nephropathy, defined as an increase in the serum creatinine levels by ≥ 25% or ≥ 0.5 mg/dL within 48 hours after contrast agent administration.

**Statistical Analyses**

Data are presented as the mean ± standard deviation for continuous variables and as percentages for categorical variables, unless otherwise indicated. *P* < 0.05 was considered statistically significant, and 95% confidence intervals (CIs) are reported where appropriate. Intergroup differences were examined using Welch’s *t*-test for continuous variables or with the chi-square test for discrete variables. The 95% CIs of proportions were estimated using the Clopper–Pearson exact method. The association of clinical characteristics with the risk of in-hospital complications was analyzed using a logistic regression model. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

### Results

The clinical profiles of patients with ALI versus those with chronic symptomatic PAD are summarized in Table 1. Patients with ALI were older and had a higher prevalence of female sex, impaired mobility, and history of cerebrovascular disease, but were less likely to have cardiovascular risk factors or history of CAD.

As shown in Table 2, the incidence of in-hospital complications of EVT for ALI was 6.1% [95% CI, 5.2% to 7.2%]. In-hospital mortality, urgent surgery, bleeding requiring transfusion, distal embolism, and acute occlusion, but not blood vessel rupture or contrast-induced nephropathy, were significantly more frequent in ALI cases than in chronic symptomatic PAD cases (Table 2).

The association of clinical characteristics with the risk of in-hospital complications in the ALI population is shown in Table 3. Notably, bedridden status, history of CAD, and a suprapopliteal lesion were identified as independent risk factors for in-hospital complications; their adjusted odds ratios were 1.74 [1.14 to 2.66] (*P*=0.010), 1.80 [1.21 to 2.68] (*P*=0.004), and 1.70 [1.05 to 2.74] (*P*=0.030), respectively. Indeed, cases with these risk factors clustered had an even higher risk of in-hospital complications (Fig. 1).
Table 2. Proportions of in-hospital complications

| In-hospital complications (overall) | ALI [5.2% to 7.2%] | Chronic symptomatic PAD [2.0% to 2.1%] | P value |
|-----------------------------------|--------------------|----------------------------------------|---------|
| In-hospital mortality             | 2.3% [1.7% to 3.0%]| 0.2% [0.2% to 0.3%]                   | <0.001 |
| Urgent surgery                    | 0.5% [0.3% to 0.9%]| 0.1% [0.1% to 0.2%]                   | <0.001 |
| Bleeding requiring transfusion    | 1.4% [1.0% to 2.0%]| 0.5% [0.5% to 0.6%]                   | <0.001 |
| Distal embolism                   | 0.7% [0.4% to 1.1%]| 0.2% [0.2% to 0.2%]                   | <0.001 |
| Blood vessel rupture              | 0.5% [0.3% to 0.9%]| 0.3% [0.3% to 0.4%]                   | 0.29    |
| Acute occlusion                   | 0.8% [0.5% to 1.3%]| 0.1% [0.1% to 0.1%]                   | <0.001 |
| Contrast-induced nephropathy      | 0.1% [0.0% to 0.4%]| 0.0% [0.0% to 0.1%]                   | 0.23    |

Data are reported as odds ratio [95% confidence interval].

Table 3. Associations of clinical characteristics with risk of in-hospital complications

| Clinical characteristic             | Crude odds ratio [95% confidence interval] | Adjusted odds ratio [95% confidence interval] |
|------------------------------------|--------------------------------------------|---------------------------------------------|
| Female sex                         | 1.33 [0.95 to 1.86] (P=0.092)               | 1.18 [0.81 to 1.72] (P=0.38)                |
| Age (per 10 years)                 | 1.26 [1.07 to 1.47] (P=0.004)               | 1.13 [0.95 to 1.34] (P=0.18)                |
| Mobility (versus self-ambulatory)  |                                            |                                             |
| In wheelchair                      | 1.26 [0.84 to 1.91] (P=0.26)               | 1.20 [0.79 to 1.84] (P=0.39)                |
| Bedridden                          | 2.07 [1.93 to 3.07] (P<0.000)               | 1.74 [1.14 to 2.66] (P=0.010)               |
| Diabetes mellitus                  | 1.00 [0.70 to 1.42] (P=0.99)               | 1.07 [0.73 to 1.55] (P=0.73)                |
| Hypertension                       | 0.92 [0.65 to 1.30] (P=0.64)               | 0.95 [0.66 to 1.37] (P=0.78)                |
| Dyslipidemia                       | 0.77 [0.53 to 1.22] (P=0.17)               | 0.75 [0.51 to 1.22] (P=0.17)                |
| Current smoking                    | 0.82 [0.54 to 1.25] (P=0.35)               | 1.01 [0.64 to 1.59] (P=0.96)                |
| Regular dialysis                   | 0.76 [0.44 to 1.29] (P=0.30)               | 0.71 [0.40 to 1.26] (P=0.24)                |
| Coronary artery disease            | 1.56 [1.08 to 2.25] (P=0.018)              | 1.80 [1.21 to 2.68] (P=0.004)               |
| Cerebrovascular disease            | 1.41 [0.94 to 2.11] (P=0.10)               | 1.09 [0.72 to 1.67] (P=0.68)                |
| Suprapopliteal lesion              | 1.94 [1.21 to 3.12] (P=0.006)              | 1.70 [1.05 to 2.74] (P=0.030)               |

Data are reported as odds ratio [95% confidence interval] (P value). Adjusted odds ratios were derived from the multivariate logistic regression model in which all of the variables listed in the Table were entered as explanatory variables.

Fig. 1. Proportion of in-hospital complications of endovascular therapy in acute limb ischemia patients by number of risk factors

The risk factors were 1) bedridden status, 2) history of coronary artery disease, and 3) a suprapopliteal lesion (see Table 3). Error bars indicate 95% confidence intervals.
Discussion

The current study revealed that 1) patients with ALI were older and had a higher prevalence of female sex, impaired mobility, and history of cerebrovascular disease, but a lower prevalence of cardiovascular risk factors or history of CAD; 2) the proportion of in-hospital complications of EVT for ALI was 6.1% [95% CI, 5.2% to 7.2%]; and 3) bedridden status, history of CAD, and a suprapopliteal lesion were independent risk factors for in-hospital complications after EVT in ALI patients.

Clinical Profiles of Patients with ALI

The clinical profiles were significantly different between patients with ALI and those with chronic symptomatic PAD. The etiology of PAD, which is a type of cardiovascular disease, is mainly atherosclerosis caused by the accumulation of lipid and fibrous material between the layers of the arterial wall. The development of PAD is associated with well-defined risk factors, including diabetes mellitus, hypertension, dyslipidemia, smoking, chronic kidney disease, and regular dialysis\(^1\), \(^4\), \(^9\)-\(^12\). Because they share numerous risk factors, about half of PAD patients have concomitant CAD\(^13\). On the other hand, the etiology of ALI includes not only acute progression on chronic presentation of PAD but also cardiac embolization, graft thrombosis, aortic dissection or embolization, popliteal artery aneurysm, hypercoagulability associated with chemotherapy or cancer, and iatrogenic causes\(^1\). Therefore, patients with ALI are less associated with atherosclerosis and are less likely to have cardiovascular risk factors or history of CAD compared with those with chronic symptomatic PAD. The higher frequency of cerebrovascular disease in the patients with ALI might reflect the higher frequency of cerebral thromboembolism due to cardiac embolization, which can also cause ALI. The proportion of impaired mobility was also higher in the patients with ALI. This might be because patients with ALI were older and had a higher prevalence of cerebrovascular disease history. In contrast, patients with cerebrovascular disease or impaired mobility, especially those with a poor general condition, may be prone to dehydration or withdrawal of antithrombotic drugs for some reason, which may lead to the development of ALI.

Proportion of In-Hospital Complications

In the current study, the proportion of in-hospital complications after EVT for ALI was 6.1% [95% CI, 5.2% to 7.2%], which was significantly higher than after EVT for chronic symptomatic PAD (2.0% [95% CI, 1.9% to 2.1%]; \(P\leq0.001\)). There are several possible reasons for the significant difference between ALI and PAD. First, the general condition of ALI patients was more severe because ALI threatens limb viability and there was insufficient time for the development of collateral arteries due to the presence of arterial lesions with chronic ischemia. Previous literature on the American Medicare population\(^14\) revealed in-hospital, 30-day, and 1-year amputation rates for patients with ALI of 6.4%, 8.1%, and 11.0%, respectively. Furthermore, the previous literature determined in-hospital, 30-day, and 1-year mortality rates for patients with ALI of 9.0%, 19.2%, and 42.0%, respectively. We believe that the difference in severity between ALI and chronic symptomatic PAD patients is related to the in-hospital complication results. Second, it can be very challenging to sufficiently restore blood flow after EVT in some cases because higher thrombus burden is observed in patients with ALI compared with patients with chronic symptomatic PAD, resulting in worse in-hospital complications. Finally, patients with ALI were older and had a higher rate of impaired mobility. This might be because most of the ALI patients with worse comorbidities had high perioperative risks and were reluctantly treated by EVT in the clinical setting. This aspect might have also contributed to the results.

Endovascular devices have improved dramatically in recent years, and the clinical data after EVT for ALI in today’s clinical setting have considerably improved\(^1\). Previous reports demonstrated that the rates of postoperative complications in ALI patients after EVT with catheter-directed thrombolysis ranged from 11% to 30.3% and that the 30-day mortality rates were 8.2% or less\(^15\)-\(^24\). De Athayde Soares et al.\(^25\) obtained similar limb salvage and overall survival estimates at 720 days in an open surgery group and EVT group (79.2% vs 90.6% \([P=0.27]\) and 53.0% vs 60.8% \([P=0.45]\), respectively). Taha et al.\(^26\) determined amputation rates of 10.0% vs 7.2% \((P=0.35)\) at 30 days and 16.3% vs 13.0% \((P=0.37)\) at 1 year, respectively, in Rutherford II patients. In the current study, in-hospital complications, including death, were even lower than those in the aforementioned reports. This may be because the current study applied various EVT strategies at the operator’s discretion to improve blood flow to the ischemic lower limb, including catheter-directed thrombolysis, catheter thrombus aspiration, plain balloon angioplasty, and stent implantation, while these previous reports reported outcomes with thrombolysis alone. These favorable results can be explained by the combination of different strategies for revascularization depending on the anatomical
location of lesion or the patient’s condition. On the other hand, the endovascularly managed ALI patients in the current study might have had milder conditions than those included in previous studies because a relatively simple lesion might have been selected for EVT rather than surgical treatment.

Risk Factors for In-Hospital Complications

In the current study, bedridden status, history of CAD, and a suprapopliteal lesion were identified as independent risk factors for in-hospital complications in ALI patients. Regarding patients with PAD, previous studies revealed that non-ambulatory patients had a significantly higher risk of mortality and perioperative complications after EVT\textsuperscript{27-28}. Bedridden patients are restricted in their ability to visit the hospital. In addition, some of these patients cannot report their symptoms accurately and in a timely manner due to other comorbidities. Therefore, hospital visits are occasionally delayed for bedridden patients, possibly worsening limb viability due to ALI progress. Although we could not evaluate the relevant data, the time from onset of ALI to treatment would be longer in bedridden patients than in ambulatory patients.

A previous report determined that CAD was an independent risk factor for a worse in-hospital outcome after EVT for ALI\textsuperscript{29}. Because patients with CAD generally have a high burden of atherosclerotic risk factors, it was not surprising that ALI patients with CAD also experienced worse in-hospital outcomes than those without CAD. Similar to the previous report, CAD was an independent risk factor in the current study. Suprapopliteal lesions were also identified as independent risk factors for in-hospital complications in ALI patients. A probable explanation for this finding was an increased thrombus burden or larger territory of lower limb ischemia, indicating a more severe underlying condition compared with isolated below-the-knee lesions.

Limitations

The present study has several limitations. First, the current study included only Japanese patients. It is unclear whether the results can be applied to patients of other ethnicities. Second, there might be a selection bias because the criteria for selecting EVT in ALI patients were at the discretion of each institution. Furthermore, we could not collect the data on ALI patients managed via surgical treatment or primary amputation during the same period. Third, the number of variables in the J-EVT is limited. Some variables were not available, such as detailed lesion characteristics, EVT procedure details (e.g., hybrid therapy, catheter-directed thrombolysis, and use of covered stent), antithrombotic drugs, time from ALI onset to treatment, creatine phosphokinase value at the time of treatment, prevalence of patients with atrial fibrillation, and the etiology of ALI. These confounders might have affected the results. Further investigation that includes these data is needed in the future. Fourth, we could not evaluate longer follow-up data, including limb salvage. Fifth, some institutions might have failed to register some in-hospital complications, which may have caused an underestimation of complication rates. Finally, the criteria used for selecting the revascularization strategy for ALI patients differed among the institutions in this study. This selection bias might have affected the results.

Conclusion

The clinical profile was significantly different between patients with ALI and those with chronic symptomatic PAD. The incidence of in-hospital complications of EVT for ALI was significantly higher than that of EVT for chronic symptomatic PAD. Bedridden status, history of CAD, and a suprapopliteal lesion were identified as independent risk factors for in-hospital complications.

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