

Clinical outcomes of acute limb ischaemia caused by femoropopliteal stent thrombosis

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ABSTRACT

BACKGROUND: Although femoropopliteal-specific stents have durable patency, stent thrombosis (ST) may occur, which can lead to acute limb ischaemia (ALI).

AIMS: We aimed to investigate the clinical features and outcomes of ALI caused by femoropopliteal ST in patients with lower extremity artery disease.

METHODS: This multicentre retrospective study included 499 patients with ALI – of whom 108 patients had ALI caused by femoropopliteal ST (ST-ALI) and 391 patients had ALI caused by other aetiologies (*de novo* ALI) – who underwent treatment between September 2011 and March 2023. Clinical features and outcomes were compared between the two groups. The primary outcome measure was 12-month amputation-free survival; factors associated with amputation or death were investigated using multivariate Cox proportional hazards regression analysis.

RESULTS: Patients with ST-ALI were significantly more likely to exhibit conventional atherosclerotic risk factors, including diabetes mellitus (63% vs 26%) and haemodialysis (51% vs 10%) compared to patients with *de novo* ALI, whereas patients with *de novo* ALI were older (80 years vs 74 years) and more likely to have atrial fibrillation (49% vs 18%) than patients with ST-ALI. The 12-month amputation-free survival rate was significantly lower in the ST-ALI group than that in the *de novo* ALI group (51% vs 76%; $p<0.001$). Multivariate analysis revealed that ST-ALI, older age, haemodialysis, atrial fibrillation, the presence of a wound, peak C-reactive protein level, and non-ambulatory status all have an independent, positive association with death or major amputation.

CONCLUSIONS: The current study revealed that patients with ST-ALI had worse clinical outcomes than those with *de novo* ALI, highlighting the need to maximise ST prevention.

KEYWORDS: clinical research; femoropopliteal disease; thrombus-containing lesion

Rapid progress in endovascular therapy (EVT) has led to the extension of its use even for complex lesions of the femoropopliteal (FP) artery, which are the primary manifestation of lower extremity artery disease (LEAD)¹⁻⁴. Although EVT using drug-coated balloons is currently regarded as the standard approach for the management of these lesions, stent-based EVT is necessary for complex FP diseases, such as diffuse, calcified, or total occlusion lesions¹. However, the use of FP stents in EVT increases the risk of acute stent thrombosis (ST), which occurs in 3-10% of cases and can ultimately result in acute limb ischaemia (ALI)⁵.

ALI is an incapacitating and potentially fatal vascular emergency^{6,7}. Its primary causes include *in situ* thrombosis, arterial embolisation, and bypass graft thrombosis, and ALI with these aetiologies has been associated with high rates of limb loss and mortality^{6,8-10}. However, few studies have focused on ALI caused by FP-ST (ST-ALI), and its clinical outcomes are yet to be fully elucidated. The present study aimed to reveal the clinical features and outcomes of ST-ALI, compared with ALI of other aetiologies.

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Methods

STUDY POPULATION

This multicentre, retrospective, observational study was conducted at 8 cardiovascular and vascular surgical centres across Japan. The study included 499 patients with ALI – of whom 108 had ST-ALI and 391 had ALI caused by other factors, including *in situ* thrombosis, arterial embolisation, and bypass graft thrombosis in the FP arterial lesions (*de novo* ALI) – treated at these centres between September 2011 and March 2023. This study was performed in accordance with the Declaration of Helsinki, and each centre obtained ethical approval for the study from the relevant institutional review board. As the study was observational, with no intervention or invasiveness and without the use of human biological specimens, it was exempt from the requirement to obtain written informed consent from patients, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant study information was made publicly available, and individuals were given the opportunity to refuse the inclusion of their data.

ACUTE LIMB ISCHAEMIA TREATMENT

Treatment strategies for ALI included conservative therapy, primary major amputation, open surgical revascularisation (OSR), and EVT; the strategy was selected at the discretion of the physician based on patient status, the severity of ischaemia, and anatomical features. Major amputation was performed in cases of irreversible limb ischaemia (Rutherford classification

Impact on daily practice

The 12-month amputation-free survival rate was lower in patients with acute limb ischaemia caused by femoropopliteal stent thrombosis (ST-ALI) compared to those with acute limb ischaemia with other aetiologies. ST-ALI is a life-threatening event, and further investigation is required to determine the risk factors for this condition after femoropopliteal stenting. A non-stenting strategy, including surgical bypass or drug-coated balloon-based endovascular therapy, and implementing optimal medical therapy after revascularisation should be considered for patients at high risk of ST-ALI.

stage III). EVT included catheter thrombectomy, catheter-directed thrombolysis, pharmacomechanical thrombolysis, or a combination of these, followed by angioplasty or stent implantation. OSR included direct thrombectomy, thrombectomy using a Fogarty catheter (Edwards Lifesciences), endarterectomy, and primary bypass with autovein or prosthetic grafts. Timing of the revascularisation procedure depended mainly on the severity of ischaemia on presentation. Mild degrees of ischaemia allowed more time for a diagnostic workup and patient optimisation.

OUTCOME MEASURES

After treatment of ALI, all patients were regularly followed up at the outpatient clinic and underwent a postinterventional examination including clinical symptoms, haemodynamic changes in ankle-brachial index, and an evaluation of restenosis via Duplex ultrasonography. The primary outcome measure was amputation-free survival (AFS), and the secondary endpoints were major adverse limb events (MALE) and occlusion at 12 months.

DEFINITIONS

AFS was defined as the time until major amputation of the index limb and/or death from any cause, whichever occurred first. MALE were defined as a composite of major amputation and major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis), and occlusion was defined as reocclusion of the treated artery¹¹. ALI severity was determined according to the Rutherford classification proposed by the Society for Vascular Surgery/International Society for Cardiovascular Surgery: stage I – the limb is not immediately threatened; stage IIa – the limb is marginally threatened; stage IIb – the limb is immediately threatened; and stage III – the limb is irreversibly threatened or non-viable¹². Major amputation was defined as above-the-ankle

Abbreviations

AFS	amputation-free survival	CRP	C-reactive protein	LEAD	lower extremity artery disease
ALI	acute limb ischaemia	EVT	endovascular therapy	MALE	major adverse limb events
CI	confidence interval	FP	femoropopliteal	OSR	open surgical revascularisation
CPK	creatine phosphokinase	HR	hazard ratio	ST	stent thrombosis

amputation. The degree of calcification was graded based on arterial wall calcium deposits detected during fluoroscopy according to the Peripheral Arterial Calcium Scoring Scale¹³.

STATISTICAL ANALYSIS

Data on baseline characteristics are presented as frequencies and percentages for discrete variables and as median (interquartile range) for continuous variables. Crude comparisons in baseline characteristics between patients with ST-ALI and *de novo* ALI were performed using the Student's t-test for continuous variables and the chi-squared test for categorical variables. Cumulative incidence rates were assessed using the Kaplan-Meier method, and the rates are reported as estimate±standard error. Differences between the groups were assessed using the log-rank test when necessary. Factors associated with amputation or death were analysed in patients with Rutherford classification stage I or II ALI, because Rutherford classification stage III ALI is generally treated with primary amputation. The association of AFS with baseline clinical and procedural variables was

first analysed using univariate Cox proportional hazards regression analysis. Next, multivariate Cox proportional hazards regression analysis was performed to adjust for confounders and identify risk factors for amputation or death. Clinical factors that were known to affect outcomes and that achieved $p<0.05$ in the univariate analysis were entered into the multivariate Cox regression analysis. The interaction effect of baseline characteristics on the association between ALI aetiology and amputation or mortality risk was also analysed using a Cox proportional hazards regression model. A p -value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software, version 24.0J (IBM).

Results

BASELINE PATIENT CHARACTERISTICS AND CLINICAL FEATURES

Baseline patient, clinical, and procedural characteristics are summarised in **Table 1** and **Table 2**. The prevalence of conventional atherosclerotic risk factors, including

Table 1. Baseline patient characteristics.

Patient characteristics				
Variable	Total N=499	ST-ALI N=108	<i>De novo</i> ALI N=391	<i>p</i> -value
Age, years	78 [69, 85]	74 [67, 80]	80 [70, 87]	<0.001
Male sex	297 (60)	72 (67)	225 (58)	0.087
Ambulatory status	337 (68)	78 (72)	259 (66)	0.240
Hypertension	368 (74)	89 (82)	279 (71)	0.020
Dyslipidaemia	182 (36)	56 (52)	126 (32)	<0.001
Diabetes	169 (34)	68 (63)	101 (26)	<0.001
Chronic kidney disease	169 (34)	69 (64)	100 (26)	<0.001
Haemodialysis	93 (19)	55 (51)	38 (10)	<0.001
Current smoker	79 (16)	12 (11)	67 (17)	0.129
Stroke	113 (23)	22 (20)	91 (23)	0.523
Coronary artery disease	155 (31)	62 (57)	93 (24)	<0.001
Atrial fibrillation	211 (42)	19 (18)	192 (49)	<0.001
Number of antithrombotic drugs	1 [0, 2]	2 [1, 2]	0 [0, 1]	<0.001
Aetiology of <i>de novo</i> ALI				
Embolism			235 (60)	
Pre-existing PAD			129 (33)	
<i>In situ</i> thrombosis			102 (26)	
Graft failure			27 (7)	
Other			27 (7)	
Thrombosed stent of ST-ALI				
BMS		44 (41)		
DCS		12 (11)		
DES		17 (16)		
SG		27 (25)		
IWS		5 (5)		
Unknown		3 (2)		

Data are presented as median [interquartile range] or number (%). ALI: acute limb ischaemia; BMS: bare metal stent; DCS: drug-coated stent; *de novo* ALI: ALI caused by other aetiologies; DES: drug-eluting stent; IWS: interwoven stent; PAD: peripheral arterial disease; SG: stent graft; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST

Table 2. Baseline clinical, and procedural characteristics.

Clinical characteristics				
Variable	Total N=499	ST-ALI N=108	<i>De novo</i> ALI N=391	p-value
Onset-to-admission time, hrs	12 [5, 60]	18 [6, 48]	12 [4.4, 72]	0.277
Peak CPK, U/L	1,148 [225, 4,380]	656 [119, 3,357]	1,200 [282, 4,762]	0.005
Peak CRP, mg/dL	7.8 [2.5, 16.0]	6.7 [1.2, 16.3]	7.8 [2.8, 15.9]	0.153
Presence of wound	54 (11)	24 (22)	30 (8)	<0.001
CIA or EIA thrombus	101 (20)	4 (4)	97 (25)	<0.001
Rutherford classification				<0.001
I	104 (21)	44 (41)	60 (16)	
IIa	187 (38)	38 (35)	149 (38)	
IIb	161 (32)	23 (21)	138 (35)	
III	47 (9)	3 (3)	44 (11)	
Procedural characteristics				
Variable	Total N=499	ST-ALI N=108	<i>De novo</i> ALI N=391	p-value
Primary bypass	28 (6)	1 (1)	27 (7)	0.017
Primary amputation	33 (7)	2 (2)	31 (8)	0.024
Conservative therapy	10 (2)	1 (1)	9 (2)	0.366
Surgical thrombectomy	209 (42)	13 (12)	197 (50)	<0.001
Catheter thrombectomy	233 (47)	79 (73)	154 (39)	<0.001
Local thrombolysis	102 (20)	44 (41)	58 (15)	<0.001
Additional stenting	155 (31)	45 (42)	110 (28)	0.007

Data are presented as median [interquartile range] or number (%). ALI: acute limb ischaemia; CIA: common iliac artery; CPK: creatine phosphokinase; CRP: C-reactive protein; *de novo* ALI: ALI caused by other aetiologies; EIA: external iliac artery; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST

hypertension (82% vs 71%; $p=0.020$), dyslipidaemia (52% vs 32%; $p<0.001$), diabetes mellitus (63% vs 26%; $p<0.001$), haemodialysis (51% vs 10%; $p<0.001$), and coronary artery disease (57% vs 24%; $p<0.001$), was significantly higher in the ST-ALI group than in the *de novo* ALI group, whereas patients in the *de novo* ALI group were older (80 years vs 74 years; $p<0.001$) and had a higher prevalence of atrial fibrillation (49% vs 18%; $p<0.001$) than those in the ST-ALI group. The onset-to-admission time (ST-ALI group: 18 hours; *de novo* ALI group: 12 hours; $p=0.277$) did not differ significantly between the two groups, whereas the ST-ALI group had a lower peak creatine phosphokinase (CPK) level (656 U/L vs 1,200 U/L; $p=0.005$) and a less severe Rutherford classification (stage I: 41% vs 16%; stage II: 56% vs 73%; stage III: 3% vs 11%; $p<0.001$) than the *de novo* ALI group. In terms of the procedures performed, primary surgical bypass therapy (7% vs 1%; $p=0.017$), primary amputation (8% vs 2%; $p=0.024$), and surgical thrombectomy (50% vs 12%; $p<0.001$) were more frequently carried out in the *de novo* ALI group than in the ST-ALI group, whereas catheter thrombectomy (73% vs 39%; $p<0.001$) and local thrombolysis (41% vs 15%; $p<0.001$) were more frequently performed in the ST-ALI group than in the *de novo* ALI group. The lesion details of the initial EVT in the ST-ALI group are summarised in **Table 3**. Chronic total occlusion accounted for 49% ($n=53$) and the popliteal artery was involved for 58% ($n=63$) of lesions before the initial EVT in the ST-ALI group.

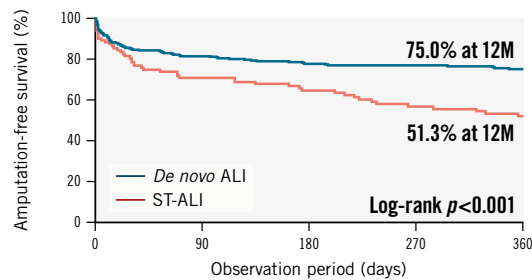
CLINICAL OUTCOMES OF ST-ALI VERSUS *DE NOVO* ALI

The 12-month AFS was significantly lower in the ST-ALI group than that in the *de novo* ALI group ($51.3\pm 5.1\%$ vs $75.0\pm 2.5\%$; $p<0.001$) (**Central illustration**). **Figure 1** shows that the 12-month rates of freedom from MALE and occlusion were also significantly lower in the ST-ALI group than those in the *de novo* ALI group ($46.5\pm 5.6\%$ vs $85.4\pm 2.2\%$; $p<0.001$ and $50.0\pm 5.5\%$ vs $86.6\pm 2.2\%$; $p<0.001$, respectively). As shown in **Supplementary Table 1** and **Supplementary Figure 1**, the ST-ALI group also had lower rates of freedom from death ($62.3\pm 5.0\%$ vs $78.4\pm 2.4\%$; $p=0.004$), freedom from major amputation ($78.6\pm 4.9\%$ vs $94.6\pm 1.4\%$; $p<0.001$), and freedom from thrombectomy/thrombolysis ($57.6\pm 5.8\%$ vs $91.4\pm 1.8\%$; $p<0.001$) than the *de novo* ALI group.

FACTORS ASSOCIATED WITH DEATH OR MAJOR AMPUTATION IN PATIENTS WITH RUTHERFORD CLASSIFICATION STAGE I OR II ACUTE LIMB ISCHAEMIA

The baseline characteristics significantly associated with death and major amputation were older age (hazard ratio [HR] 1.04 per 1-year increase, 95% confidence interval [CI]: 1.02-1.06; $p<0.001$), female sex (HR 1.69, 95% CI: 1.25-2.30; $p<0.001$), non-ambulatory status (HR 4.19, 95% CI: 2.93-5.99; $p<0.001$), haemodialysis (HR 2.39, 95% CI: 1.66-3.46; $p<0.001$), current smoking (HR 0.24, 95% CI: 0.11-0.50; $p<0.001$), coronary artery disease (HR 1.51, 95% CI: 1.06-2.16; $p=0.024$), atrial fibrillation (HR

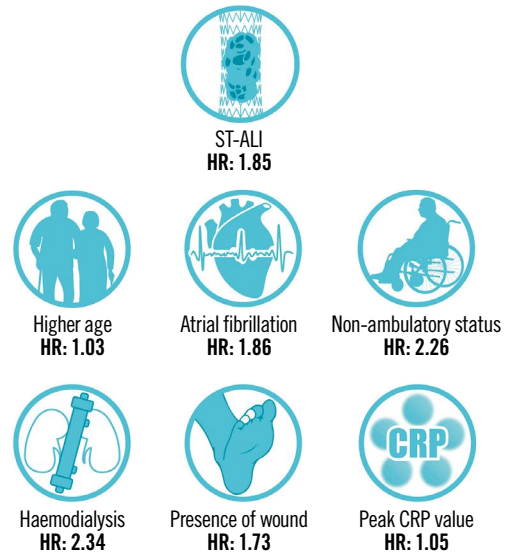
Amputation-free survival rate and prognostic factors after acute limb ischaemia.

A Amputation-free survival after acute limb ischaemia**De novo ALI**

No. at risk 347 229 200 189 167
 %±SE 100 81.3±2.2 77.5±2.4 76.3±2.5 75.0±2.5

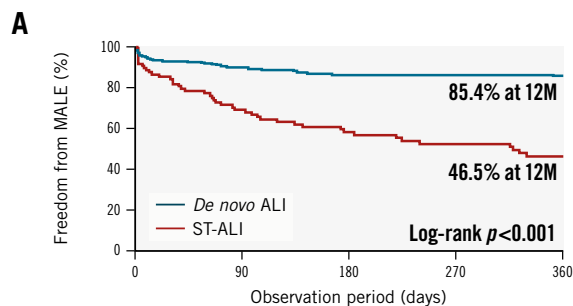
ST-ALI

No. at risk 105 70 59 48 41
 %±SE 100 71.2±4.4 65.0±4.7 56.0±5.0 51.3±5.1

B Factors associated with amputation or death after acute limb ischaemia

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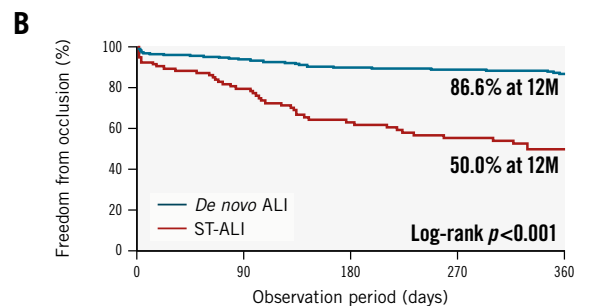
A) The 12-month AFS was significantly lower in the ST-ALI group than in the de novo ALI group (51.3±5.1% vs 75.0±2.5%; $p < 0.001$), indicating better outcomes for patients with de novo ALI than for those with ST-ALI. B) ST-ALI as well as older age, haemodialysis, atrial fibrillation, the presence of wound, peak CRP level, and non-ambulatory status remained significantly associated with an increased risk of death or amputation. ALI: acute limb ischaemia; CRP: C-reactive protein; de novo ALI: ALI caused by other aetiologies; HR: hazard ratio; SE: standard error; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST

**De novo ALI**

No. at risk 347 216 181 170 148
 %±SE 100 89.4±1.8 85.9±2.1 85.9±2.1 85.4±2.2

ST-ALI

No. at risk 105 58 43 36 29
 %±SE 100 68.9±4.8 58.1±5.3 52.5±5.4 46.5±5.6

**De novo ALI**

No. at risk 347 227 191 177 151
 %±SE 100 93.7±1.4 89.8±1.9 88.8±2.0 86.6±2.2

ST-ALI

No. at risk 105 72 51 41 36
 %±SE 100 79.4±4.1 63.1±5.1 55.6±5.3 50.0±5.5

Figure 1. Twelve-month rates of MALE and occlusion. The incidence of MALE and occlusion of the treated artery were measured over a 12-month period following treatment for ALI and compared between patients with ST-ALI and those with de novo ALI. The 12-month rates of freedom from MALE (A) and occlusion (B) were significantly lower in the ST-ALI group than those in the de novo ALI group (46.5±5.6% vs 85.4±2.2%; $p < 0.001$, and 50.0±5.5% vs 86.6±2.2%; $p < 0.001$, respectively), indicating better outcomes for patients with de novo ALI than for those with ST-ALI. ALI: acute limb ischaemia; de novo ALI: ALI caused by other aetiologies; MALE: major adverse limb events; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST

Table 3. Baseline characteristics at initial treatment in the ST-ALI group.

Lesion characteristics	
Variables	N=108
Angiographical data missing	4 (4)
Rutherford category	
2	10 (9)
3	32 (30)
4	13 (12)
5	47 (44)
6	6 (5)
TASC II classification	
A	3 (3)
B	11 (10)
C	56 (52)
D	34 (31)
Chronic total occlusion	53 (49)
In-stent restenosis	12 (11)
Ostial lesion	35 (32)
Popliteal artery involvement	63 (58)
Below-the-knee vessel run-off	
0	10 (9)
1	56 (52)
2	26 (24)
3	12 (11)
Lesion length, cm	25 [15, 30]
PACSS classification	
0	35 (33)
1	11 (10)
2	10 (9)
3	11 (10)
4	37 (34)

Data are presented as number (%) or median [interquartile range].
ALI: acute limb ischaemia; PACSS: Peripheral Arterial Calcium Scoring System; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST; TASC: TransAtlantic Inter-Society Consensus

1.49, 95% CI: 1.04-2.11; $p=0.028$), ST-ALI (HR 2.06, 95% CI: 1.44-2.96; $p<0.001$), peak C-reactive protein (CRP) level (HR 1.06 per 1 mg/dL increase, 95% CI: 1.04-1.07; $p<0.001$), and the presence of a wound (HR 2.63, 95% CI: 1.71-4.05; $p<0.001$). After multivariate analysis, ST-ALI (HR 1.85, 95% CI: 1.14-2.99; $p=0.012$) as well as older age (HR 1.03 per 1-year increase, 95% CI: 1.01-1.05; $p=0.023$), haemodialysis (HR 2.34, 95% CI: 1.45-3.79; $p<0.001$), atrial fibrillation (HR 1.86, 95% CI: 1.25-2.77; $p=0.002$), the presence of a wound (HR 1.73, 95% CI: 1.08-2.76; $p=0.022$), peak CRP level (HR 1.05 per 1 mg/dL increase, 95% CI: 1.03-1.07; $p<0.001$), and non-ambulatory status (HR 2.26, 95% CI: 1.49-3.43; $p<0.001$) remained significantly associated with an increased risk of death or amputation (Table 4). Subgroup analyses showed that no baseline characteristics had any interaction effect on the association between ST-ALI and the primary outcome (Figure 2).

Discussion

SUMMARY OF THE CURRENT STUDY

Previous studies have shown that patients with ST-ALI experience a higher rate of MALE and a composite of mortality and major amputation compared with those without ST^{5,14}. However, no studies have compared the clinical features and outcomes of patients with ST-ALI to those of patients with ALI with other aetiologies. The current study highlighted that patients with ST-ALI were more likely to exhibit conventional atherosclerotic risk factors than patients with *de novo* ALI and presented with a less severe Rutherford classification and lower CPK values. Patients with ST-ALI had a significantly lower rate of 12-month AFS than patients with *de novo* ALI, even after adjusting for baseline characteristics.

CLINICAL FEATURES OF ACUTE LIMB ISCHAEMIA CAUSED BY FEMOROPOPLITEAL STENT THROMBOSIS

All patients presenting with ST-ALI were previously treated for LEAD, and therefore, it is reasonable that they exhibited more atherosclerotic risk factors. In contrast, the aetiology of *de novo* ALI includes not only *in situ* thrombosis and graft failure of LEAD but also cardiac embolisation, aortic dissection or embolisation, popliteal artery aneurysm, hypercoagulability associated with chemotherapy or cancer, and iatrogenic causes¹. Therefore, patients with *de novo* ALI are less likely to exhibit atherosclerotic risk factors, are older, and have a higher prevalence of atrial fibrillation.

In terms of limb characteristics, the lesser severity of symptoms in patients with ST-ALI may be attributable to the development of collateral circulation in patients with LEAD. A greater degree of collateral circulation in the FP artery is reported to be associated with better lower-extremity functional performance, as assessed by the 6-minute walk and 4-metre walking velocity tests¹⁵. In ST-ALI, limbs exposed to chronic ischaemia may develop collateral circulation, resulting in milder symptoms and lower CPK values compared to those in patients with *de novo* ALI.

Regarding treatment strategy, Taha et al reported that OSR was more commonly performed than EVT for the treatment of ALI caused by cardiac embolism and prosthetic graft failure⁹. This was consistent with our findings, in which OSR, including primary bypass and surgical thrombectomy, was more frequently conducted in the *de novo* ALI group, whereas EVT, such as catheter thrombectomy and local thrombolysis, was performed more often in the ST-ALI group. Although the safety and efficacy of an EVT-first approach to ALI have recently been reported, treatment strategies are often dependent on the aetiologies of ALI (e.g., surgical thrombectomy would be preferred for cardiac embolism and prosthetic graft failure, and thrombolysis would be preferred for small vessel emboli, vein bypass graft, and stent thrombosis)^{9,16-18}.

PROGNOSIS OF PATIENTS WITH ST-ALI

Another important finding of this study was that the clinical outcomes of patients with ST-ALI were significantly worse than those of patients with *de novo* ALI. One reason for the lower AFS rate in patients with ST-ALI may be the different baseline characteristics, such as the higher prevalence of atherosclerotic risk factors and the presence of wounds.

Table 4. Univariate and multivariate analyses to identify factors associated with death or amputation.

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value
Age	1.04 [1.02-1.06]	<0.001	1.03 [1.01-1.05]	0.023
Female sex	1.69 [1.25-2.30]	<0.001	1.24 [0.84-1.82]	0.277
Non-ambulatory status	4.19 [2.93-5.99]	<0.001	2.26 [1.49-3.43]	<0.001
Hypertension	0.92 [0.62-1.38]	0.692		
Dyslipidaemia	0.89 [0.62-1.28]	0.526		
Diabetes mellitus	1.28 [0.89-1.82]	0.183		
Haemodialysis	2.39 [1.66-3.46]	<0.001	2.34 [1.45-3.79]	<0.001
Current smoker	0.235 [0.11-0.50]	<0.001	0.54 [0.24-1.20]	0.130
Coronary artery disease	1.51 [1.06-2.16]	0.024	1.13 [0.73-1.73]	0.590
Cerebral infarction	1.18 [0.78-1.78]	0.446		
Atrial fibrillation	1.49 [1.04-2.11]	0.028	1.86 [1.25-2.77]	0.002
Number of antithrombotic drugs	1.12 [0.93-1.36]	0.227		
ST-ALI	2.06 [1.44-2.96]	<0.001	1.85 [1.14-2.99]	0.012
Onset to admission	0.99 [0.99-1.01]	0.775		
Peak CPK	1.00 [0.99-1.00]	0.143		
Peak CRP	1.06 [1.04-1.07]	<0.001	1.05 [1.03-1.07]	<0.001
Presence of a wound	2.63 [1.71-4.05]	<0.001	1.73 [1.08-2.76]	0.022
CIA or EIA thrombus	0.91 [0.57-1.47]	0.708		
Rutherford classification	1.36 [0.87-2.12]	0.181		
Pre-existing PAD	1.36 [0.87-1.99]	0.198		
Primary bypass	0.59 [0.22-1.60]	0.301		
Conservative therapy	1.03 [0.26-4.17]	0.966		
Surgical thrombectomy	0.75 [0.52-1.09]	0.129		
Catheter thrombectomy	1.01 [0.71-1.44]	0.951		
Local thrombolysis	1.00 [0.66-1.52]	0.988		
Additional stenting	1.32 [0.92-1.89]	0.134		

ALI: acute limb ischaemia; CI: confidence interval; CIA: common iliac artery; CPK: creatine phosphokinase; CRP: C-reactive protein; EIA: external iliac artery; PAD: peripheral arterial disease; ST: stent thrombosis

This is supported by the fact that the Kaplan-Meier curves began to separate after the first month. However, even after adjusting for these confounding factors in the multivariate analysis, ST-ALI remained an independent risk factor for death or amputation. This may be because ST-ALI has a higher recurrence rate than *de novo* ALI, worsening the prognosis. The 12-month freedom from occlusion rates in the native artery and bypass graft have been reported as 87% and 60%, respectively¹⁹, which is consistent with the findings of the current study, where the 12-month freedom from occlusion rate was 86.6% in *de novo* ALI, which included a relatively high proportion of patients with native artery ALI. In contrast, the recurrence rate of ST-ALI was greater, consequently leading to a lower AFS rate and higher incidence of MALE. Another reason for the poorer prognosis of patients with ST-ALI may be the greater anatomical complexity of ST-ALI, such as the higher proportion of popliteal artery involvement (**Table 3**). Although angiography was not performed before or after treatment in some patients who underwent OSR, making it difficult to directly compare the anatomical complexity, the anatomical findings at the

initial treatment in ST-ALI patients revealed that popliteal stenting, which may lead to worse limb prognosis, accounted for 58% of cases. Interventions in a diseased popliteal artery interrupt the collateral circulation to the lower extremities, and popliteal artery lesions have been reported to be a risk factor for ALI after EVT using a stent⁵.

Several factors other than ST-ALI – such as age, haemodialysis, atrial fibrillation, non-ambulatory status, the presence of a wound, and peak CRP value – were also risk factors for amputation or death. These findings are consistent with the results of previous studies²⁰⁻²³.

PREVENTION OF ST-ALI

This study demonstrates that patients with ST-ALI have significantly worse clinical outcomes than those with *de novo* ALI, highlighting the need to prevent ST occurrence. Previously, haemodialysis and lesions involving the popliteal artery were the predictors for acute thrombotic occlusion⁵. Therefore, selection of a non-stenting strategy would be considered for patients at high risk of ST-ALI. One option within this approach is drug-coated balloon-based EVT. EVT with

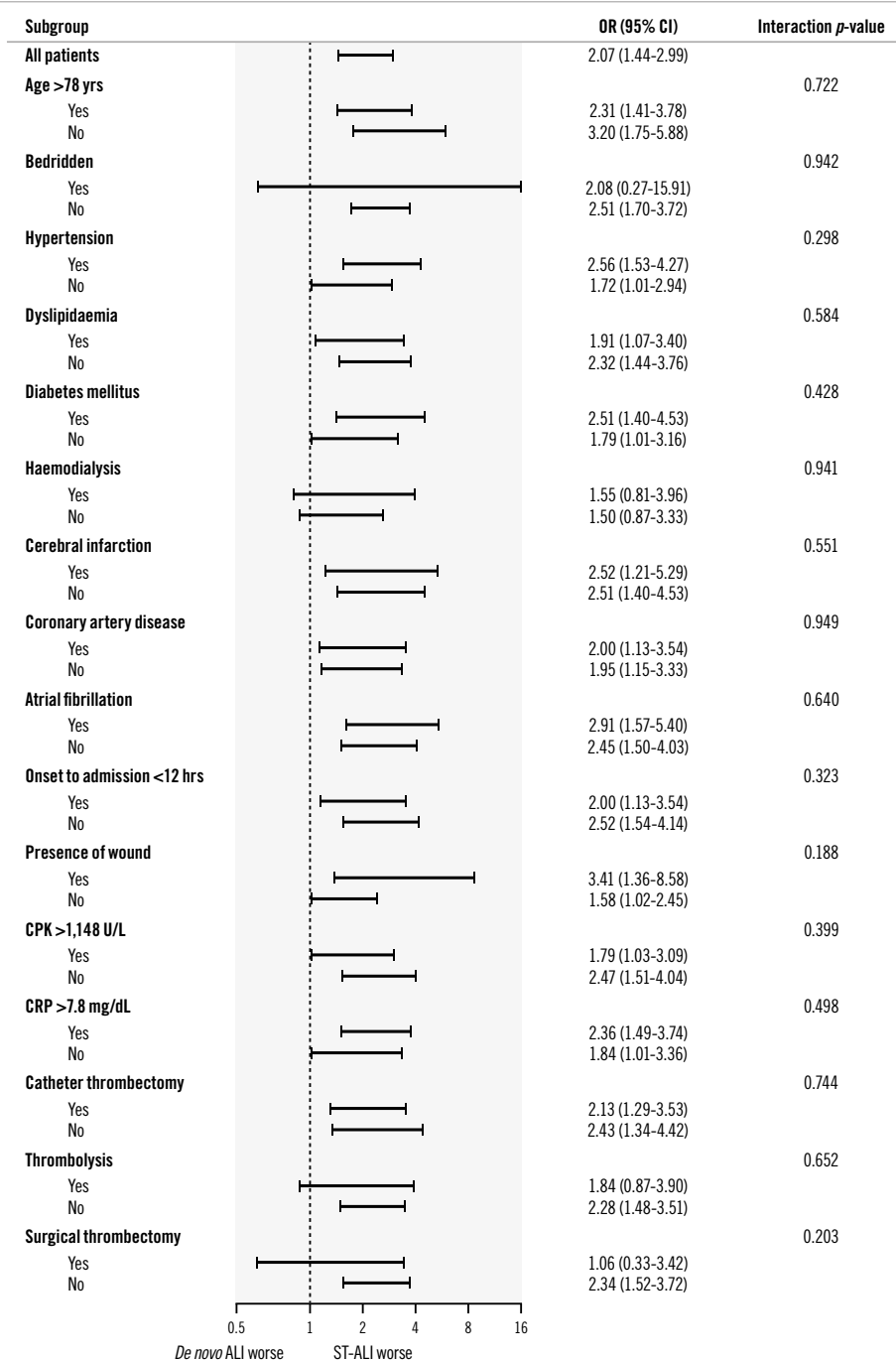


Figure 2. Interaction effect on the association of the aetiology of ALI with amputation or mortality risk. The interaction effect of baseline characteristics on the association between ALI aetiology and amputation or mortality risk was analysed using a Cox proportional hazards regression model. Interactions for baseline characteristics between patients with ST-ALI and those with de novo ALI were not observed in the AFS. AFS: amputation-free survival; ALI: acute limb ischaemia; CI: confidence interval; CPK: creatine phosphokinase; CRP: C-reactive protein; de novo ALI: ALI caused by other aetiologies; OR: odds ratio; ST: stent thrombosis; ST-ALI: ALI caused by femoropopliteal ST

drug-coated balloons have demonstrated durable patency and a lower thrombosis risk than stent-based EVT⁵. Therefore, whenever the outcome of drug-coated balloon angioplasty is deemed acceptable, deferred stenting should be considered. Another alternative treatment strategy is surgical bypass, as reported in the BEST-CLI trial, particularly for critical

limb-threatening ischaemia patients with a well-functioning saphenous vein graft²⁴.

In addition, implementing optimal medical therapy after revascularisation that may mitigate the occurrence of stent thrombosis is also crucial. Dual pathway inhibitor therapy, which combines an antiplatelet agent and a direct oral

anticoagulant, has recently emerged as a promising approach to reduce cardiovascular and lower extremity vascular events, including ALI after EVT²⁵. Further investigation is required to determine the optimal postprocedural antithrombotic regimen for reducing the incidence of ST-ALI.

Limitations

This study has certain limitations. First, although our study represents one of the largest series to investigate ST-ALI, its retrospective nature means that some data, including the antithrombotic therapy following treatment for ALI, were missing. The type, dose and duration of the postprocedural antithrombotic drug, especially whether a low-dose oral anticoagulant was used, would have been interesting to know, but these were not available. In addition, some anatomical information before and/or after treatment for ALI was not available, because many patients treated with OSR did not undergo angiography.

Second, *de novo* ALI affects a heterogeneous population, and the aetiology and background characteristics of ALI differ, resulting in variations in characteristics and risk factors. In addition, this study included only *de novo* ALI in FP arterial lesions for comparison with FP-ST, which is clinically challenging. However, the patient characteristics and aetiology of *de novo* ALI in the current study were similar to those in the previously reported comprehensive national registry of ALI, and the clinical outcomes of *de novo* ALI in the current study were comparable to those of previous studies that included similar patient and clinical characteristics, supporting the generalisability of the current study^{6,7-9}.

Third, there may be interfacility variations in treatment strategies and technical success rates. Although this multicentre registry included both high-volume cardiovascular and vascular surgical centres, the first-line treatment strategy and its detailed procedure steps may have differed between hospitals, and these differences may have affected patient prognosis. However, recent studies have revealed comparable results between OSR and EVT, and the multivariate analysis of the current study showed that the treatment approach did not affect AFS^{9,17-19}. Future studies to determine the optimal treatment strategy are needed.

Finally, the precise aetiology of ALI was clinically challenging to distinguish. There may be stent thrombosis cases where thrombotic stent occlusion, due to embolism to the stented segment with superimposed thrombosis, impaired run-in and run-off (e.g., in-stent restenosis or poor below-the-knee vessel run-off).

Conclusions

Patients with ST-ALI were associated with a lower 12-month AFS rate than those with *de novo* ALI, highlighting the need to maximise ST prevention.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Cumulative events rate.

Supplementary Figure 1. Twelve-month rates of death, major amputation, major reintervention and thrombectomy/thrombolysis.

The supplementary data are published online at:
[https://eurointervention.pcronline.com/](https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00016)
 doi/10.4244/EIJ-D-24-00016

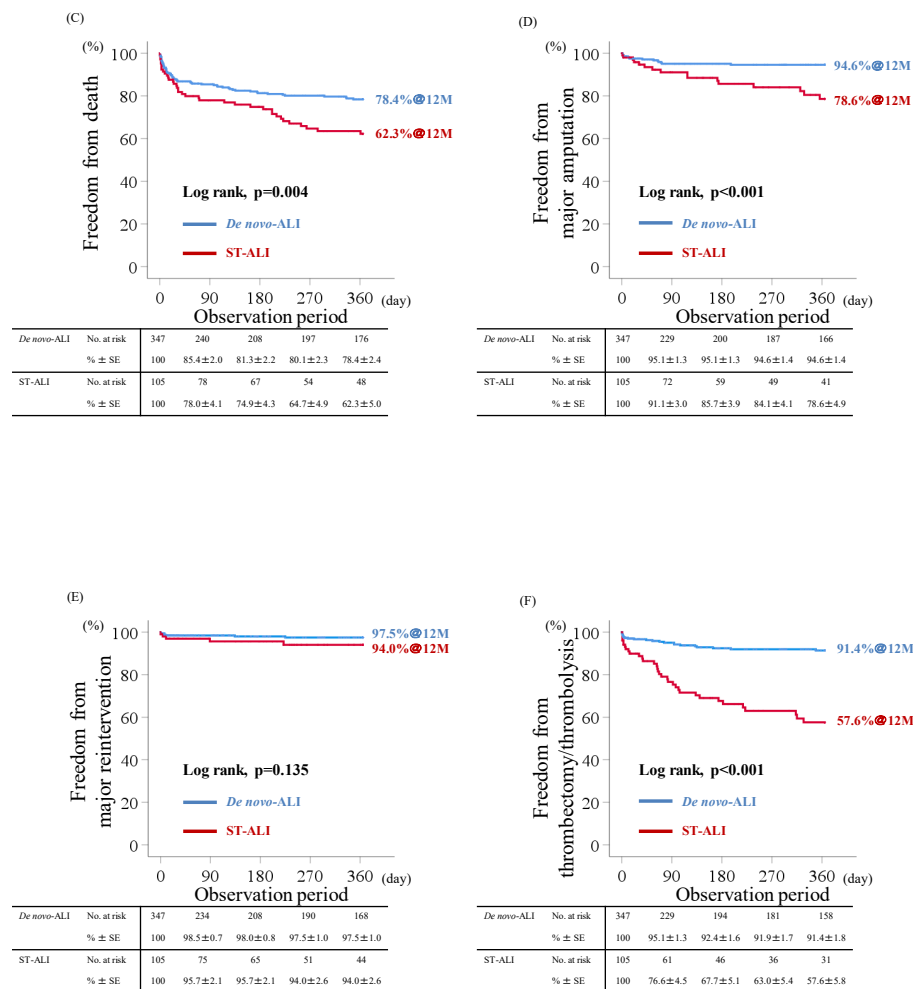


Supplementary data
Supplementary Table 1. Cumulative events rate.

Outcome measure	ST-ALI	<i>De novo</i> -ALI	<i>p</i> -value
Composite of death or major amputation			<0.001
No. of events	48	76	
1-year event rate	48.7±5.1	25.0±2.5	
MALE			<0.001
No. of events	46	41	
1-year event rate	53.5±5.6	14.6±2.2	
Occlusion			<0.001
No. of events	44	34	
1-year event rate	50.0±5.5	13.4±2.2	
All-cause death			0.004
No. of events	37	65	
1-year event rate	37.7±5.0	21.6±2.4	
Major amputation			<0.001
No. of events	17	16	
1-year event rate	21.4±4.9	5.4±1.4	
Bypass surgery			0.135
No. of events	5	7	
1-year event rate	6.0±2.6	2.5±1.0	
Thrombolysis required			<0.001
No. of events	34	23	
1-year event rate	42.4±5.8	8.6±1.8	

Data are presented as mean $\pm$ standard deviation or number.

ALI: acute limb ischaemia; MALE: major adverse limb events; ST: stent thrombosis



Supplementary Figure 1. Twelve-month rates of death, major amputation, major reintervention and thrombectomy/thrombolysis.

The incidence of death, major amputation, major reintervention and thrombectomy/thrombolysis were measured over a 12-month period following treatment for ALI and compared between patients with ST-ALI and those with de novo-ALI. The ST-ALI group also had lower rates of freedom from death (62.3 $\pm$ 5.0% vs. 78.4 $\pm$ 2.4%, $p=0.004$), freedom from major amputation (78.6 $\pm$ 4.9% vs. 94.6 $\pm$ 1.4%, $p<0.001$), and freedom from thrombectomy/thrombolysis (57.6 $\pm$ 5.8% vs. 91.4 $\pm$ 1.8%, $p<0.001$) than the de novo-ALI group.