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ORIGINAL ARTICLE
Peripheral Vascular Disease

Incidence of Angiographic Deterioration Following Inframalleolar Angioplasty and Its Impact on Outcomes in Patients With Chronic Limb-Threatening Ischemia Requiring Repeat Intervention

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Background: Clinical impact of inframalleolar (IM) angioplasty in patients with chronic limb-threatening ischemia (CLTI) is still controversial.

Methods and Results: This single-center, retrospective study included 168 patients with CLTI and tissue loss who underwent angioplasty for IM lesions. Angiographic follow up was performed at reintervention between April 2010 and December 2020. The outcome measure was the incidence of angiographic deterioration characterized by severe restenosis or occlusion of mildly stenotic lesions, occlusion of severely stenotic lesions, or extension of the occlusion length at reintervention. Angiographic deterioration was observed in 47.7% of patients, with the majority attributed to occlusion in severely stenotic lesions. Multivariate analysis revealed that a distal reference vessel diameter ≤1.0 mm in the initial angioplasty (hazard ratio 1.91 [95% confidence interval 1.20–3.04]; P=0.006) was significantly associated with angiographic deterioration of IM lesions at reintervention.

Conclusions: Angiographic deterioration occurred in approximately half of the patients with CLTI who underwent IM angioplasty and reintervention.

Key Words: Angiographic deterioration; Chronic limb-threatening ischemia; Endovascular therapy; Inframalleolar lesion

Chronic limb-threatening ischemia (CLTI) is the most severe manifestation of lower extremity artery disease, which is characterized by ischemic rest pain and ulceration or gangrene, and is associated with a high risk of major amputation.[1]

Over 70% of patients with CLTI have inframalleolar (IM) lesions,[2,3] and the severity of IM lesions was reported to have an impact on clinical outcomes.[3,4] Although global vascular guidelines[1] suggest a novel classification for IM lesions as a Global Limb Anatomic Staging System (GLASS) IM/pedal descriptor, the clinical impact of IM angioplasty in patients with CLTI remains controversial. In addition, the angiographic changes before and after IM angioplasty have not been systematically studied.

In this study, we aimed to investigate the details of angiographic changes in IM lesions and explore the predictive factors in patients with CLTI accompanied by tissue loss who underwent endovascular therapy (EVT) for IM lesions and follow-up angiography at reintervention.

Methods

Study Participants

This retrospective study used a clinical database consisting of 1,712 patients with CLTI and tissue loss who underwent EVT between April 2010 and December 2020 at a single cardiovascular center. We excluded 1,347 patients treated only for above-ankle lesions. Of the remaining 365 patients who underwent EVT for IM lesions, 168 patients who underwent reintervention during the follow-up period were included in the present study. This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the ethics committee of Kansai Rosai Hospital. As this was an observational study that did not use human biological specimens and was without intervention, the requirement for written informed consent was waived following the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study was open

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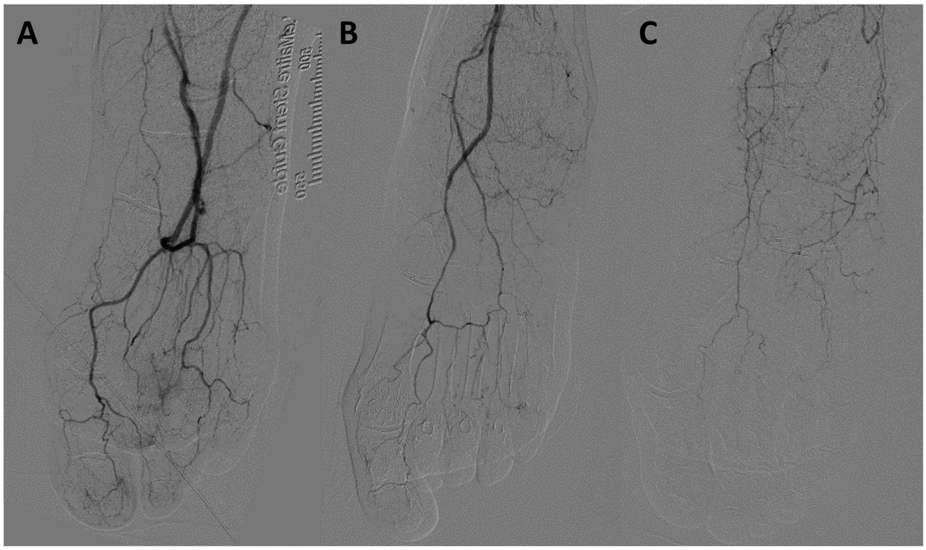


Figure 1. Representative cases of small artery disease (SAD). (**A**) An example of SAD score 0: tarsal, metatarsal, and digital arteries were patent without any signs of obstruction. (**B**) An example of SAD score 1: all the small calcaneal, tarsal, metatarsal, and digital arteries were patent but diffusely diseased and narrowed. (**C**) An example of SAD score 2: the plantar, dorsal system and planter arch are occluded, and the toes have a complete 'desert' appearance.

to the public, and opportunities to refuse participation were provided.

Baseline Assessment and Revascularization Strategy

The severity of limb ischemia in the index limb was routinely evaluated using the ankle-brachial index and skin perfusion pressure. The severity and location of the lower limb arterial lesions were evaluated using duplex ultrasonography. Hemodynamically significant arterial lesions were diagnosed using digital subtraction angiography before EVT. In this study, the revascularization strategy for IM lesions was not prespecified and depended on the operator's discretion. Generally, we performed EVT for infrapopliteal and IM lesions using the ipsilateral antegrade approach to obtain 1 straight blood flow to the wound. If wire crossing using the antegrade approach failed, we switched to the bidirectional approach using a tibial puncture, trans-collateral, or trans-pedal route. After successful wire crossing, the lesions were treated using plain angioplasty. The main target vessels for IM lesions were the dorsalis pedis, lateral plantar, medial plantar, or pedal arch, depending on the distribution of the wound and the operator's discretion. Reintervention was conducted for delayed healing or worsening of wound conditions accompanied by decreased arterial flow in infrapopliteal lesions. Drug-coated balloons, bare metal stents, drug-eluting stents, and atherectomy devices were not used for IM lesions because they were not approved for use in Japan during the study period.

Definitions

CLTI was classified according to global vascular guidelines.[1] The GLASS[1] was assessed using high-quality digital subtraction angiography before revascularization. Disease below the arch was classified using the small artery disease (SAD)[2] score, defined as follows: SAD 0, no or mild stenosis; SAD 1, significant stenosis; and SAD 2, occlusion of at least 1 lesion in the pedal arch, metatarsal, digital, or calcaneal arteries (**Figure 1**). Major amputation was defined as an amputation above the ankle. Complete wound healing was defined as complete epithelialization of all wounds without death or major amputation. The date of wound healing was defined as the date when complete wound epithelialization was observed.

Study Outcome Measures

The main outcome measure was the frequency of angiographic deterioration of IM lesions, defined as severe restenosis or occlusion of mildly stenotic lesions, occlusion of severely stenotic lesions, or extension of occlusion length at reintervention. We also explored predictors of angiographic deterioration in IM lesions and their impact on amputation-free survival. The frequency and predictors of SAD progression, defined as an increase in SAD score ≥1 at reintervention, were also investigated.

Statistical Analysis

Data are presented as means±standard deviations and percentages for continuous and discrete variables, unless otherwise specified. The association between angiographic deterioration and anatomical characteristics was evaluated using a Cox regression hazards model with hazard ratios (HRs) and 95% confidence intervals (CIs). Independent associations were explored using a multivariable model in which anatomic characteristics with statistical significance in univariate analysis, as well as age, body mass index, ambulatory status, diabetes, hemodialysis, and Wound, Ischemia, foot Infection (WIfI)[5] clinical stages were entered as explanatory variables. Amputation-free survival rates were estimated using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test when necessary. Time-dependent Cox regression anal-

Table 1. Baseline Characteristics

	All	Angiographic deterioration (+)	Angiographic deterioration (–)	P value
No. patients	168	80	88	
Patient characteristics				
Male	114 (67.9)	52 (65.0)	62 (70.5)	0.51
Age (years)	70±9	71±8	69±10	0.13
BMI (kg/m²)	22.0±3.9	22.0±3.7	22.1±4.1	0.82
Non-ambulatory status	61 (36.3)	32 (40.0)	29 (33.0)	0.42
Diabetes	115 (68.9)	55 (68.8)	60 (69.0)	1.00
Hemodialysis	119 (70.8)	62 (77.5)	57 (64.8)	0.09
Coronary artery disease	79 (47.3)	40 (50.6)	39 (44.3)	0.44
Cerebrovascular disease	23 (13.8)	13 (16.5)	10 (11.4)	0.38
Congestive heart failure	15 (12.7)	10 (18.2)	5 (7.9)	0.11
LVEF (%)	60±13	59±15	60±12	0.44
Serum albumin (g/dL)	3.3±0.6	3.4±0.6	3.3±0.6	0.29
Medical therapy				
Antiplatelet agent	130 (77.4)	72 (90.0)	78 (88.6)	0.81
Anticoagulant	38 (22.6)	18 (22.5)	22 (25.0)	0.72
Statins	130 (77.4)	28 (35.0)	22 (25.0)	0.18
Oral hypoglycemic agent	38 (22.6)	22 (27.5)	30 (34.1)	0.41
Insulin	130 (77.4)	24 (30.0)	37 (42.0)	0.11
Limb characteristics				
Ankle-brachial index	0.70±0.17	0.69±0.17	0.70±0.18	0.79
Skin perfusion pressure (mmHg)	24±12	25±12	23±12	0.34
Rutherford classification				0.096
5 (minor tissue loss)	130 (77.4)	57 (71.2)	73 (83.0)	
6 (major tissue loss)	38 (22.6)	23 (28.7)	15 (17.0)	
Clinical stages in WIfI classification				0.50
1 (Very low risk)	11 (6.5)	4 (5.0)	7 (8.0)	
2 (Low risk)	19 (11.3)	10 (12.5)	9 (10.2)	
3 (Moderate risk)	58 (34.5)	32 (40.0)	28 (31.7)	
4 (High risk)	80 (47.6)	34 (42.5)	44 (50.0)	
Arterial lesion characteristics				
GLASS femoropopliteal				0.46
Grade 0	109 (64.9)	56 (70.0)	53 (60.2)	
Grade 1	17 (10.1)	7 (8.8)	10 (11.4)	
Grade 2	18 (10.7)	9 (11.2)	9 (10.2)	
Grade 3	9 (5.4)	4 (5.0)	5 (5.7)	
Grade 4	15 (8.9)	4 (5.0)	11 (12.5)	
GLASS infrapopliteal				0.21
Grade 0	8 (4.8)	1 (1.2)	7 (8.0)	
Grade 1	10 (6.0)	6 (7.5)	4 (4.5)	
Grade 2	16 (9.5)	6 (7.5)	10 (11.4)	
Grade 3	33 (19.6)	15 (18.8)	18 (20.5)	
Grade 4	101 (60.1)	52 (65.0)	49 (55.7)	
GLASS stage				0.057
Stage I	28 (16.7)	12 (15.0)	16 (18.2)	
Stage II	44 (26.2)	15 (18.8)	29 (33.0)	
Stage III	96 (57.1)	53 (66.2)	43 (48.9)	
GLASS inframalleolar/pedal descriptor				0.064
Grade P0	47 (28.0)	29 (36.2)	18 (20.5)	
Grade P1	77 (45.8)	34 (42.5)	43 (48.9)	
Grade P2	44 (26.2)	17 (21.2)	27 (30.7)	
SAD score				0.27
SAD 0	32 (19.0)	13 (16.2)	19 (21.6)	
SAD 1	73 (43.5)	40 (50.0)	33 (37.5)	
SAD 2	63 (37.5)	27 (33.8)	36 (40.9)	

Data are presented as n (%) or mean±standard deviation. BMI, body mass index; GLASS, Global Limb Anatomic Staging System; LVEF, left ventricular ejection fraction; SAD, small artery disease; WIfI, wound, ischemia, and foot infection.

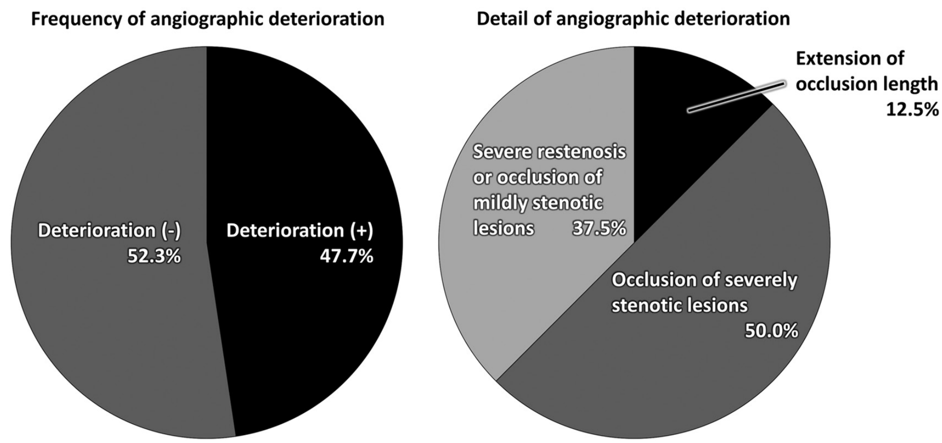


Figure 2. The frequency and distribution of angiographic deterioration in inframalleolar lesions at reintervention. Angiographic deterioration was observed in 47.7% (n=80) of patients. Among the cases with angiographic deterioration, the details are as follows: 50% had occlusion of severely stenotic lesions; 37.5% had severe restenosis or occlusion of mildly stenotic lesions; and 12.5% had extension of occlusion length.

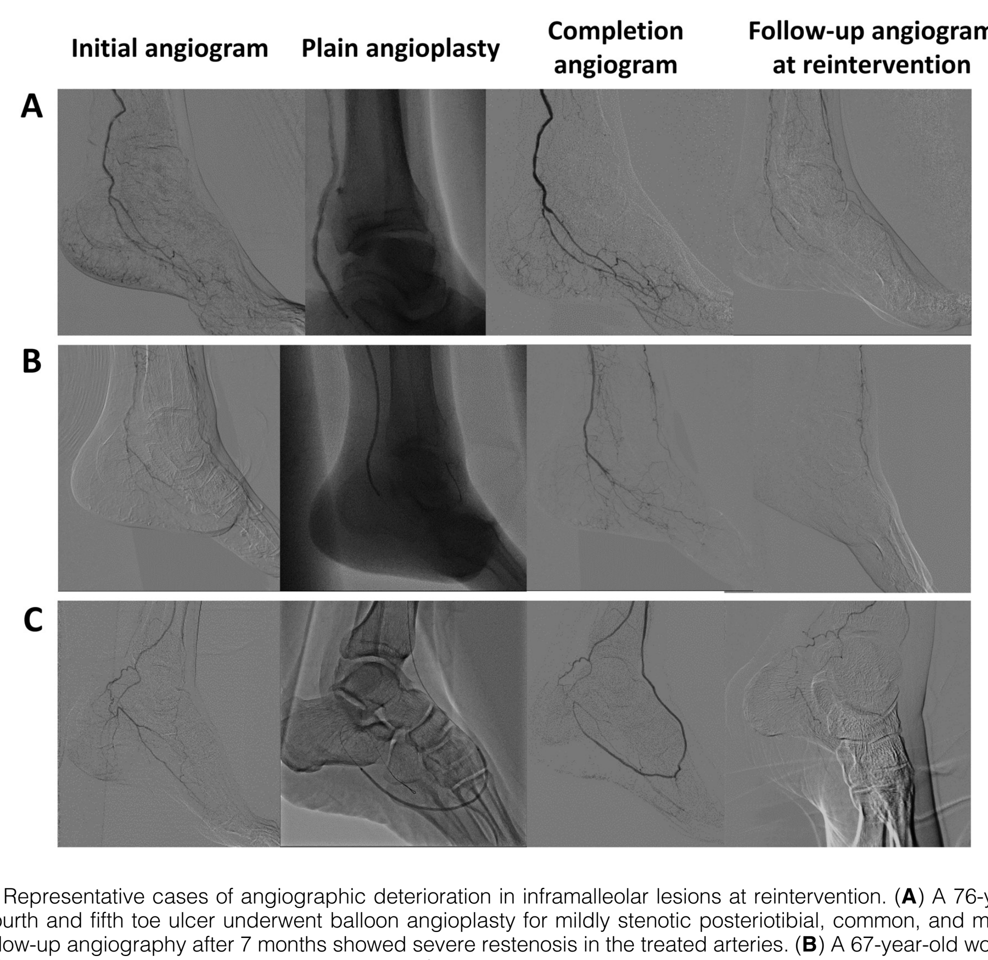
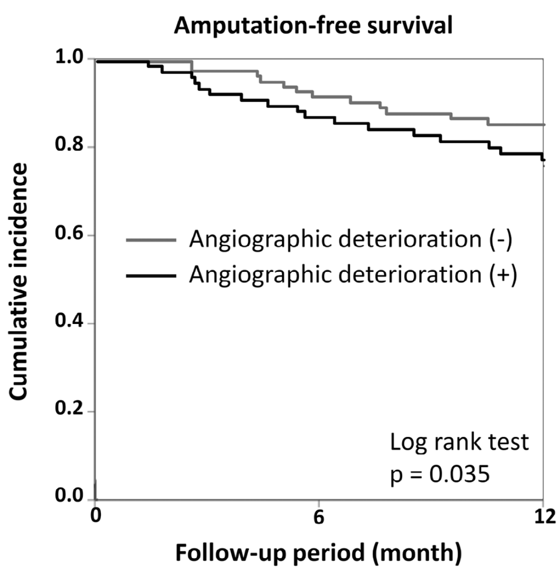


Figure 3. Representative cases of angiographic deterioration in inframalleolar lesions at reintervention. (**A**) A 76-year-old man with left fourth and fifth toe ulcer underwent balloon angioplasty for mildly stenotic posteriotibial, common, and medial planter artery. Follow-up angiography after 7 months showed severe restenosis in the treated arteries. (**B**) A 67-year-old woman with left heel and first toe ulcer underwent balloon angioplasty for severe stenosis in posteriotibial, common, and medial planter artery. Follow-up angiography after 4 months showed occlusion in all treated arteries. (**C**) A 74-year-old man with left first and second toe ulcer underwent balloon angioplasty for pedal arch occlusion. Follow-up angiography after 1 month showed extension of occlusion length.

Table 2. Association Between Angiographic Characteristics and Angiographic Deterioration of Inframalleolar Lesions at Reintervention

	Univariate model		Multivariate model	
	HR (95% CI)	P value	HR (95% CI)	P value
GLASS infrapopliteal	1.21 (0.97–1.51)	0.085		
GLASS inframalleolar/pedal descriptor	0.81 (0.60–1.10)	0.17		
SAD score	1.25 (0.92–1.70)	0.16		
Bilateral calcification in inframalleolar lesions	1.33 (0.85–2.08)	0.21		
Distal reference vessel diameter ≤1.0 mm	1.99 (1.27–3.14)	0.003	1.91 (1.20–3.04)	0.006

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Multivariate model adjusted for age, BMI, ambulatory status, diabetes, hemodialysis, and WIfI clinical stage (used to predict 1-year amputation risk). Age and BMI were treated as continuous in the analysis. Abbreviations as in Table 1.



	month	0	6	12
Angiographic deterioration (-)	at risk	88	78	68
	% ± SE	100	91.7 ± 3.0	85.5 ± 3.9
Angiographic deterioration (+)	at risk	80	68	55
	% ± SE	100	87.1 ± 3.8	77.3 ± 4.9

Figure 4. Amputation-free survival in patients with or without angiographic deterioration. The 12-month amputation-free survival rate was significantly lower in patients with angiographic deterioration compared with those without (77.3% vs. 85.5%; log rank P=0.035).

ysis was used for time-dependent covariates. Statistical significance was set at P<0.05. Statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) and R (version 4.2.2; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Table 1 summarizes the patient, limb, and lesion characteristics. Specifically, 67.9% of the patients were male, and the mean age was 70±9 years. The prevalence of diabetes and hemodialysis was 68.9% and 70.8%, respectively. Moreover, 47.6% of the patients were classified as clinical stage 4 according to the WIfI classification. Using the GLASS classification, 8.9% and 60.1% of patients were classified as grade 4 in the femoropopliteal and infrapopliteal territories, respectively. GLASS IM/pedal descriptor P2 and SAD 2 accounted for 26.2% and 37.5%, respectively. There were no statistically significant differences in baseline characteristics between patients with angiographic deterioration and those without.

Frequency of Angiographic Deterioration at Reintervention

Angiographic deterioration was observed in 47.7% (n=80) of patients (**Figure 2**). Among the cases with angiographic deterioration, occlusion of severely stenotic lesions, severe restenosis or occlusion of mildly stenotic lesions, and extension of occlusion length accounted for 50.0%, 37.5%, and 12.5% of cases, respectively. Representative cases of angiographic deterioration are shown in **Figure 3**.

Association Between Baseline Characteristics and Angiographic Deterioration

As shown in **Table 2**, the univariable analysis revealed that a distal reference vessel with diameter ≤1.0 mm in the initial angioplasty was a significant predictor of angiographic deterioration of IM lesions at reintervention. The multivariable analysis confirmed an independent association for a distal reference vessel diameter ≤1.0 mm in the initial angioplasty (HR 1.91 [95% CI 1.20–3.04]; P=0.006).

Impact of Angiographic Deterioration on Amputation-Free Survival and Wound Healing

Figure 4 shows the Kaplan-Meier curve for amputation-free survival. The 12-month amputation-free survival rate was significantly lower in patients with angiographic deterioration than in those without (77.3% vs. 85.5%; log-rank P=0.035). The multivariate time-dependent Cox regression analysis revealed that angiographic deterioration for a time-dependent covariate was significantly associated with amputation-free survival (HR 3.43 [95% CI 1.75–6.71]; P<0.001; **Table 3**).

The **Supplementary Figure** shows the Kaplan-Meier curve for wound healing. The 12-month wound-healing rate was not significantly different between patients with angiographic deterioration and those without (49.0% vs. 57.4%; log-rank P=0.17).

Frequency and Predictors of SAD Progression at Reintervention

Additionally, in 105 patients with SAD 0–1 in the initial procedure, SAD progression at reintervention was observed in 45 (42.9%) patients, and a distal reference vessel diam-

Table 3. Association Between Angiographic Deterioration and Amputation-Free Survival in Time-Dependent Cox Regression Analysis

	Univariate model		Multivariate model	
	HR (95% CI)	P value	HR (95% CI)	P value
Angiographic deterioration	4.06 (2.12–7.79)	<0.001	3.43 (1.75–6.71)	<0.001
Male	1.42 (0.71–2.81)	0.31		
Age >75 years	1.43 (0.75–2.72)	0.28		
BMI <18.5 kg/m²	1.34 (0.63–2.83)	0.44		
Non-ambulatory status	1.96 (1.04–3.68)	0.036	1.71 (0.90–3.26)	0.11
Diabetes	1.43 (0.70–2.94)	0.33		
Hemodialysis	2.38 (1.05–5.41)	0.039	2.04 (0.89–4.69)	0.093
WIfI clinical stage 4	1.53 (0.82–2.85)	0.19		
LVEF <50%	1.71 (0.85–3.47)	0.13		
Serum albumin <3.0 g/dL	1.56 (0.78–3.13)	0.21		

Data are presented as HRs with 95% CIs. Angiographic deterioration was analysed as a time-dependent covariate. Abbreviations as in Tables 1,2.

Table 4. Association Between Angiographic Characteristics and SAD Progression at Reintervention

	Univariate model		Multivariate model	
	HR (95% CI)	P value	HR (95% CI)	P value
GLASS infrapopliteal	0.99 (0.77–1.28)	0.96		
GLASS inframalleolar/pedal descriptor	1.09 (0.76–1.57)	0.63		
Bilateral calcification in inframalleolar lesions	1.42 (0.78–2.58)	0.25		
Distal reference vessel diameter ≤1.0 mm	4.90 (2.58–9.31)	<0.001	4.61 (2.30–9.25)	<0.001

Data are presented as HRs with 95% CIs. Multivariate model adjusted for age, BMI, ambulatory status, diabetes, hemodialysis, and WIfI clinical stage (used to predict 1-year amputation risk). Age and BMI were treated as continuous in the analysis. Abbreviations as in Tables 1,2.

eter ≤1.0 mm was significantly associated with SAD progression at reintervention (HR 4.61 [95% CI 2.30–9.25]; P<0.001) after multivariate analysis (**Table 4**).

Discussion

Summary of the Present Study

The present study revealed that angiographic deterioration in IM lesions and SAD progression were observed in 47.7% and 42.9% of patients with CLTI accompanied by tissue loss who underwent IM angioplasty and follow-up angiography at reintervention, respectively. In the multivariate analysis, a distal reference vessel diameter ≤1.0 mm in the initial angioplasty was identified as an independent predictor for both angiographic deterioration in IM lesions and SAD progression. To the best of our knowledge, this is the first report of angiographic changes after IM angioplasty.

The restenosis rate after EVT in infrapopliteal lesions has been reported to be as high as 74% at 3 months, which is higher than the angiographic deterioration rate observed in our study.[6] However, in infrapopliteal lesions, if the outflow arteries in IM lesions are preserved, reintervention is relatively straightforward. In contrast, when angiographic deterioration occurs in IM lesions, it often results in a 'desert foot' with no outflow arteries, making it difficult to achieve effective blood flow even after reintervention. The significant increase in mortality or major amputation risk observed after angiographic deterioration in our study may be influenced by this mechanism.

Controversy in Outcomes of EVT for IM Lesions and Their Causes

In the 2017 Society for Cardiovascular Angiography and Interventions guidance, appropriate use criteria for peripheral arterial interventions were updated and the negative influence of IM disease on wound-healing rates were documented.[7] Although global vascular guidelines in 2019 suggested the anatomic classification system for IM lesions as a GLASS IM/pedal descriptor, the outcomes and indications of IM angioplasty remain unclear.[1]

Nakama et al.[8] reported results from the RENDEZVOUS registry regarding EVT for IM lesions. They found a higher wound-healing rate and shorter wound-healing time in patients who underwent pedal arch intervention than in those who did not. Similarly, Jung et al.[9] conducted a single-center retrospective study using propensity score matching to compare patients with CLTI who underwent pedal arch angioplasty with those who did not. They reported that the wound-healing rate was significantly higher in patients who underwent successful pedal arch angioplasty than in those who did not. These results suggest that maximizing short-term blood flow to wounds using pedal arch angioplasty may be beneficial. However, it is not rare in clinical practice to encounter cases in which stenotic IM lesions in the initial procedure become totally occluded at reintervention. Previous studies have not mentioned the details of lesion morphology at reintervention, and angiographic changes after IM angioplasty remain unknown.

A recent report has also indicated that additional intervention for IM to infrapopliteal lesions was associated with an increased risk of major amputation and major adverse limb events.[10] Based on the results of this study, the angiographic deterioration in IM lesions at reintervention, accompanied by a reduction in the peripheral vascular bed, may be associated with an increased risk of these clinical events.

Mechanism of Angiographic Deterioration in IM Lesions and SAD Progression

The exact mechanisms underlying angiographic deterioration and SAD progression remain unclear. However, considering that a distal reference vessel diameter ≤1.0 mm was detected as a predictor of both phenomena, oversized balloons may lead to a larger arterial dissection by involving the ostium of small branches and occluding these branches, resulting in angiographic deterioration in IM lesions. Additionally, thrombus microemboli, dispersed plaques, and guidewire polymers during EVT may obstruct the peripheral vascular bed more distally than lesions treated with balloon angioplasty,[11] resulting in SAD progression. Further investigation is required to elucidate these mechanisms.

Clinical Implications

While the effectiveness of bypass surgery over EVT has been demonstrated in the BEST-CLI study,[12] it has been reported that suitability of the Japanese population in the inclusion criteria is limited.[13] Therefore, an endovascular-first strategy remains mainstream for patients with CLTI, especially for frail patients. However, this study suggests that intervention for IM lesions increases the risk of deteriorating arterial lesion severity at reintervention. If IM angioplasty is performed, active intervention for wounds, such as early minor amputation, will be necessary before blood flow is diminished. In particular, for patients with small distal reference vessels, assessment of the great saphenous vein and the procedural feasibility of early bypass conversion should be considered instead of repeated EVT. In the future, further research is required to evaluate the efficacy and safety of this treatment strategy for IM lesions after consideration of the patient's background, angiographic features, and wound severity.

Study Limitations

The present study has several limitations. First, this was a retrospective observational study that did not adopt a prospective randomized design. Second, the sample size was small. Third, patients who did not undergo reintervention were excluded. Details of the patients who did not undergo reintervention are as follows: 85 cases achieved complete wound healing; 16 cases underwent major amputations; 54 cases died with unhealed wounds; and 42 cases discontinued follow up. While angiographic changes cannot be examined in these groups of patients, the findings of this study may be helpful for cases with a high risk for reintervention, which are clinically problematic. Of course, future studies, including those who did not require reintervention, will be needed. Last, angiography was assessed by a single observer only; therefore, intra- and interobserver validation and evaluation in the core laboratory were not conducted.

Conclusions

Angiographic deterioration occurred in approximately half of the patients with CLTI who underwent IM angioplasty and reintervention. Small vessel diameter was significantly associated with angiographic deterioration.

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Disclosures

The other authors declare no association with any individual, company, or organization having a vested interest in the subject matter/products mentioned in this article.

IRB Information

This study was approved by the ethics committee of Kansai Rosai Hospital (Reference no. 23D109g).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-24-0103