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ORIGINAL ARTICLE

Independent predictors of loss of primary patency at 1 year after aortoiliac stent implantation

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Abstract

To identify the risk factors for restenosis at 1 year after aortoiliac stenting for symptomatic peripheral artery disease in real-world practice. We performed subgroup analysis of a large-scale prospective multicenter registry study enrolling Japanese patients with peripheral arterial disease who underwent aortoiliac endovascular therapy from April 2014 to April 2016. The subgroup comprised 880 patients (1108 limbs) who received iliac stenting. The Rutherford class was 2, 3, and 4 in 42%, 51%, and 7% of the patients, respectively. TASC II class D disease was noted in 18% of the patients and 35% had chronic total occlusion. Mean total stent length was 82.1 ± 48.5 mm and minimum stent diameter was 9.0 ± 1.3 mm. Balloon-expandable stents were used in 8% of the limbs. Concomitant femoropopliteal lesions were present in 36% of the limbs with aortoiliac lesions. In the overall patient population, the risk of restenosis at 1 year after stenting was 11.4%. Femoropopliteal lesions and the minimum stent diameter were identified as independent risk factors for restenosis at 1 year. When the study population was stratified according to these two risk factors, the restenosis rate at 1 year was 27.1% in the patients with a minimum stent diameter < 8 mm and femoropopliteal lesions, whereas it was only 5.3% in those with a minimum stent diameter ≥ 10 mm and no femoropopliteal lesions. Femoropopliteal lesions and a smaller stent diameter were independent risk factors for restenosis at 1 year after aortoiliac stenting.

Keywords Peripheral artery disease · Endovascular therapy · Aortoiliac stent implantation

Abbreviations

EVT Endovascular therapy
PAD Peripheral arterial disease
PCI Percutaneous coronary intervention
TVR Target vessel revascularization

Introduction

The number of patients with peripheral arterial disease (PAD) is increasing [1]. Intermittent claudication due to PAD reduces the quality of life and is also associated with

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a poor prognosis [2]. In addition, PAD is closely associated with advanced age and various comorbidities, such as diabetes and chronic kidney disease [3], all of which show an increasing prevalence worldwide. Thus, PAD has become a major medical issue in many countries, and validation of the efficacy of treatment for this condition based on reliable data is required. Endovascular techniques have developed rapidly in recent decades and endovascular therapy (EVT) for aortoiliac lesions is now considered to be an interventional modality that is as well established as percutaneous coronary intervention (PCI) for coronary artery disease [4]. Indeed, performance of EVT with stent implantation has shown a marked increase based on the TASC II and European Society of Cardiology (ESC) guidelines [2, 5], and is even employed as a first-line treatment for TASC II class D disease. However, there have been no large-scale prospective studies of current EVT for aortoiliac disease, and the factors associated with loss of patency after stenting have not been fully evaluated. A previous retrospective study investigated predictors of primary patency after aortoiliac EVT with stent implantation [4], but its retrospective design means that loss of patency may have been underestimated (i.e., the patency rate may have been overestimated). Because loss of patency or restenosis cannot be confirmed without examination, it is likely that restenosis will be overlooked if patency is not evaluated periodically. Therefore, a large-scale prospective study with periodical assessment of patency is required to identify the true predictors of patency after aortoiliac stenting. The Observational prospective Multicenter registry study on Outcomes of peripheral arTErial disease patieNts treated by AngioplaSty tHerapy for aortoIliac artery (OMOTENASHI) registry study is an ongoing prospective multicenter study that enrolls real-world patients undergoing aortoiliac EVT (with or without stent implantation) [6]. It is hoped that the prognosis and clinical features of PAD patients will be clarified by data obtained in this study, providing information that can assist with selection of treatment and contribute to improving management of this condition. The aim of this study was to identify the risk factors for restenosis at 1 year after aortoiliac stenting in patients with symptomatic peripheral artery disease from the OMOTENASHI registry database.

Methods

The current study analyzed a subgroup of the OMOTENASHI registry population [6]. The OMOTENASHI registry study is being conducted at 64 centers in Japan to clarify the 3-year clinical outcomes of aortoiliac EVT with or without stenting in the real-world setting. A total of 893 patients (1128 limbs) with symptomatic peripheral arterial disease (Rutherford class 2, 3, or 4) undergoing EVT (either balloon angioplasty alone or stent implantation) for de novo aortoiliac lesions were registered between April 2014 and April 2016. This study is being performed in accordance with the Declaration of Helsinki and has been approved by the ethics committee of each center, where participants have been registered. Written informed consent was obtained from each patient. Among the 893 patients (1128 limbs) registered, 880 patients (1108 limbs) received stent implantation and were analyzed in the current study.

Endovascular therapy

We mainly employed a 6 Fr system for EVT. We infused 5,000 U of heparin during the procedure and additional doses of heparin were given as appropriate to maintain an activated clotting time of 200 s or longer. The lesion was crossed with a 0.014 in., 0.018 in., or 0.035 in. guidewire. After crossing with the guidewire was successful, pre-dilation and stenting of the lesion were performed with optimum devices, in principle. Either self-expandable or balloon-expandable stents were used. Post-dilation was done with a balloon of the optimal diameter when the self-expandable stent was not fully expanded. Treating physicians selected the antiplatelet therapy, EVT strategy, guidewires, balloons, and stents according to the operator's discretion.

Follow-up

After revascularization, follow-up assessment was scheduled at 30 days, 6 months, and 1, 2, and 3 years. The attending doctors examined patency, as well as assessing symptoms and performing hemodynamic evaluation in the clinical setting.

Endpoints

The primary endpoint was the restenosis rate at 1 year. Restenosis was defined as $\geq 50\%$ stenosis on computed tomography or angiography, a peak systolic velocity ratio ≥ 2.5 on duplex ultrasound, or requirement for target vessel revascularization (TVR). An independent clinical events panel whose members were not directly involved in this study and had relevant expert knowledge determined each case of TVR.

Statistical analysis

Data on baseline characteristics are presented as the mean $\pm$ standard deviation (SD) for continuous variables and as the frequency (percentage) for categorical variables, if not otherwise mentioned. Significance was accepted at $P < 0.05$. Risk factors for restenosis after 1 year of follow-up were explored using a generalized linear mixed model with a logit

link function, in which restenosis was the dependent variable and inter-institution and inter-subject variability were random effects. We first developed crude models in which each variable of interest was entered as the fixed effect. The independent influence of the variables on restenosis was investigated by an adjusted model in which, all variables showing statistical significance in the crude models were entered as the fixed effects. The association of baseline characteristics with restenosis was assessed by calculating odds ratios, which were derived from the generalized linear mixed model with a logit link function. Inter-institution variability and inter-subject variability were treated as random effects in this model. Multiple imputation (up to 50 times) was adopted to handle missing data. Point estimates are reported with 95% confidence intervals. All statistical analyses were performed with R version 3.1.0 (R Development Core Team, Vienna, Austria).

Results

Table 1 summarizes the baseline characteristics of the study population. The patients were aged 73 ± 9 years and 83% were men. The Rutherford class was 2, 3, and 4 in 42%, 51%, and 7% of the patients, respectively; 18% of them had TASC II type D lesions and 35% had chronic total occlusion. Thienopyridines and aspirin were both administered to 74% of the patients, but only 58% received dual antiplatelet therapy. Total stent length was 82.1 ± 48.5 mm and minimum stent diameter was 9.0 ± 1.3 mm. Balloon-expandable stents were implanted in 85 limbs (8%). Of the 370 patients with femoropopliteal lesions, 117 patients (32%) underwent femoropopliteal revascularization. In the total patient population, the risk of restenosis at 1 year was estimated to be 11.4% (95% confidence interval 8.7–14.1%). During the 1-year follow-up period, we did not observe any thrombosis in the study population.

The association of the baseline characteristics with the risk of restenosis at 1 year is summarized in Table 2. The presence of a femoropopliteal lesion was identified as an independent risk factor for restenosis [adjusted odds ratio 1.95 (95% confidence interval 1.07–3.55)], and the minimum stent diameter was another independent risk factor [adjusted odds ratio per 1-mm increase: 0.71 (95% confidence interval 0.56–0.91)]. When the study population was classified according to these two risk factors, the 1-year restenosis rate was a high 27.1% (95% confidence interval 11.2–43.0%) for patients with a minimum stent diameter < 8 mm and femoropopliteal lesions, whereas it was only 5.3% (95% confidence interval 2.3–8.3%) for patients with a minimum stent diameter ≥ 10 mm and no femoropopliteal lesions (Table 3).

Table 1 Baseline characteristics of the study population

Patient characteristics ($n = 880$)	
Age (years)	73 ± 9
Male sex	731 (83%)
Current smoking	313 (36%)
Hypertension	828 (94%)
Dyslipidemia	719 (82%)
Diabetes mellitus	422 (48%)
End-stage renal disease on dialysis	111 (13%)
Thienopyridine use	651 (74%)
Aspirin use	652 (74%)
Dual antiplatelet therapy	514 (58%)
Anticoagulant use	70 (8%)
Statin use	451 (51%)
Rutherford classification	
Category 2	371 (42%)
Category 3	447 (51%)
Category 4	62 (7%)
TASC II class D	161 (18%)
Limb characteristics ($n = 1108$)	
Ankle-brachial index	0.67 ± 0.21
Missing data	25 (2%)
Chronic total occlusion	393 (35%)
Calcification	894 (82%)
Missing data	15 (1%)
Common iliac lesion	767 (69%)
Missing data	1 (0%)
External iliac lesion	632 (57%)
Missing data	1 (0%)
Ostial lesion	471 (43%)
Femoropopliteal lesion	370 (36%)
Missing data	94 (8%)
Balloon-expandable stent	85 (8%)
Total stent length (mm)	82.1 ± 48.5
Minimum stent diameter (mm)	9.0 ± 1.3
Pre-ballooning	787 (71%)
Post-ballooning	1035 (93%)

Discussion

The present subgroup analysis of a multicenter prospective study population demonstrated that the estimated 1-year restenosis rate after iliac artery stenting was 11.4% (8.7–14.1%), i.e., the 1-year primary patency rate was 88.6% (85.9–91.3%). In addition, the independent predictors of loss of primary patency were a smaller stent diameter and coexisting femoropopliteal disease (Table 2). Especially, when patients had both risk factors, the restenosis rate was about five times higher than in patients without these risk factors [27.1% (11.2–43.0%) versus 5.3% (2.3–8.3%)] (Table 3). The primary patency rate was somewhat lower in this study

Table 2 Risk factors for restenosis at 1 year

	Crude odds ratio (crude model)	Adjusted odds ratio (adjusted model)
Age (per 1-year increase)	0.99 [0.95–1.02] ($P=0.42$)	N/I
Male sex	1.67 [0.73–3.82] ($P=0.22$)	N/I
Current smoking	1.27 [0.75–2.16] ($P=0.37$)	N/I
Hypertension	1.00 [0.33–2.98] ($P=1.00$)	N/I
Dyslipidemia	0.60 [0.30–1.22] ($P=0.16$)	N/I
Diabetes mellitus	1.19 [0.71–2.02] ($P=0.51$)	N/I
End-stage renal disease on dialysis	1.35 [0.60–3.04] ($P=0.47$)	N/I
Thienopyridine use	0.55 [0.28–1.09] ($P=0.085$)	N/I
Aspirin use	1.25 [0.63–2.48] ($P=0.53$)	N/I
Dual antiplatelet therapy	0.67 [0.37–1.24] ($P=0.20$)	N/I
Anticoagulant use	1.88 [0.80–4.43] ($P=0.15$)	N/I
Statin use	0.81 [0.45–1.46] ($P=0.49$)	N/I
Rutherford classification	1.34 [0.80–2.23] ($P=0.26$)	N/I
TASC II class D	1.52 [0.79–2.94] ($P=0.21$)	N/I
Ankle-brachial index	0.52 [0.13–2.01] ($P=0.34$)	N/I
Chronic total occlusion	1.19 [0.64–2.21] ($P=0.57$)	N/I
Calcification	0.68 [0.35–1.32] ($P=0.26$)	N/I
Common iliac lesion	0.61 [0.33–1.12] ($P=0.11$)	N/I
External iliac lesion	1.79 [1.00–3.20] ($P=0.051$)	N/I
Ostial lesion	1.05 [0.61–1.82] ($P=0.85$)	N/I
Femoropopliteal lesion	2.12 [1.18–3.82] ($P=0.013$)	1.95 [1.07–3.55] ($P=0.029$)
Balloon-expandable stent use	1.18 [0.47–2.97] ($P=0.72$)	N/I
Total stent length (per 1 mm increase)	1.01 [1.00–1.01] ($P=0.063$)	N/I
Minimum stent diameter (per 1 mm increase)	0.69 [0.55–0.88] ($P=0.003$)	0.71 [0.56–0.91] ($P=0.007$)
Pre-ballooning	0.77 [0.40–1.49] ($P=0.44$)	N/I
Post-ballooning	1.35 [0.38–4.75] ($P=0.64$)	N/I

Data are expressed as the odds ratio [95% confidence intervals] (*P* values) for restenosis at 1 year

N/I not included in the adjusted model

Table 3 Restenosis rate at 1 year in relation to the presence/absence of femoropopliteal lesions and minimum stent diameter

	Femoropopliteal lesion		
	No	Yes	Overall
Minimum stent diameter			
< 8 mm	17.8% [4.0–31.5%]	27.1% [11.2–43.0%]	22.1% [11.2–33.0%]
8–10 mm	9.6% [5.2–13.9%]	17.6% [10.9–24.4%]	12.8% [9.0–16.6%]
≥ 10 mm	5.3% [2.3–8.3%]	12.3% [4.9–19.8%]	7.3% [4.2–10.5%]
Overall	8.2% [5.3–11.1%]	17.0% [11.6–22.4%]	11.4% [8.7–14.1%]

Data are estimated 1-year restenosis ratio [95% confidence interval]

compared to previous retrospective studies [6]. However, the apparently high patency rates found in these retrospective studies might have been due to use of Kaplan–Meier analysis to assess patency. Our finding that a smaller stent diameter was associated with a higher risk of restenosis probably reflects the fact that a smaller vessel diameter increases the risk of restenosis. A previous retrospective study showed that a small vessel diameter was a predictor of poor patency in patients with aortoiliac lesions [4], and this has also been demonstrated in the femoropopliteal region [7]. Thus, 'bigger is better' seems to be correct and vessel diameter may be an important predictor of future restenosis after aortoiliac EVT, as is the case for femoropopliteal EVT. We did not collect data on how vessels were sized in the in the present study, so further investigation of this issue is needed.

As noted in previous studies, outflow lesions also had a large influence on patency. This suggests that the outflow vascular bed is an important determinant of patency and that

additional clinically driven distal revascularization should be considered. When performing aortoiliac EVT, it is important to assess the presence or absence of distal lesions by angiography. We plan to repeat the same risk analysis for loss of patency after 3 years to validate the current findings.

Previous clinical guidelines expanded the indications for EVT to TASC II class D lesions [5, 8]. In the present study, 161 limbs with TASC II class D lesion were treated by stenting, showing no significant difference of 1-year restenosis from TASC II class A to C lesions (Table 2). If the long-term patency rate is confirmed to be as high in the future as was shown in the BRAVISSIOM study [9], EVT could come to be positioned as a comprehensive standard treatment for all aortoiliac disease. However, if the procedural time is very long or the total contrast medium volume is large in a few patients with TASC II class D lesions, it seems that surgery should be considered rather than persisting with EVT in such cases.

It was previously reported that a self-expandable stent is used in about 70% of procedures [4], but there was an increase to > 90% in this study (Table 1). Technical advances have allowed more accurate positioning of self-expandable stents and their radial force has also increased. In addition, the long-term stent fracture rate has decreased, even after deployment in long lesions. Moreover, self-expandable stents are available in a wide variety of diameters and lengths, making these devices easier for interventionists to use. We confirmed that use of self-expandable stents was not significantly associated with the risk of restenosis.

DAPT was only provided for 58% of the patients and use of DAPT was not significantly associated with the risk of restenosis. Thus, the treatment with a single antiplatelet agent was more frequent than after PCI. In Japan, DAPT is not mandatory after aortoiliac stenting, so antiplatelet therapy was selected by the treating physicians based on each patient's condition. A previous study conducted in Japan showed that thienopyridines and aspirin were not used so frequently [4], consistent with the low frequency of DAPT in the current study. Accordingly, we believe that the current study population was representative of the PAD population receiving revascularization in Japan. The optimal antiplatelet agents and administration period for patients undergoing aortoiliac EVT have not been clarified. The OMOTENASHI study is designed to follow the antiplatelet regimens of registered patients until 3 years after EVT. It is hoped that the data thus obtained will provide clinically useful information on the optimal antiplatelet agents and treatment period.

Limitations

There were several limitations of this study. First, the patients were all treated by interventional cardiologists with expertise in EVT. Second, the study only included Japanese patients and it is unknown whether similar results would be obtained in other ethnic groups. Third, judgment of patency was not performed by a core laboratory. Although this might have potentially undermined the reliability of assessing restenosis, each participating site had experience with conducting pivotal clinical trials which considered likely to minimize variation in assessment. Fourth, the current study did not collect the data on how individual interventionalists evaluated lesion diameter or length, or how they selected the diameter and length of the stents or balloons.

Conclusion

Concomitant femoropopliteal lesions and a smaller stent diameter were independent risk factors for restenosis at 1 year after aortoiliac stenting.

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Compliance with ethical standards

Conflict of interest There was no conflict of interest regarding this manuscript.

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