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ORIGINAL ARTICLE

Clinical impact of self-expandable stent diameter after femoropopliteal stenting

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Abstract The optimal diameter of a self-expandable stent for femoropopliteal (FP) artery disease remains unclear. The aim of this study is to investigate the influence of stent diameter on the clinical outcome after FP stenting and to identify optimal stent diameter of self-expandable stent implantation. This study was a prospective observational study. Eighty patients who underwent successful self-expandable stent implantation for FP disease were enrolled in this study. A commercially available self-expandable stent was used. The operator determined the type, diameter and length of the stent based on a visual estimate in angiography. A peak systolic velocity ratio >2.0 was defined as restenosis. Primary patency was defined as treated vessel without restenosis and repeat revascularization. Secondary patency was defined as target vessel which subsequently become totally occluded and is reopened by repeat revascularization. As a result, restenosis was found in 34 patients (42.5%) during the follow-up of 24 months. In-stent restenosis was independently predicted by stent fracture [hazard ratio (HR) 2.6, $p = 0.01$], chronic total occlusion (HR 2.4, $p = 0.02$) and stent diameter ×10/vessel diameter (S/V) ratio (HR 1.7, $p = 0.04$). Using receiver-operator characteristic analysis, S/V ratio >1.30 best separated patients with and without in-stent restenosis. Primary and secondary patency was significantly lower in patients with S/V ratio >1.30 (85 vs. 44%, $p = 0.002$ and 90 vs. 65%, $p = 0.009$, respectively). In conclusion, an S/V ratio was an independent predictor of in-stent restenosis after FP stenting, and it was also associated with the clinical outcome.

Keywords Stent diameter · Self-expandable stent · Femoropopliteal artery · Restenosis

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Introduction

Optimal treatment for chronic limb ischemia due to femoropopliteal (FP) lesions remains unclear. Balloon angioplasty in management of FP artery disease has a poor outcome and the restenosis rate is particularly high [1–4]. Complications such as recoil, dissection and acute occlusion have been reduced by use of stents [5–8] and treatment of chronic total occlusion, which was previously considered difficult, has been attempted [9, 10]. Use of stents has also achieved good short-term outcomes, but the long-term patency is unsatisfactory [11–13]. Obtaining a larger lumen size is well known to be important in coronary artery stenting, but there is no standard procedure for FP stenting and it remains unclear if standards for coronary stenting apply to placement of a self-expandable stent in FP artery. With this background, we studied the influence of stent diameter on patency in the FP artery.

Methods

Study population

This study was a non-randomized prospective observational study enrolling patients undergoing self-expandable stent implantation for FP artery disease. Between January 2003 and December, 2005, we enrolled 80 (84 limbs)

consecutive patients from our institution. All patients had native and de novo or restenotic lesions with a stenosis diameter of more than 50% by visual estimate on angiography, with symptom classified as Rutherford stages 2–4 [14]. Other inclusion criteria were age ≥20 years old, an ankle-brachial index (ABI) of ≤0.9. Patients with acute onset limb ischemia, or severe lower extremity ischemic symptoms classified into Rutherford Category 5 or 6 were excluded. Other exclusion criteria were popliteal artery lesion below the knee joint, in-stent restenosis, known bleeding diathesis, hepatic dysfunction, active gastrointestinal bleeding or peptic ulcer disease, intolerance to cilostazol, aspirin or ticlopidine, pregnant women, and major life-threatening illness. Informed consent was obtained from all patients. The procedure and follow-up treatment were approved by our institutional review board.

Procedure

All patients were medicated with dual antiplatelet therapy from more than 2 days before the procedure. After insertion of a 6-Fr sheath, an intra-arterial bolus of 5000 IU of heparin was injected. A hydrophilic 0.035-in. guidewire was used initially to cross the lesion. When this wire could be passed no further, a 0.014 or a 0.018-in. guidewire was used. After passing the wire through the lesion, balloon angioplasty was performed. All lesions were dilated with an optimal size balloon. If suboptimal result caused by flow-limiting dissection or residual stenosis of more than 50% was found after dilatation, repeat balloon angioplasty with long inflation was performed again. When favorable result was not still obtained, stent was implanted. Three types of stent were used: Luminexx (Bard, Murray Hill, NJ), SMART (Cordis J&J, Miami, FL) and Wallstent RP (Boston Scientific, Natick, MA). The operator determined the type, diameter and length of the stent based on a visual estimate in angiography. In the preoperative quantitative angiographic analysis, calibration was performed with a 6-Fr guide-sheath using software (CAASII v. 4.0) provided with the cineangiography system.

Follow-up and definition

Routine follow-up duplex ultrasound was performed at 6, 12, 18, and 24 months. This examination was performed by vascular technicians with extensive experience with this procedure. Treated lesions were visualized by duplex ultrasound. Doppler spectral analysis was used to determine the peak systolic velocity ratio (PSVR) at lesions: PSVR >2.0 was defined as restenosis [15] and no detectable signal was taken to indicate complete occlusion. The target lesion was defined as the treated segment from 10 mm proximal to 10 mm distal.

Primary patency was defined as treated vessel without restenosis and repeat revascularization. Assisted primary patency was defined as target vessel which subsequently requires a repeat revascularization to assist patency, without a total occlusion. Secondary patency was defined as target vessel which subsequently becomes totally occluded and is reopened by repeat revascularization.

The reference vessel diameter was defined as the mean vessel diameters at normal sites proximal and distal to the treated lesion and the ratio of the maximum stent diameter (as defined by the manufacturer)/reference vessel diameter (S/V ratio) was calculated. Stent fracture was defined as single or multiple strut fracture or complete separation.

Statistical analysis

Values are expressed as mean ± SD. Categorical variables were analyzed by chi-square test. Serial paired numerical data were compared with a paired t test and continuous variables were examined with an unpaired t test. To evaluate the predictive accuracy for S/V ratio, receiver-operator characteristic (ROC) analyses were performed in the entire cohort. Event-free survival curve was analyzed using the Kaplan–Meier method, and survival curves were compared using log-rank test. Clinical and variables were evaluated for study endpoint by using Cox proportional hazard models. All variables with a significant association with endpoint were entered in a multivariate Cox model to identify independent predictors. A p value <0.05 was considered to be statistically significant.

Results

The age of the patients ranged from 44 to 88 years old (mean 70.3 ± 6.8 years old), and 12 patients were female (15%) (Table 1). The mean diameter of the treated vessels was 5.1 ± 0.6 mm, the mean lesion length was 94 ± 44 mm, and 1.7 ± 0.6 stents were used per lesion (Table 2). Each S/V ratio of three different stent was 1.29 ± 0.74 (Luminexx), 1.28 ± 0.94 (SMART) and 1.28 ± 0.95 (Wall), respectively. No significant difference was found among three types of stent ($p = 0.86$). During the follow-up period, one patient (1.3%) dropped out, one (1.3%) underwent a major amputation for diabetic gangrene, one (1.3%) died suddenly, and one (1.3%) had a stroke. Therefore, follow-up at 24 months was completed in 76 patients (95%).

During the observation period, binary restenosis was found in 34 (43%) patients, and 16 had complete reocclusion. Baseline characteristics of the study population and comparison of patients with and without restenosis were listed in Tables 1 and 2. History of diabetes, the

Table 1 Patient characteristics

Variables	Total $N = 80$	Restenosis (+) $N = 34$	Restenosis (−) $N = 46$	p value
Age (years)	70 ± 7	69 ± 9	71 ± 9	0.42
>75 years	60 (75)	26 (76)	34 (74)	0.79
Female gender (%)	12 (15)	8 (23)	4 (9)	0.07
Hypertension (%)	64 (80)	29 (85)	35 (76)	0.31
Diabetes mellitus (%)	24 (30)	13 (38)	11 (24)	0.17
Hypercholesterolemia (%)	30 (38)	14 (41)	16 (35)	0.56
Coronary artery disease (%)	54 (68)	18 (53)	36 (78)	0.02
Chronic renal failure (%)	14 (18)	7 (21)	7 (15)	0.53
Hemodialysis	12 (15)	5 (15)	7 (15)	0.95
Current smoke (%)	40 (50)	18 (53)	22 (48)	0.65
Exercise habit	28 (35)	14 (41)	14 (30)	0.32
TASC (A/B/C/D)	0/14/39/27	0/4/16/14	0/10/23/13	0.35
Rutherford (II/III/IV)	6/54/20	2/22/10	4/32/10	0.69
BTK run-off				
0/1/2/3	6/27/27/20	0/11/13/10	6/16/14/10	0.15
Pre-procedure ABI	0.55 ± 0.15	0.53 ± 0.16	0.56 ± 0.23	0.53
Post-procedure ABI	0.75 ± 0.14	0.77 ± 0.15	0.74 ± 0.23	0.53
Medication				
Aspirin	73 (91)	31 (91)	42 (91)	0.98
Tichropidine	59 (74)	25 (74)	34 (74)	0.97
Cilostazol	26 (33)	11 (32)	15 (33)	0.98
Statins	17 (21)	7 (20)	10 (21)	0.90
Beta-blocker	7 (9)	3 (9)	4 (9)	0.98

BTK below-the-knee, *ABI* ankle-brachial index

Table 2 Lesion and procedural characteristics

Variables	Total $N = 80$	Restenosis (+) $N = 34$	Restenosis (−) $N = 46$	p value
Mean lesion length (mm)	94 ± 44	111 ± 48	81 ± 54	0.01
Reference diameter (mm)	5.1 ± 0.6	5.0 ± 0.8	5.2 ± 0.7	0.13
Pre-MLD (mm)	0.8 ± 0.7	0.7 ± 0.7	0.9 ± 0.8	0.19
Pre-diameter stenosis (%)	84 ± 14	86 ± 14	83 ± 16	0.45
Post-MLD (mm)	4.0 ± 0.6	4.1 ± 0.7	4.0 ± 0.6	0.24
Post-diameter stenosis (%)	26 ± 7	25 ± 8	27 ± 8	0.26
Number of stent/lesion	1.7 ± 0.6	1.8 ± 0.9	1.6 ± 0.6	0.34
Total stent length (mm)	107 ± 42	116 ± 49	100 ± 47	0.13
Mean stent diameter (mm)	6.7 ± 0.7	6.5 ± 0.7	6.8 ± 0.9	0.06
Calcified lesion[a] (%)	15 (18.8)	7 (21)	8 (17)	0.72
Chronic total occlusion (%)	26 (32.5)	18 (53)	8 (17)	<0.001
Modality of stent				
Luminexx/SMART/Wall	31/27/22	12/14/8	19/13/14	0.48
S/V ratio[b]	1.28 ± 0.07	1.32 ± 0.08	1.26 ± 0.09	0.006
Pre-balloon size (mm)	4.8 ± 0.6	4.7 ± 0.8	4.8 ± 0.7	0.25
Pre-balloon pressure (atm)	12 ± 1.0	12 ± 0.7	12 ± 0.8	0.44
Post-balloon size (mm)	5.7 ± 0.5	5.6 ± 0.7	5.8 ± 0.7	0.15
Post-balloon pressure (atm)	12 ± 0.1	12 ± 0.8	12 ± 0.9	0.66
Stent fracture (%)	16 (20)	13 (38)	3 (7)	<0.001
Luminexx/SMART/Wall	8/7/1	6/6/1	2/1/0	0.08

MLD minimal lumen diameter

[a] Calcified lesion defined as obvious densities noted within the apparent vascular wall in the angiogram

[b] S/V ratio defined as maximum stent diameter (mm)/ reference stent diameter (mm)

Table 3 Multivariate cox regression analysis: predictors of restenosis

Variables	HR	95% CI	*p* value
Stent fracture[a]	2.63	1.24–5.58	0.011
Chronic total occlusion	2.39	1.17–4.87	0.017
S/V[b] ratio (per 0.1 increase)	1.69	1.03–5.58	0.038

[a] Stent fracture defined as single or multiple strut fracture or complete separation

[b] S/V defined as maximum stent diameter (mm)/reference vessel diameter (mm)

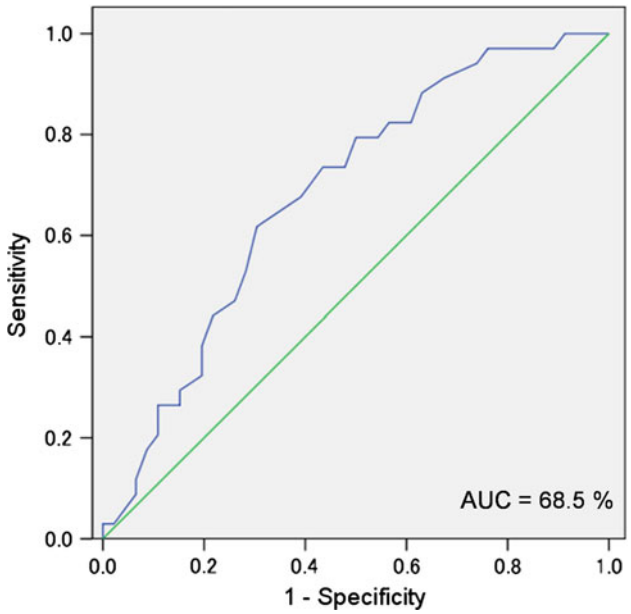

Fig. 1 Receiver-operator characteristic (ROC) analysis for separating patients with or without restenosis

number of stents, post-procedure ABI, final percent diameter stenosis, final minimal luminal diameter and pharmacological therapy were similar in patients with and without restenosis. Used stents were made of nitinol or stainless steel and the use of the various commercially available stents in patients with and without restenosis was similar ($p = 0.48$). In patients with restenosis, lesion length was longer (111 vs. 81 mm, $p = 0.01$), an S/V ratio was greater (1.32 vs. 1.26, $p = 0.006$), and occlusive disease and fracture were observed more frequently (53 vs. 17%, $p < 0.001$, 38 vs. 7%, $p < 0.001$, respectively). On multivariate Cox analysis, stent fracture [hazard ratio (HR) 2.63, 95% confidence interval (CI) 1.24–5.58, $p = 0.011$], chronic total occlusion (HR 2.39, 95% CI 1.17–4.87, $p = 0.017$) and S/V ratio (HR 1.69, 95% CI 1.03–5.58, $p = 0.038$) were independent predictors of restenosis (Table 3). Stent fracture occurred in 16% (20/80). No statistical difference was found in each stent (Table 2). However, stent fracture of stainless steel stent was significantly less frequently than that of nitinol stent (1 vs. 15, $p = 0.03$). Small size vessel (especially <5.0 mm) tended to be restenosis (HR 1.49, 95% CI 0.94–2.35, $p = 0.087$). Poor runoff was not a predictor of restenosis (HR 0.6, 95% CI 0.3–1.3, $p = 0.17$) in this study. In the entire cohort, the area under the ROC curve for S/V ratio was 0.69, and a cut-off value of 1.30 best separated patients with and without restenosis (sensitivity 61.8%, specificity 71.7%, positive predict value 61.8%, negative predict value 71.7%; Fig. 1).

Kaplan–Meier analysis showed that primary patency was significantly lower in patients with S/V ratio >1.30 in comparison to patients with S/V ratio <1.30 (36 vs. 73%, $p = 0.0005$; Fig. 2) and assisted primary and secondary patency were also significantly lower in patients with S/V ratio >1.30 in comparison to patients with S/V ratio <1.30 (44 vs. 85%, $p = 0.0002$; Fig. 3, 90 vs. 65%, $p = 0.009$, Fig. 4, respectively).

Discussion

Restenosis and reocclusion are major problems after stent placement in the FP artery, but the mechanism of in-stent restenosis remains unclear. In the present study, maximum self-expandable stent diameter for vessel diameter affected in-stent restenosis in addition to the known predictors. And the cut-off value of S/V ratio was 1.30 using ROC curve. Patients with an S/V ratio >1.30 was found in 38 (48%). In patients with an S/V ratio >1.30, age was younger (68 ± 9 vs. 72 ± 8, $p = 0.04$) and current smoker was more frequently (63 vs. 38%, $p = 0.03$). Lesion length was longer (115 ± 52 vs. 75 ± 47 mm, $p = 0.0006$), minimum lumen diameter before procedure was smaller (0.6 ± 0.7 vs. 1.0 ± 0.7 mm, $p = 0.004$), percent diameter stenosis was greater (88 ± 15 vs. 81 ± 15%, $p = 0.003$) and post-balloon size after stenting was smaller (5.5 ± 0.7 vs. 5.9 ± 0.7 mm, $p = 0.04$) compared with those with S/V ratio <1.3. Other baseline characteristics were similar.

Based on these findings, the following mechanisms that induced in-stent restenosis in patients with S/V ratio >1.30 could be considered. In patients with an S/V ratio >1.3, marked formation of in-stent neointimal proliferation may have occurred through vascular injury caused by stent strut-induced contact stress [16] and compliance mismatch at the stent edge causing restenosis [17]. External expansion of self-expandable stents leads to chronic stimulation that impairs the tunica intima and induces inflammation, and an increased expansion force caused by selection of a self-expandable stent with a diameter larger than the vascular diameter may lead to restenosis via post-dilatation wall overstretching and intimal damage.

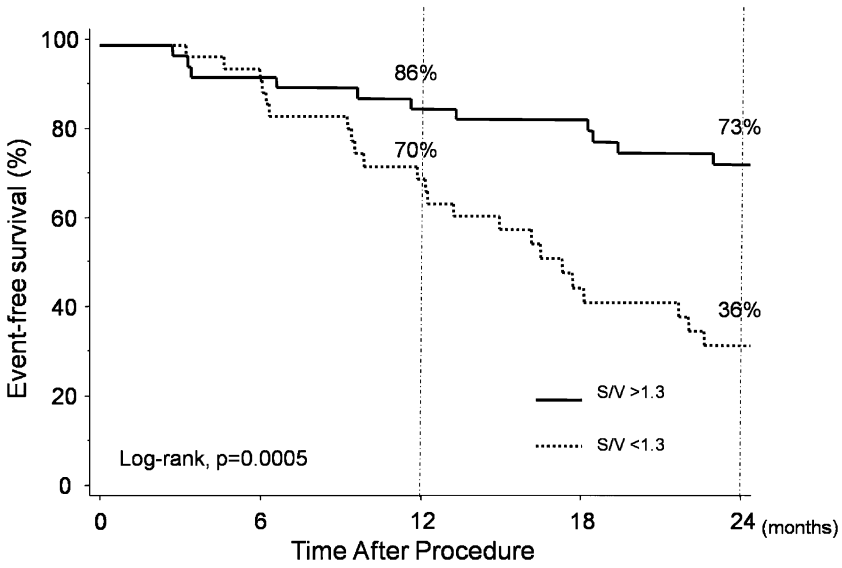

Fig. 2 Primary patency rate between patients with an S/V ratio <1.3 and >1.3. Primary patency was significantly lower in patients with S/V ratio >1.3 compared with those with S/V ratio <1.3

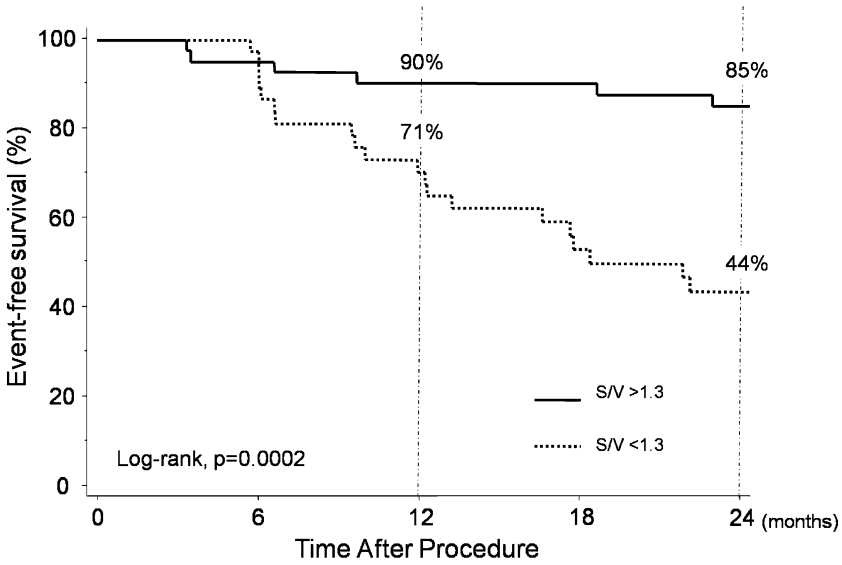

Fig. 3 Assisted primary patency rate between patients with an S/V ratio <1.3 and >1.3. Assisted primary patency was also significantly lower in patients with S/V ratio >1.3 compared with those with S/V ratio <1.3

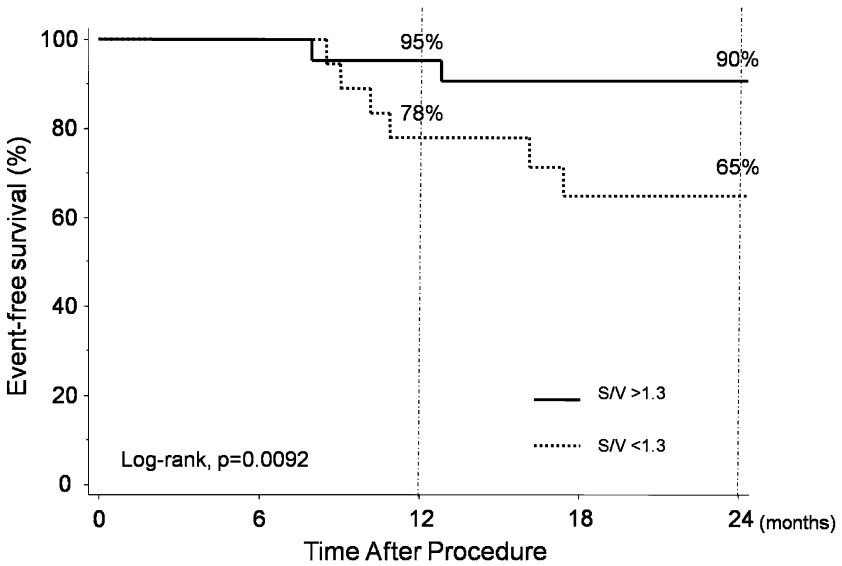

Fig. 4 Secondary patency rate between patients with an S/V ratio <1.3 and >1.3. Secondary patency was significantly lower in patients with S/V ratio >1.3 compared with those with S/V ratio <1.3

Stainless steel self-expanding stents have been reported to have lower long-term patency compared to nitinol stents [18], but we found no significant difference in the rate of in-stent restenosis at 24 months among the stents (Luminexx 39%, SMART 52%, Wall RP 36%; $p = 0.48$). Nitinol stents (Luminexx and SMART) are used in many cases because of good mid-term patency [19], but fracture frequently occurs and causes restenosis [20, 21], consistent with our findings. The efficacy of coronary stenting in reducing restenosis was found to depend on achievement of a large initial luminal gain in comparison trials of balloon angioplasty and coronary stenting [22, 23]. Subsequently, the concept of "bigger is better" has spread in the field of coronary intervention with bare-metal stent, but our results suggest that this paradigm might not always be correct in placement of self-expandable stents for FP lesions.

The present study has several important limitations which should be considered before interpreting the final results. The patients were non-randomized and were treated at a single center, and the S/V ratio was analyzed retrospectively. S/V ratio-based differences in outcome were found in cases with small vessels and long lesions, and these results may differ in patients with relatively larger vessels or with shorter lesions. The small sample size also limits the study reliability and prospective larger studies are required to validate the results. However, within these limitations, our most important finding is that determination of the optimal stent diameter for a self-expandable stent may play an important role in patency after FP stenting.

Conclusion

Despite studies in larger sample size and longer follow-up periods are required to confirm our results, we would conclude that an S/V ratio was a strong predictor of restenosis after stent implantation for FP disease and it was also associated with the clinical outcome. In addition, our result support an S/V ratio of <1.30 should be selected in FP stenting.

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Conflicts of interest None of the authors have any real or perceived conflicts of interest.

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