The prevalence of lower-extremity peripheral artery disease (LE-PAD) is now increasing all over the world, and was reported in 200 million people worldwide in 2010. Endovascular therapy (EVT) has recently been developed as the first-line revascularization strategy for symptomatic LE-PAD. Superficial femoral artery (SFA) lesions are complicated in approximately half of symptomatic LE-PAD patients, in whom combined self-expanding nitinol stents are widely used. The 1-year patency rate, however, remains as low as 63–79%. In the coronary artery era, the stent-to-vessel (S/V) diameter ratio is associated with the risk of restenosis. It is speculated that stress due to excessive dilation induces intimal proliferation, leading to restenosis. An animal experiment also shows the influence of stent size on late restenosis. In the peripheral artery era, especially in SFA disease, a high S/V ratio has been similarly reported as an indicator of risk of restenosis after stent implantation in symptomatic LE-PAD. The reference vessel diameter, however, is often measured distally at a healthy site. It remains unclear whether the S/V diameter ratio assessed at the lesion site would be more predictive than that assessed distally at a healthy site.

Methods and Results: A total of 117 patients (mean age, 73±7 years; 74% male) who underwent successful nitinol stent implantation in SFA lesions (mean lesion length, 172±104 mm) on intravascular ultrasound (IVUS) were retrospectively analyzed. S/V ratio at the proximal and distal healthy site, and at the smallest lesion site, was evaluated on IVUS. One-year restenosis predictors were evaluated on multivariate analysis. Mean S/V diameter ratio on IVUS at proximal and distal healthy sites, and at the lesion site, was 0.98±0.11, 1.02±0.11 and 1.15±0.16, respectively. One-year primary patency was 77%. On multivariate analysis, lesion length (OR, 1.06 per 10-mm increment; P=0.046) and S/V ratio measured at the lesion site (OR, 1.34 per 0.1 increment; P=0.032), but not that at the distal healthy site (OR, 1.05 per 0.1 increment; P=0.705), were significantly associated with 1-year restenosis.

Conclusions: S/V ratio assessed on IVUS at the lesion site, but not at the distal healthy site, was independently associated with 1-year restenosis after SFA stenting.

Key Words: Femoropopliteal artery; Peripheral artery disease; Self-expandable nitinol stent; Stent/vessel ratio
Impact of Stent-to-Vessel Ratio on SFA Restenosis

The vessel diameter was calculated as the mean of the major and minor axis diameters of the external elastic membrane area, and the S/V ratio was obtained by calculating the ratio of the placed stent diameter and the mean vessel diameter at the proximal healthy site, the lesion site and the distal healthy site. The reference vessel diameter at the proximal and distal healthy site was assessed at the site without atherosclerotic lesions on IVUS. The lesion site was identified on IVUS as the site presenting both period) were excluded from the current study. This study complied with the Declaration of Helsinki, and was approved by the hospital ethics committee.

**EVT**

After ipsilateral or contralateral puncture of the common femoral artery under local anesthesia, a 6-Fr guiding sheath was generally inserted. After the guiding sheath was placed, 5,000 units of heparin was routinely injected. Indication for revascularization was ≥75% angiographic stenosis of target lesions. Guidewires of 0.035, 0.014, or 0.018 inches were passed through the lesion. After passing through the lesion, the vessel diameter at the distal healthy site and that at the lesion were evaluated on IVUS (OptiCross or Atlantis™ SR Pro, Boston Scientific, Marlborough, MA, USA). If the IVUS catheter could not be advanced, pre-dilatation was performed with a ≤3-mm balloon catheter, and thereafter IVUS was performed. IVUS was manually recorded at approximately 10 mm/s. Based on IVUS, pre-dilatation was added before stenting. Stenting was done if there was flow-limiting dissection, pressure gradient >10 mmHg, or >30% residual stenosis. Stent size was determined at physician discretion. In general, a stent size approximately 1 mm larger than the distal reference diameter was routinely selected, and it was evaluated not only on angiography but also on IVUS. Post-dilatation was additionally performed using a balloon of the same size or 1 mm smaller than the selected stent. Procedural success was defined as residual stenosis ≤30% without flow-limiting dissection and without pressure gradient ≤10 mmHg.

**IVUS**

The vessel diameter was calculated as the mean of the major and minor axis diameters of the external elastic membrane area, and the S/V ratio was obtained by calculating the ratio of the placed stent diameter and the mean vessel diameter at the proximal healthy site, the lesion site and the distal healthy site. The reference vessel diameter at the proximal and distal healthy site was assessed at the site without atherosclerotic lesions on IVUS. The lesion site was identified on IVUS as the site presenting both

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**Figure 1.** Vessel diameter assessment on intravascular ultrasound (IVUS) and measurement of stent-to-vessel (S/V) ratio. **(A)** Proximal healthy site, **(B)** distal healthy site and **(C)** lesion site. Distal mean vessel diameter was calculated as the mean of the major and minor axis diameter.

**Table 1. Patient Baseline Characteristics**

| Overall (n=117) Mean±SD or n (%) |
|----------------------------------|
| Age (years) 73±7                  |
| Male 86 (74)                      |
| Risk factors                     |
| Hypertension 87 (73)             |
| Dyslipidemia 52 (44)             |
| Diabetes mellitus 54 (46)        |
| Smoking 47 (40)                  |
| Hemodialysis 34 (29)             |
| CAD 45 (39)                      |
| CVD 13 (11)                      |
| CLI 34 (29)                      |
| Iliac artery involvement 41 (35) |
| ABI 0.60±0.16                    |
| DAT 94 (80)                      |
| Aspirin 107 (91)                 |
| Thienopyridine 96 (82)           |
| Cilostazol 36 (31)               |
| Warfarin 14 (12)                 |

ABI, ankle-brachial index; CAD, coronary artery disease; CLI, critical limb ischemia; CVD, cerebrovascular disease; DAT, dual antiplatelet therapy.
Continuous variables are described as mean ± SD, and binary independent variables as number (percentage). Predictors associated with 1-year restenosis were investigated on logistic regression analysis; results are given as OR and 95% CI. Level of significance was set at P<0.05. For all analyses SPSS ver. 20.0 was used.

Results

Baseline characteristics are listed in Table 1. Mean age was 73±7 years, male subjects accounted for 74%, and the prevalence of critical limb ischemia was 29%. History of coronary artery disease was observed in 39% of patients, and cerebrovascular disease in 11%; 80% of the patients were on dual antiplatelet therapy. Table 2 lists the lesion and procedural characteristics. Mean lesion length was 172±104 mm, Trans-Atlantic Inter-Society Consensus II class C/D was observed in 56%, calcified lesion in 58%, and occlusion in 43%. In terms of stent used, bare metal stent (BMS) was used by 34% of the patients, and drug-eluting stent (DES) in 66%; SMART (Cordis J&J, Miami, FL, USA) stent in 19%, Misago (Terumo, Tokyo, Japan) stent in 14%, Zilver (Cook Medical, Bloomington, IN, USA) stent in 1%, and Zilver PTX (Cook Medical) stent in 66%. In terms of balloon size, 5 mm (n=31, 65%) for pre-dilation and 6 mm (n=66, 47%) for post dilatation were mainly used. The 7-mm stent size was most frequently used in both BMS and DES. Use of more than 1 stent was observed in 59% of cases. When distal vessel diameter was assessed on IVUS, diameter >7 mm was observed in 29% of lesions (41/143). The 8-mm diameter of stent was mainly deployed in these cases. IVUS measurements are listed in Table 3.

Statistical Analysis

Continuous variables are described as mean±SD, and binary independent variables as number (percentage). Predictors associated with 1-year restenosis were investigated on logistic regression analysis; results are given as OR and 95% CI. Level of significance was set at P<0.05. For all analyses SPSS ver. 20.0 was used.

Outcome Measures

The outcome measure was the primary patency rate at 1 year after EVT, and the impact of the S/V ratio on restenosis occurrence was investigated. Primary patency was defined as treated vessels without restenosis or repeat revascularization. Restenosis was defined as peak systolic velocity ratio ≥2.4 on duplex ultrasound; signal not detected in the stent segment; or ≥50% angiographic stenosis.

Table 2. Lesion and Procedure Baseline Characteristics

| Overall (n=143) | Mean±SD or n (%) |
|-----------------|------------------|
| **Lesion** | | |
| Lesion length (mm) | 172±104 |
| TASC II classification | | |
| A | 33 (24) |
| B | 29 (20) |
| C | 32 (22) |
| D | 49 (34) |
| **Run-off vessel** | | |
| 0/1/2/3 | 9 (6)/51 (36)/66 (46)/17 (12) |
| **Calcification** | | |
| 83 (58) |
| **CTO** | 61 (43) |
| **Pre-balloon diameter (mm)** | 4.3±0.7 |
| 3.0 | 7 (7) |
| 4.0 | 52 (55) |
| 5.0 | 31 (65) |
| 6.0 | 4 (4) |
| **Stent type** | | |
| BMS (mm) | 48 (34) |
| 6.0 | 24 (30) |
| 7.0 | 37 (46) |
| 8.0 | 19 (24) |
| DES (mm) | 95 (66) |
| 6.0 | 67 (35) |
| 7.0 | 117 (60) |
| 8.0 | 10 (5) |
| **No. stents** | 1.9±0.9 |
| **Stent length (mm)** | 198±114 |
| **Mean stent size (mm)** | 6.8±0.8 |
| **Post-balloon diameter (mm)** | | |
| 4.0 | 2 (1) |
| 5.0 | 62 (44) |
| 6.0 | 66 (47) |
| 7.0 | 10 (7) |

Table 3. Intravascular Ultrasound Results

| Overall (n=143) | Mean±SD or n (%) |
|-----------------|------------------|
| **Proximal healthy site** | | |
| Vessel diameter (mm) | 7.0±0.8 |
| Vessel area (mm²) | 39.2±9.3 |
| **Lesion site** | | |
| Vessel diameter (mm) | 6.0±0.9 |
| Vessel area (mm²) | 28.7±8.5 |
| **Distal healthy site** | | |
| Vessel diameter (mm) | 6.6±0.8 |
| Vessel area (mm²) | 34.3±8.3 |
| **S/V diameter ratio** | | |
| Proximal healthy site | 0.9±0.11 |
| Smallest lesion site | 1.15±0.16 |
| Distal healthy site | 1.02±0.11 |
| Stent symmetry index | 0.83±0.11 |
| Stent edge dissection | 22 (15) |
| Minimum stent area (mm²) | 16.1±4.0 |

S/V, stent-to-vessel.

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Impact of Stent-to-Vessel Ratio on SFA Restenosis

Table 4. Predictors of Restenosis After SFA Stent Implantation

|                          | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|--------------------------|------------------------|---------|----------------------|---------|
| Lesion length (per 10-mm increment) | 1.07 (1.03–1.12) | 0.002   | 1.06 (1.01–1.11) | 0.046   |
| Calcification            | 1.41 (0.67–2.94)      | 0.364   | 1.46 (0.65–3.30) | 0.360   |
| CTO                      | 1.68 (0.83–3.40)      | 0.153   | 1.04 (0.49–2.21) | 0.926   |
| Drug-eluting stent       | 0.88 (0.42–1.83)      | 0.726   | 0.86 (0.40–1.87) | 0.705   |
| S/V diameter ratio at the lesion site (per 0.1 increment)  | 1.43 (1.18–1.73) | <0.001  | 1.34 (1.02–1.74) | 0.032   |
| S/V diameter ratio at the distal healthy site (per 0.1 increment) | 1.39 (1.05–1.83) | 0.022   | 1.05 (0.75–1.48) | 0.705   |

CTO, chronic total occlusion; SFA, superficial femoral artery; S/V, stent-to-vessel.

healthy site, the lesion site, and the distal healthy site was 0.98±0.11, 1.15±0.16, and 1.02±0.11, respectively. The primary patency rate was 94% at 6 months and 77% at 1 year. On multivariate analysis, IVUS-assessed S/V diameter ratio at the lesion site (OR, 1.34; 95% CI: 1.02–1.74, P=0.032), but not that at the distal healthy site (OR, 1.39; 95% CI: 0.75–1.48, P=0.705), and lesion length (OR, 1.06; 95% CI: 1.01–1.11, P=0.046) were independent determinants of loss of patency (Table 4). The subjects were classified into quartiles according to S/V ratio at the lesion site: Q1, <1.03; Q2, 1.03–1.15; Q3, 1.16–1.23; and Q4, ≥1.24. As shown in Figure 3, the unadjusted OR of Q4 relative to Q1 was 1.29 (95% CI: 1.10–1.51, P=0.002). After adjustment for lesion length, calcification, chronic total occlusion, and DES use, the OR of Q4 relative to Q1 was 1.28 (95% CI: 1.08–1.50) and was still statistically significant (P=0.003).

The number of below-the-knee (BTK) run-offs was 0–3 based on anterior tibial, peroneal, and posterior tibial arteries. BTK run-off was not significantly associated with loss of primary patency (OR, 0.59; 95% CI: 0.34–1.01, P=0.056). Furthermore, S/V ratio was still significantly and

Figure 2. Lesion vessel diameter vs. distal vessel diameter. The vessel diameter at the lesion site was smaller than that at the distal healthy site (6.0±0.9 vs. 6.6±0.8 mm, P<0.001).

Figure 3. Quartile of stent-to-vessel diameter ratio vs. odds ratio for restenosis and 95% CI.
independently associated with loss of patency even after further adjustment for BTK run-off ($P=0.029$), whereas BTK run-off again had no significant association with loss of patency in the multivariate model ($P=0.187$).

**Discussion**

The main findings of this study are (1) vessel diameter at the distal healthy site was not smaller than that at the lesion; (2) S/V diameter ratio at the lesion site, but not at the distal healthy site, was an independent determinant of restenosis after stent implantation in de novo SFA lesions; and (3) lower patency rate was observed when the S/V diameter ratio at the lesion site was in the largest quartile (i.e., $>1.24$).

The size of self-expanding nitinol stents for de novo SFA lesions is often determined in reference to the vessel diameter. The reference vessel diameter, however, is often evaluated at the distal healthy site. This is simply because angiography is unable to accurately visualize the diameter at the lesion site, and the distal vessel is expected to provide the smallest value in the lesion site. Approximately 60% of atherosclerotic lesions in the SFA, however, present negative remodeling. Consequently, as shown in the current study, the vessel diameter at the lesion is smaller than that at the distal site. In the coronary artery, stent implantation with a high S/V diameter ratio induces stress on the vessels and intimal proliferation, increasing the risk of restenosis. The inverse association between S/V ratio at the lesion site and vessel patency could be explained by potential pathophysiological mechanisms: artery stretch and vascular injury attributable to an oversized stent would possibly trigger neointimal hyperplasia. In the current stent-supported strategy for SFA treatment, optimal stent expansion in the initial treatment plays an important role in ensuring better long-term patency. In the process of ensuring better stent expansion, however, high-pressure dilatation, wide strut openings, symmetrical stent deployment, and increased balloon compliance could not prevent, and may also contribute to, neointimal formation, leading to increased incidence of in-stent restenosis. Therefore, it is important to ensure a balance between adequate final stent dimensions and reduction of vascular injury, because vascular injury is intimately linked to in-stent neointima formation. Also, self-expanding stents produce a continuous outward force on the vessel, which may increase with time. It is possible that artery stretch and vascular injury attributable to stent oversizing could be associated with deep penetration of the artery wall, leading to proliferation of neointimal hyperplasia.

In the present study, only 53% of vessels had optimal stent expansion, defined as 90% of the cross-sectional area of the distal reference vessel lumen on IVUS. Optimal stent expansion at the time of the initial procedure, however, was not significantly associated with loss of patency (OR, 1.08; 95% CI: 0.49–2.40, $P=0.85$). This might be associated with the characteristic of self-expanding stents: in clinical settings, sufficient expansion is commonly observed in the chronic phase even though the stent was not fully expanded at the initial procedure. Little is known, however, about how frequently stent expansion is observed in the chronic phase. Further investigation is needed to clarify this.

There is general agreement that intravascular imaging can more accurately measure vessel diameter than angiography. IVUS can provide the vessel diameter not only at the distal healthy site but also at the lesion site. There is a report on the measurement of stent diameter on IVUS in the coronary artery lesion, but none on that in SFA lesions, to the best of our knowledge. The present study suggests that an appropriate selection of stent size in reference to the vessel diameter would play an important role in ensuring better patency in de novo SFA intervention, and that the assessment of the vessel diameter at the lesion site would be more important than that at the distal healthy site.

This study had several limitations. First, this was a single-center and retrospective analysis. Second, IVUS data collected before and after stent implantation were not also evaluated at a centralized core lab. Also, IVUS was conducted manually not automatically; and duplex ultrasound assessment for restenosis was not conducted under core laboratory observation; although this might undermine the reliability of restenosis assessment, the present site and the physician had clinical experience conducting pivotal trials on nitinol stents for FP lesions. Third, information on continuation or discontinuation of antiplatelet drugs was lacking. This information was available only at the time of the initial procedure. Fourth, arterial stretch and deep injury, which are associated with growth of neointimal hyperplasia, were not assessed. Further investigation is needed on the impact of S/V ratio on outcomes in a well-structured study.

**Conclusions**

S/V diameter ratio at the lesion site but not at the distal healthy site was an independent determinant of restenosis after treatment with a self-expanding nitinol stent in de novo SFA lesions.

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**Disclosures**

The authors declare no conflict of interest.
Impact of Stent-to-Vessel Ratio on SFA Restenosis

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