

Original Article

Nitinol Self-Expanding Stents for the Treatment of Obstructive Superficial Femoral Artery Disease: Three-Year Results of the RELIABLE Japanese Multicenter Study

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Objective: To assess the use of a nitinol stent to treat symptomatic stenoses or occlusions of the native superficial femoral artery (SFA).

Materials and Methods: Seventy-four patients were treated at 12 Japanese sites. The primary endpoint, freedom from target-limb failure (TLF), was a composite of device- or procedure-related death, target-limb amputation, target-vessel revascularization (TVR), or restenosis compared to an objective performance goal (OPG) at 12 months. Secondary endpoints, including primary patency, freedom from TVR/target-lesion revascularization (TLR), improvements in clinical parameters, and major adverse events (MAEs) were evaluated through 36 months.

Results: The mean overall lesion length was 80.7±38.9 mm (mean stented length: 98.8±46.1 mm). Freedom from TLF was 81.2% ($p<0.001$ compared to OPG) with a Kaplan–Meier estimate of 84.2% [95% confidence interval (95%CI) 73.3%, 90.9%] at 12 months. Primary patency was 71.0% at 12 months and 67.8% at 36 months. A total of 94.7%

of patients improved by at least one Rutherford category and 70.2% of patients improved ankle–brachial indices ≥ 0.10 from baseline to 36 months. Freedom from TVR/TLR (Kaplan–Meier) was 90% at 12 months and 79.5% at 36 months. Four MAEs were reported; none were found to be device or procedure related.

Conclusion: A self-expanding stent was used safely to treat stenotic and occlusive lesions of the SFA in a Japanese patient population. The composite endpoint, freedom from TLF, was superior to an historical control at one year, with low rates of revascularization and good functional and clinical outcomes through three years.

Keywords: superficial femoral artery, peripheral arterial disease, self-expanding stents, obstructive atherosclerotic lesions, peripheral vascular disease

Introduction

Peripheral artery disease (PAD) is a primary cause of cardiovascular morbidity.^{1,2} The prevalence of PAD increases exponentially with age, and affects up to 20% of individuals over 70 years old.³ In addition, cardiovascular risk factors such as smoking and diabetes mellitus increase the risk.⁴ Revascularization is often indicated if medical therapy and exercise do not relieve symptoms.⁵ Endovascular therapy (EVT), less invasive than surgery with a low risk of complications, has become the primary method of revascularization for TASC A–C lesions^{6,7}; bypass surgery still has a place in more complex, multilevel, TASC D lesions.⁸ Nearly 50% of patients referred for revascularization have a lesion in the superficial femoral artery (SFA).⁹ Results using percutaneous transluminal angioplasty (PTA) alone to treat SFA lesions are often hampered by vessel recoil and trauma (e.g., dissection), but primary or provisional stent placement can prevent recoil, cover a flow-limiting intimal flap, and restore blood flow.^{10–17} Achieving durable results with EVT in the SFA, however, remains challenging because of the unique characteristics

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of the vessel; the burden of atherosclerosis, and mechanical forces such as elongation, compression, and torsion caused by muscle and joint movement from ambulation, can result in restenosis caused by neointimal hyperplasia and stent failure.^{18–21)} Therefore, newer generation stents have been designed to overcome many of the problems of SFA stent placement. We conducted the RELIABLE study (REconstruction of obstructive Lesions of the superficial femoral Artery or proximal popliteal artery by Bard Life stent) to evaluate the performance of a helically structured, nitinol, bare-metal stent for the treatment of SFA obstructive disease in a Japanese patient population.

Materials and Methods

Study design

Between December 2012 and September 2013, 77 patients were prospectively enrolled in the RELIABLE study at 12 centers in Japan. The study protocol was approved by the institutional review board at each site, and patients gave written informed consent prior to participation in the study. Study procedures were conducted in accordance with the Declaration of Helsinki, good clinical practices, and other applicable laws issued by the Japanese Ministry of Health, Labor, and Welfare (MHLW). The Cardiovascular Research Foundation Core Laboratory (New York, NY, USA) analyzed plain-film radiographs and angiographic films while the Vascular Ultrasound Core Laboratory (VasCore, Boston, MA, USA), independently reviewed duplex-ultrasound (DUS) images. Data were collected by on-site investigators on standardized case report forms, and a medical adjudicator reviewed serious adverse events for relationship to the device or procedure. RELIABLE was registered on clinicaltrials.gov (Unique Identifier: NCT01746550) prior to patient enrollment, and was supported by Medicon, Inc. (Osaka, Japan).

Patients eligible for inclusion in the study were at least 20 years old and had symptoms of lifestyle-limiting claudication or ischemic rest pain (Rutherford categories 2–4).²²⁾ Angiographic eligibility required the presence of target-lesion stenosis or restenosis ($\geq 50\%$ of the reference vessel diameter) or occlusion in the SFA, a total lesion length (one or a series of lesions) of no more than 150 mm, and at least one patent infrapopliteal runoff vessel to the foot. To allow for proper stent sizing, target vessels were limited to between 4 mm and 6.5 mm in diameter. Key exclusion criteria included previous bypass surgery of the target vessel, an aneurysm or previously implanted stent at the proposed treatment site, renal insufficiency (creatinine > 2.5 mg/dL), critical limb ischemia resulting in tissue loss (Rutherford Category 5 or 6), or the lesion was not suitable for stent placement (e.g., anatomical anomaly).

Endpoints

The primary composite endpoint was the proportion of patients free from target-limb failure (TLF) at 12 months. TLF consisted of device- or procedure-related death, target-limb amputation, target-vessel revascularization (TVR), or restenosis. Restenosis was either measured directly by angiography or derived by DUS. DUS-derived restenosis was defined as either a peak systolic velocity ratio (PSVR) ≥ 2.5 (stenosis $\geq 50\%$) or abnormal DUS wave form with worsening clinical symptoms (e.g., decline in Rutherford classification by at least one category), or a PSVR ≥ 3.5 (stenosis $\geq 70\%$) without clinical symptoms. Deaths were independently reviewed by the medical adjudicator, and restenosis was analyzed by either the angiographic or DUS core laboratories.

Secondary efficacy endpoints included acute procedural success, primary patency, and an assessment of patient function by Rutherford categories, ankle-brachial indices (ABI), and quality-of-life measurements (SF-36) at baseline and post-procedure. Acute procedural success was defined as successful delivery of the stent to the intended location, attainment of $\leq 30\%$ residual stenosis following stent deployment, absence of a procedural complication or unresolved issue requiring additional intervention (e.g., unsolved flow-limiting dissection), and successful withdrawal of the delivery catheter. Primary patency was defined as freedom from target-lesion restenosis (luminal narrowing of $\geq 50\%$ with or without clinical symptoms) and/or target-lesion revascularization (TLR). Secondary safety endpoints included the rate of major adverse events (MAEs) defined as device- or procedure-related death, stroke, myocardial infarction, or target-limb amputation; the overall rate of adverse events; the rate of TVR/TLR; and stent fractures independently assessed by the radiographic and angiographic core laboratory.

Baseline patient and lesion characteristics

Seventy-seven patients signed informed consent to participate in the study while 74 were included in the intention-to-treat (ITT) population. Patients were included in the ITT population once the guidewire crossed the lesion; in one patient the guidewire could not be passed across the target lesion, one patient withdrew consent to participate before the procedure, and one was withdrawn because of worsening renal function. Baseline patient demographics, medical risk factors, and medical history are summarized in Table 1. Mean patient age was 72.8 years old (range: 51–89 years), and the majority were male (75.7%). Seventy-seven percent of patients had a history of progressive PAD, 37.8% a history of angina pectoris, 17.6% a history of coronary artery disease, 23% a history of stroke or transient ischemic attack, 58.1% had diabetes mellitus (Type II), 68.9% were current or former smokers, and

64.9% had a history of previous coronary and/or peripheral artery interventions.

Seventy-seven lesions were treated in the 74 enrolled patients. Lesions were described by the clinical sites as stenoses (77.9%), restenoses (1.3%), or occlusions (20.8%) with 48.1% classified as TASC A, 49.4% as TASC B, and 2.6% as TASC C. Baseline lesion characteristics, pre-procedure angiographic morphology, and procedural details are summarized in **Table 2**. Most lesions were located in the middle or distal SFA (61.0% or 24.7%, respectively), and 52.6% of lesions were described by the angiographic core laboratory as moderately to severely calcified. The mean total lesion length per patient was 80.7 ± 38.9 mm (range: 18.5–149.5 mm), and the pre-procedure percent diameter stenosis was $75.8 \pm 17.6\%$. Fifteen patients had inflow lesions in the iliac or common femoral arteries

treated prior to the study procedure; two patients had PTA only, six patients received stent placement only, and seven patients received a combination of PTA and bare-metal stent placement.

Study device

The LifeStent Solo Vascular Stent (Becton, Dickinson Peripheral Interventions, Tempe, AZ, USA) is a helically-designed, self-expanding stent made of nitinol (i.e., shape-memory alloy of nickel and titanium), designed to alleviate stent fractures and help prevent restenosis. The stent has been described previously¹⁰; however, the delivery system was redesigned from the system used in earlier U.S. studies (i.e., RESILIENT), and consists of a tri-axial delivery sheath (i.e., inner guidewire sheath, stent delivery sheath, and system stability sheath) with an ergonomic-grip handle and trigger release mechanism. The delivery system was available in working lengths of 80 cm and 135 cm, was 0.035 inch guidewire compatible, and could be introduced through a 6-F introducer sheath. When possible, one stent was used per patient with a maximum of two stents per patient allowed in the trial. Eighty-one stents were deployed in 74 patients (1.1 stents per patient); 66.7% were 6 mm and 33.3% were 7 mm in diameter. Approximately 20% of stents deployed in the study were 170 mm in length, followed by 120 mm (18.5%), 100 mm (12.3%), and 60 mm (16%) with a mean total stent length of 98.8 ± 46.1 mm quantified by the angiographic core laboratory.

Study procedures

Patient medications prior to the procedure were determined by the investigators; post-procedure, patients were prescribed acetylsalicylic acid (75–325 mg per day) through study completion and clopidogrel (75 mg per day) or ticlopidine (200–300 mg per day) for at least 60 days.

Vascular access was achieved through the femoral artery with a contralateral approach used in 93.2% of cases. An initial dose of 5000 IU intra-arterial heparin was recommended, while additional administration during the procedure was left to the discretion of the physician. All patients underwent pre-dilation of the target lesion with PTA prior to stent placement. Atherectomy, cryoplasty, lasers, or other endovascular devices were not allowed to improve the PTA result prior to stent placement. Pre- and post-stent deployment angiograms were performed to evaluate lesion and stent characteristics, distal vessel runoff, and PTA success. Completion angiography was performed using the same angles and technique used during the pre-procedure baseline study, and antero-posterior and lateral x-rays of the stent (straight-leg and bent-knee positions) were completed to assess baseline stent integrity. All images were analyzed by the angiographic core

Table 1 Baseline patient demographics, medical risk factors, and medical history

Demographics	
Mean age, y \pm SD	72.8 \pm 8.0
Gender, % (n/N)	
Male	75.7 (56/74)
Female	24.3 (18/74)
Race, % (n/N)	
Japanese	100.0 (74/74)
Weight, kg \pm SD	58.8 \pm 10.2
Mean height, cm \pm SD	160.3 \pm 8.6
Mean BMI, kg/m ² \pm SD	22.9 \pm 3.6
Rutherford categories, % (n/N)	
Category 2	54.1 (40/74)
Category 3	41.9 (31/74)
Category 4	4.0 (3/74)
Medical risk factors, % (n/N)	
Cigarette smoking (current)	21.6 (16/74)
Previous smoker (quit >6 months)	47.3 (35/74)
Hypertension	90.5 (67/74)
Dyslipidemia	75.7 (56/74)
Diabetes mellitus–Type II	58.1 (43/74)
Medical history and previous interventions, % (n/N)	
Peripheral vascular disease	77.0 (57/74)
Angina	37.8 (28/74)
Cardiac PTCA and/or stent	35.1 (26/74)
Peripheral stent	27.0 (20/74)
Stroke	20.3 (15/74)
Renal insufficiency/failure	18.9 (14/74)
Peripheral PTA	17.6 (13/74)
Coronary artery disease	17.6 (13/74)
Cancer	12.2 (9/74)
Myocardial infarction	10.8 (8/74)
Gastrointestinal disorder	10.8 (8/74)

SD: standard deviation; BMI: body mass index; PTCA: percutaneous transluminal coronary angioplasty; PTA: percutaneous transluminal angioplasty

Table 2 Baseline lesion characteristics, angiographic findings, and procedural details

Lesion characteristics ^a	
Number of target lesions, ^b % (n/N)	
One	95.9 (71/74)
Two	4.1 (3/74)
Lesion type, ^c % (n/N)	
Occlusion	20.8 (16/77)
Stenosis	77.9 (60/77)
Restenosis (not previously stented)	1.3 (1/77)
TASC II Classification, ^c % (n)	
Type A	48.1 (37/77)
Type B	49.4 (38/77)
Type C	2.6 (2/77)
Baseline angiographic findings ^d	
Mean lesion length, ^e mm±SD	77.4±40.2
Mean total lesion length, ^e mm±SD	80.7±38.9
Lesion location, % (n/N)	
Ostial SFA	1.3 (1/77)
Proximal SFA	13.0 (10/77)
Middle SFA	61.0 (47/77)
Distal SFA	24.7 (19/77)
Degree of calcification, ^c % (n)	
None/Mild	47.4 (36/76)
Moderate	23.7 (18/76)
Severe	28.9 (22/76)
Mean reference vessel diameter (RVD), mm±SD	4.8±0.6
Mean pre-procedure % diameter stenosis, %±SD	75.8±17.6
Procedural details	
Femoral artery access, ^b % (n/N)	100 (74/74)
Access side, ^b % (n/N)	
Ipsilateral	6.8 (5/74)
Contralateral	93.2 (69/74)
Number of stents placed	81
One stent, % (n/N)	91.4 (74/81)
Distal overlap, % (n/N)	4.9 (4/81)
Tandem/separate, % (n/N)	3.7 (3/81)
Stent diameter, % (n/N)	
6 mm	66.7 (54/81)
7 mm	33.3 (27/81)
Stent length, % (n/N)	
30 mm	11.1 (9/81)
40 mm	8.6 (7/81)
60 mm	16.0 (13/81)
80 mm	11.1 (9/81)
100 mm	12.3 (10/81)
120 mm	18.5 (15/81)
150 mm	2.5 (2/81)
170 mm	19.8 (16/81)
Mean final deployed stent length, ^d mm±SD	98.8±46.1
Mean procedure duration, min±SD	63.1±40.8
Mean % stenosis post-stent deployment, %±SD	11.7±9.9
Acute lesion success, ^f % (n/N)	88.3 (68/77)
Acute procedural success, ^g % (n/N)	86.5 (64/74)

^aSite reported. ^bBased on the total number of patients (74). ^cBased on the total number of discrete lesions (77). ^dBased on evaluable images analyzed by the angiographic core laboratory. ^eMean total lesion length takes into account multiple lesions per patient (number of patients=74). ^fResidual stenosis of <30% determined by the angiographic core laboratory following stent placement. ^gLesion success and the absence of peri-operative complications determined by the angiographic core laboratory, investigators, and medical adjudicator. SFA: superficial femoral artery

laboratory.

Follow-up

Follow-up visits at 1, 6, 12, 24, and 36 months included physical examination, laboratory tests, and DUS evaluation. In addition, ABIs were calculated, symptoms were assessed and Rutherford categories determined, and the change in quality-of-life was measured with the SF-36 questionnaire. Instructions about seiza—"correct sitting"—were not part of the formal precautions given to patients in the trial. Considering, however, that this was an elderly Japanese patient population, most investigators, as a matter of common practice, advised their patients to avoid sitting straight.

Radiographs of the stent were also taken at all follow-up intervals to assess stent integrity (i.e., two orthogonal views using the same standardized procedural protocol).

Radiographs, angiograms, and DUS images were analyzed by the core laboratories for the presence of restenosis and stent fracture.

Statistical analysis

A minimum sample size of 57 patients was needed to detect a 15% difference in the primary endpoint, the proportion of patients free from TLF at 12-months, compared to an objective performance goal (OPG) of 60%. The OPG was extrapolated from the 12-month primary patency rate of the PTA control group in the RESILIENT trial [15% higher than the upper 95% confidence interval (95%CI) of 45%].¹⁰ Assuming a 20% patient attrition rate, 70 patients were needed to complete the study.

All patients were analyzed on an ITT basis. Categorical variables such as demographic characteristics were summarized using frequency counts and percentages. The

Table 3 Primary endpoint analyses

Primary endpoint (12 months)		(95%CI) p-value
Freedom from target limb-failure (TLF), ^a % (n/N)	81.2 (56/69)	(69.9, 89.6) p=0.001 ^b
Device- or procedure-related death	0.0 (0/69)	
Target limb amputation	0.0 (0/69)	
Target vessel revascularization (TVR)	10.1 (7/69)	
Restenosis ^c	8.7 (6/69)	
Time to TLF (cox regression), hazard ratio		
Age	1.00	(0.92, 1.09)
Gender	0.38	(0.10, 1.50)
Hypertension	0.86	(0.09, 8.02)
Dyslipidemia	1.20	(0.31, 4.69)
Current smoking	0.58	(0.11, 2.94)
Freedom from TLF by subgroup, % (n/N)		
Male	84.3 (43/51)	(71.4, 93.0) p=0.21 ^d
Female	70.6 (12/17)	(44.0, 89.7)
Total lesion length ≤80 mm	82.9 (29/35)	(66.4, 93.4) p=0.67 ^d
Total lesion length >80 mm	78.8 (26/33)	(61.1, 91.0)
TASC A	87.9 (29/33)	(71.8, 96.6) p=0.24 ^d
TASC B	75.8 (25/33)	(57.7, 88.9)
TASC C	50.0 (1/2)	(1.3, 98.7)

^aDevice- or procedure-related death, target limb amputation, target vessel revascularization (TVR), or angiographic or duplex-ultrasound (DUS). DUS-derived restenosis was defined as either: 1) peak systolic velocity ratio (PSVR) ≥ 2.5 (stenosis $\geq 50\%$) or abnormal DUS wave form with worsening clinical symptoms (e.g., decline in Rutherford classification by at least one category), or 2) PSVR ≥ 3.5 (stenosis $\geq 70\%$) without clinical symptoms.

^bPre-specified, per-protocol analysis compared to a performance goal of 60% derived from the RESILIENT trial—one-sided, exact binomial test.

^cMet the clinical criteria for re-intervention, but did not have a procedure—(a) a residual target stenosis of $\geq 50\%$ by angiography, or core lab adjudicated stenosis or occlusion by Duplex Ultrasonography (DUS), and worsening symptoms of ≥ 1 Rutherford category; or (b) a residual target stenosis of $\geq 70\%$ by angiography, or PSVR ≥ 3.5 by DUS with or without clinical symptoms.

^dHomogeneity tested using Chi-square.

primary endpoint was calculated as a proportion of the patients reporting at 12 months along with the 95%CI, and was compared to the OPG using an exact binomial test (one-sided alpha of 2.5%; power of 90%) to test for superiority. A protocol-specified Kaplan–Meier (K–M) analysis of freedom from TLF was also performed to account for missing data in the proportional analysis; the survival estimate was presented along with the 95%CI. Secondary outcomes were reported using descriptive statistics, and were presented as means \pm standard deviation (SD). Finally, the number of adverse events (AEs), AEs by relationship to the device and to the procedure, AEs by severity, and deaths were summarized and reported descriptively.

Results

Angiographic analysis immediately post-procedure (i.e., after stent placement and post-dilation), quantitatively assessed by the angiographic core laboratory, demonstrated a mean residual stenosis of $11.7 \pm 9.9\%$, and acute lesion success (residual stenosis of $<30\%$) of 88.3% (68/77 lesions); in nine cases the post-procedure residual stenosis was $>30\%$ (Table 3). Acute procedural success (i.e., lesion success plus successful delivery and deployment of the stent with an absence of peri-operative complications) was 86.5% (64/74 patients/procedures). In addition to the nine cases where the residual stenosis was $>30\%$, one stent was not deployed to the intended location. No devices failed to deploy or malfunctioned during deployment.

Post-procedure follow-up and endpoint analyses

Follow-up data were available for 57 patients at 36 months (57/77; 74.0%); eight patients died, four patients withdrew from the study, six were withdrawn at the discretion of their physician, one patient was lost to follow up, and one was not treated because the lesion could not be crossed with a guidewire.

Analyses of the primary composite endpoint are summarized in Table 3. Using a proportional analysis at 12 months, freedom from TLF was 81.2% (56/69 patients; 95%CI 69.9%, 89.6%), significantly better than the derived PTA historical control of 60% ($p < 0.001$). TLF was composed of device- or procedure-related death (0%), target limb amputation (0%), TVR (10.1%; 7/69), or restenosis (8.7%; 6/69). Since patients were missing from the proportional analysis at 12 months, a K–M analysis was used to account for missing (i.e., censored) data. The K–M estimate of freedom from TLF at 365 days was 84.2% (95%CI 73.3%, 90.9%; Fig. 1). Time to TLF was evaluated (Cox regression) by medical risk factors (e.g., hypertension, obesity, smoking, diabetes), and none had a significant impact on the time to TLF. Freedom from TLF

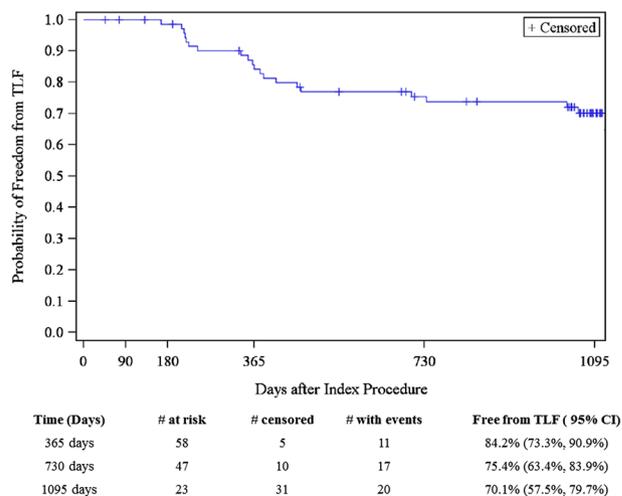


Fig. 1 Freedom from target-limb failure (TLF) through three years. The Kaplan–Meier curve represents the probability of freedom from TLF through 1095 days. The Kaplan–Meier table provides the number of patients at risk, patients censored (e.g., deaths and lost to follow up), and patients who experienced a TLF. The estimated probability of survival was 84.2% at 365 days, 75.4% at 730 days, and 70.1% at 1095 days.

was also compared (homogeneity tested by Chi-square) between various pre-specified subgroups (e.g., male/female, lesion length, and TASC classification); there were no major differences in TLF between groups.

Secondary outcomes are summarized in Table 4. Freedom from TLF was evaluated at 24 and 36 months; the proportion of patients free from TLF was 72.3% (47/65; 95%CI 59.8%, 82.7%) at 24 months and 66.1% (41/62; 95%CI 53.0%, 77.7%) at 36 months, and the estimated freedom from TLF by K–M analysis was 75.4% at 24 months (730 days) and 70.1% at 36 months (1095 days; Fig. 1). Primary patency was 71.0% (49/69) at 12 months, 71.0% (44/62) at 24 months, and 67.8% (40/59) at 36 months. Again, to account for the patients missing from the proportional analysis, a K–M analysis of primary patency was performed; estimates of primary patency were 69.5% at 12 months (365 days), 66.2% at 24 months (730 days), and 64.1% at 36 months (1095 days). Rutherford category was assessed at baseline through 36 months post-procedure. Per protocol, all patients had a Rutherford category 2–4 at baseline while 76.5% of patients were asymptomatic (category = 0) at 12 months, 78.0% at 24 months, and 63.2% at 36 months. Improvement from baseline in Rutherford category was 88.2% at 12 months, 94.9% at 24 months, and 94.7% at 36 months, with 94.7% of patients improving by at least one Rutherford category, 82.5% by at least two categories, and 24.6% by at least three categories at 36 months. Overall, there was a mean improvement in ABI at all time points during the follow-up period. The mean ABI at baseline was 0.73 ± 0.15 ;

Table 4 Secondary outcomes

		(95%CI)
Primary patency, ^a % (n/N)		
12 months	71.0 (49/69)	(58.8, 81.3)
24 months	71.0 (44/62)	(58.1, 81.8)
36 months	67.8 (40/59)	(54.4, 79.4)
36-month secondary patency, ^b % (n/N)	100.0 (56/56)	(93.6, 100.0)
Freedom from TLF, % (n/N)		
24 months	72.3 (47/65)	(59.8, 82.7)
36 months	66.1 (41/62)	(53.0, 77.7)
Freedom from target vessel and target lesion revascularization (TVR/TLR), % (n/N)		
12 months	89.7 (61/68)	(79.9, 95.8)
24 months	81.0 (51/63)	(69.1, 89.8)
36 months	77.4 (48/62)	(65.0, 87.1)
36-month freedom from TVR/TLR (K–M analysis), %	79.5	(67.8, 87.3)
Mean improvement in Rutherford categories from baseline, ^c % (n/N)		
12 months	88.2 (60/68)	(78.1, 94.8)
24 months	94.9 (56/59)	(85.9, 98.9)
36 months	94.7 (54/57)	(85.4, 98.9)
Improvement by ≥ 1 category ^d	94.7 (54/57)	(85.4, 98.9)
Improvement by ≥ 2 categories	82.5 (47/57)	(70.1, 91.3)
Improvement by ≥ 3 categories	24.6 (14/57)	(14.1, 37.8)
Mean improvement in ankle–brachial index (ABI) from baseline, mean \pm SD		
12 months	0.17 \pm 0.14	
24 months	0.18 \pm 0.16	
36 months	0.18 \pm 0.16	
Improvement by $\geq 0.10^e$	70.2 (40/57)	(56.6, 81.6)
Improvement by ≥ 0.15	52.6 (30/57)	(39.0, 66.0)
Physical function score (SF-36)		
12-month mean change from baseline, $\bar{x}\pm$ SD	7.3 \pm 16.2	
24-month mean change from baseline	7.0 \pm 16.6	
36 month mean change from baseline	8.2 \pm 16.7	
Physical component summary (SF-36)		
12-month mean change from baseline, $\bar{x}\pm$ SD	7.4 \pm 14.8	
24-month mean change from baseline	6.6 \pm 16.9	
36 month mean change from baseline	9.4 \pm 14.2	

^aPrimary patency was defined as freedom from target lesion restenosis (luminal narrowing of $\geq 50\%$) and/or target lesion revascularization (TLR). A $\geq 50\%$ stenosis was determined by angiography, a DUS-derived peak systolic velocity ratio (PSVR) ≥ 2.5 , or an abnormal DUS wave pattern determined by the DUS core laboratory.

^bSecondary patency was defined as patency independent of whether or not re-established via an endovascular procedure following restenosis or occlusion. Loss of secondary patency was defined as permanent loss of blood flow or surgical bypass of the vessel.

^cAll patients had a Rutherford category 2–4 at baseline. Mean improvement from baseline of at least one Rutherford category at 12, 24, and 36 months.

^dImprovement by the number of Rutherford categories at 36 months.

^eImprovement in ABI of greater than or equal to 0.10 or 0.15 at 36 months.

the mean ABI was 0.91 ± 0.15 at 12 months, 0.92 ± 0.15 at 24 months, and 0.93 ± 0.14 at 36 months. The mean change from baseline at 12 months was 0.17 which was maintained through 36 months (mean change 0.18). At 36 months, 70.2% of patients had an improvement from baseline ABI of ≥ 0.10 , and 52.6% had an improvement of ≥ 0.15 . Quality-of-life was measured using the SF-36 (v2). The mean physical function score at baseline was 25.4 ± 18.0 , while at 12 months the physical function

score improved to 32.2 ± 21.4 and at 36 months was 35.2 ± 18.9 (a sustained mean change of 7.0–8.2 points).

Seven patients had target-vessel and/or target-lesion revascularizations (TVR/TLR; 10.3%) through 12 months, and 14 patient had TVR/TLR through 36 months (22.6%). Patients were treated based on clinical symptoms and lesion morphology; all lesions were classified as TASC A–C, and were successfully treated endovascularly.⁷⁾ Seven patients had an additional stent placed (11 stents) while

the remaining patients received repeat PTA or additional endovascular therapy (e.g., laser atherectomy). The mean residual stenosis following the revascularization procedure was $13.6 \pm 15.2\%$. No patients received a surgical bypass. The proportion of patients free from TVR/TLR was 89.7% (61/68) at 12 months and 77.4% (48/62) at 36 months, while the estimated freedom from TVR/TLR based on K–M analysis was 90% at 12 months (365 days), 82.7% at 24 months (730 days), and 79.5% at 36 months (1095 days).

Anterior-posterior and lateral radiographs were analyzed by the core laboratory at 1, 6, 12, 24, and 36 months. Three stent fractures were noted in three patients through 36 months (3.7% of 81 stents). Two of the fractures were classified by the core laboratory as type 1 (i.e., single-strut fracture) and one as type 4 (i.e., fracture with mal-alignment of components).²³⁾ The type 4 fracture was noted at the 30-day follow up, and occurred in a stent that was severely elongated at the time of deployment (i.e., $\geq 150\%$ of the labeled stent length); restenosis was reported and adjudicated as possibly related to the device or procedure, and two additional non-study stents were placed. One type 1 fracture was noted at 6 months and a second was reported at 12 months; no device- or procedure-related adverse events were reported in the two patients with type 1 fractures. Freedom from stent fracture was estimated at 95.8% (K–M analysis) at 12 months, and remained the same at 24 and 36 months.

A total of 353 adverse events were reported in 70 patients. The most frequently reported adverse events included vascular disorders (28.4%), peripheral artery restenosis (25.7%), cardiac disorders (21.6%), and renal and urinary disorders (16.2%). No MAEs were reported within 30 days of the procedure. A stroke was reported at 12 months, and two additional strokes were reported through 36 months. No MAEs were adjudicated as related to the device or procedure. Twelve serious adverse events were determined by the medical adjudicator to be possibly related to the device and one related to the procedure; all were due to peripheral vascular restenosis. Eight patients died through the 36-month follow up; one death was due to myocardial ischemia, two patients committed suicide, two died from cancer-related symptoms (i.e., lung neoplasm and esophageal carcinoma), two died from infection, and one death was reported as a result of syncope and then sudden death. All patient deaths were reviewed by the medical adjudicator, and no deaths were considered to be related to the device or the procedure.

Discussion

The impact of race on outcomes following stent placement in the femoropopliteal arteries is not well established.²⁴⁾

The Asian cohort in most prospective international trials is small, often less than 1%,^{10,13,14)} while other data come mainly from retrospective database reviews.^{25–27)} RELIABLE was the first prospective, multicenter controlled trial of LifeStent Solo in an entirely Japanese patient population; the results compared favorably to an OPG derived from the prospective, randomized, multicenter RESILIENT trial using a predicate stent system in a non-Japanese patient population.^{10,11)} In the current trial, the stent was delivered to the intended treatment location 99% of the time; acute lesion and procedural success were high (88% and 87%, respectively), while residual stenosis after stent placement was low (on average 12%). Freedom from reintervention was 90% at one year, and there was a mean improvement in clinical parameters (e.g., Rutherford category, ABI, and quality-of-life) that was sustained through three years.

The primary endpoint, freedom from TLF, was a quantitatively-derived, independently-analyzed composite of stent performance and safety, consisting of device- or procedure-related death, target limb amputation, TVR, and restenosis of $\geq 50\%$ with worsening clinical symptoms or $\geq 70\%$ (PSVR ≥ 3.5) without symptoms. The 12-month freedom from TLF—81.2% (56/69 patients)—was superior ($p < 0.001$) to the historical control of 60% derived from the RESILIENT trial. Also at one year, primary patency which included TLR and all restenoses whether symptomatic or not, was 71.0%. Primary patency, although not hypothesis tested, was numerically better than the OPG derived from RESILIENT, and both freedom from TLF and loss of primary patency were better than the historical control established by the VIVA physicians for bare-metal stent patency at one year (66%).²³⁾

Results from the current trial compared favorably to other multicenter studies using bare-metal stents as a primary treatment for obstructive lesions of the SFA or proximal popliteal artery. Vardi and colleagues,²⁸⁾ in a meta-analysis of data from 11 prospective trials, reported a 12-month primary patency rate of 71.6% (95%CI 66.4%, 76.7%) while Rocha-Singh et al.,²⁹⁾ in a meta-analysis of patient-level data (999 patients) from six prospective trials, reported a 12-month primary patency rate of 69.8% and an overall TLR rate of 13.1%. Results from RELIABLE were also similar to data reported for Japanese patients treated with self-expanding, bare-metal stents for obstructive femoropopliteal lesions. Suzuki and colleagues, in a retrospective analysis of 432 Japanese patients treated with the S.M.A.R.T. Control stent (Cordis Corp., Fremont, CA, USA), observed a primary patency rate of 66% at three years compared to primary patency in the current trial of 67.8% at three years.²⁵⁾ In a retrospective comparison of over 1500 Japanese patients treated with either the S.M.A.R.T. Control stent or the

Misago stent (Terumo Corp., Tokyo, Japan), Suzuki et al. reported two-year K–M estimates of primary patency of 67% and 55%, respectively, compared to 66.2% in the current study (K–M analysis at 730 days).²⁶⁾ Ohki and colleagues reported the one-year outcomes from the Asian patient subset (50 Japanese and 10 Taiwanese and Korean patients) of the prospective, multicenter OSPREY study (Misago stent).¹⁶⁾ Clinically-driven TLR in the Asian subgroup at 12 months was 11.7%, compared to a 10.6% rate of TVR/TLR in the RELIABLE trial.

Biomechanical characteristics of the SFA, such as external compression and longitudinal axis deformation, have been well characterized.¹⁸⁾ Early-generation SFA stents were not designed to withstand the extreme mechanical loading conditions of the SFA, with stent fracture rates, often associated with restenosis, reported as high as 28%.^{30,31)} Studies using more flexible stents designed to accommodate to the tortuous anatomy of the SFA, have shown reductions in stent fractures compared to first-generation stents with fracture rates ranging from 0–8%.^{10,13,14,16,17)} Laird et al. reported nine stent fractures in the RESILIENT trial at 12 months (3.1% of 291 stents examined); the angiographic core laboratory determined that four of the nine stent fractures were single-strut, type 1 fractures and five were full longitudinal, type 4 fractures.¹⁰⁾ Schulte et al. reported 15 fractures in the MISAGO 2 study (3.1% of 484 stents examined); 13 fractures were classified as type 1 and two as type 2.³²⁾ Ohki et al. reported two stent fractures in the overall OSPREY study (0.5% of 383 stents examined) with no fractures reported in the Asian sub-group (60 patients) through 12 months.¹⁶⁾ In the present study, three stent fractures were reported at 12 months. Two fractures were classified by the core laboratory as type 1 and one as type 4; the type 4 fracture was noted early in the trial (30-day follow), and occurred in a stent that was elongated at the time of deployment. The single-strut fractures were reported at 6 months and 12 months, with no additional fractures reported through 36 months. The freedom from stent fracture was 95.8% at three years.

Possibly more important to patient function than the anatomical and quantitative endpoints, clinical criteria improved from baseline to post-stent placement, and were sustained through 36 months. A total of 82.5% of patients improved from baseline by at least two Rutherford categories and 52.6% had an improvement of ≥ 0.15 in ABI at 36 months. The mean physical function score (SF-36) improved by a mean of 7.0 points at one year that was sustained and slightly increased through 36 months (8.2 points). No MAEs were reported within 30 days of the procedure which more than met the 30-day criteria of 12% set in the VIVA OPG.²³⁾ Eight patients died through three years; but all MAEs and patient deaths

were reviewed by the medical adjudicator, and none were considered to be related to the device or the procedure.

Limitations

RELIABLE was prospective; but patients were not randomized, nor was there a concurrent control. Patient and lesion characteristics in controlled clinical trials often do not match those in standard clinical practice. The majority of lesions in the current study were of moderate length (on average 8 cm), and were classified mainly as stenoses and as TASC A and B. Patients with foot ulcers, renal failure and on dialysis, and those with lesions longer than 150 mm were excluded from the current study. The study demonstrated superiority to a historical control derived from a prospective, controlled, randomized, multicenter trial, but it was not designed to provide guidance regarding the optimal use of bare-metal stents in standard clinical practice.

Conclusion

RELIABLE was the first prospective, controlled trial of the LifeStent Solo, a “second generation” self-expanding stent, to treat obstructive lesions in the SFA in Japanese patients with severe claudication and ischemic rest pain. The composite endpoint (TLF) was superior to an historical control at one year ($p < 0.001$); revascularization rates were low and clinical outcomes improved following the procedure with the improvements sustained through three years. Results from post-hoc comparisons to numerous prospective, controlled bare-metal stent trials in non-Japanese patients, and to various retrospective and prospective series with Japanese patients, were similar to the results of the current trial. These comparisons were observational only, and must be viewed as exploratory or hypothesis generating. Outcomes from the current study of the LifeStent Solo Vascular Stent in a controlled group of Japanese patients are encouraging; additional studies, directly comparing the use of bare-metal stents in patients with more complex lesions (e.g., TASC C and D), and use with other current therapies, such as drug-coated balloons, are warranted.

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Clinical Trial Registration

<https://clinicaltrials.gov/ct2/show/NCT01746550>

Disclosure Statement

MN and KK report no conflicts of interest. RAS is a paid employee of the study sponsor, Becton, Dickinson and Company. MRJ reports stock ownership in Embolitech and Primacea.

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Analysis: MRJ, RAS, KK

Investigation: MN, KK

Writing: MN, RAS, MRJ

Funding acquisition: all authors

Critical review and revision: all authors

Final approval of the article: all authors

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