One-year outcomes of the U.S. and Japanese regulatory trial of the Misago stent for treatment of superficial femoral artery disease (OSPREY study)

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Objective: **The purpose of this study was to assess the safety and efficacy of the Misago stent (Terumo Corp, Tokyo, Japan) in occlusive and stenotic superficial femoral artery (SFA) disease.**

Methods: **The safety and efficacy of the Misago SFA stent were evaluated prospectively in this initial collaboration trial between Japan and the United States. Because this trial enrolled patients mainly from Japan and the United States and because there is a question as to whether a race difference exists in SFA stent performance, the race difference on outcome was also analyzed. In addition, results were compared with a prior SFA stent trial.**

Results: **The Misago stent was implanted in 261subjects with TransAtlantic Inter-Society Consensus (TASC) type A and type B SFA lesions (201 subjects in the United States, 50 in Japan, 9 in Taiwan, 1 in South Korea). The mean age of the patients was 69.3 ± 10.0 years, and the mean lesion length was 83.8 ± 41.3 mm. The overall 12-month primary patency rate and clinically driven target lesion revascularization were 82.9% and 13.0%, respectively. Regional differences within the Occlusive/Stenotic Peripheral Artery Revascularization Study (OSPREY) and outcomes between U.S. and Asian patients were similar, including primary patency (82.9% vs 83.0%; $P = .889$), clinically driven target lesion revascularization (13.4% vs 11.7%; $P = .829$), stent fracture rate (1.3% vs 0.0%; $P = 1.000$), and stent thrombosis rate (0.5% vs 0.0%; $P = 1.000$).**

Conclusions: **OSPREY 12-month data showed satisfactory outcome of the Misago stent for the treatment of TASC type A and type B SFA lesions and appears to be comparable to recent stent trials. In addition, the lack of difference in outcome among races supports the value of international trials. (J Vasc Surg 2016;63:370-6.)**

Stenting has become the most commonly performed procedure for the treatment of superficial femoral artery (SFA) occlusive disease owing to the improved performance of advanced stent technology, although questions remain about ideal stent design.[1] Because the SFA elongates, flexes, and twists, the implanted stent is subjected to harsh mechanical stress, and therefore stent fracture remains an important clinical issue.[2-4] In addition, recurrent stenosis secondary to neointimal hyperplasia, which is partially due to the strong radial force applied to the vessel wall by the stent, is another unsolved problem.[5,6] The Misago stent (Terumo Corp, Tokyo, Japan), a nickel-titanium bare-metal stent featuring a linkless structure that minimizes the mechanical stress at the link site, may reduce the rate of fracture. The stent showed high durability in a bench test compared with pre-existing SFA stents.[7] Furthermore, MISAGO 1 and MISAGO 2 trials, which were performed in Europe, demonstrated low fracture and in-stent restenosis rates and confirmed the advantages of the Misago design in a clinical setting.[8-10] The Occlusive/Stenotic Peripheral Artery Revascularization Study (OSPREY) is an international trial designed to evaluate the safety and efficacy of the Misago stent for the treatment of SFA disease in both the United States and Japan.

METHODS

Study device. The Misago self-expanding stent has a spineless linkage to avoid concentration of mechanical stress that leads to stent fracture. The Misago self-expanding stent system consists of a flexible nitinol self-expanding stent premounted on the distal end of a 6F rapid exchange monorail delivery catheter system.

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A full list of investigators can be found in the Appendix (online only).

The OSPREY study was sponsored by Terumo Corporation, Tokyo, Japan.

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Study design. OSPREY is an international, multicenter, single-arm, nonrandomized, prospective clinical trial. Subjects underwent an SFA stent procedure using the Misago peripheral self-expanding stent. The efficacy end points were evaluated immediately after the procedure (adverse events only) and at 30 days, 6 months, and 12 months. Efficacy was also evaluated at 24 and 36 months on the basis of the Rutherford classification, ankle-brachial index (ABI), quality of life (QoL) questionnaires, and radiographs for evaluation of stent fractures. The safety end points were evaluated immediately after the procedure, at 30 days, and at 6, 12, 24, and 36 months.

Inclusion and exclusion criteria. The study was approved by each local Institutional Review Board. All subjects signed a written informed consent. Major inclusion criteria were the following: 18 years and older, Rutherford classification category 2 to 4, resting ABI of <0.9 or abnormal exercise ABI, de novo lesion, reference vessel diameter of ≥ 4.0 mm and ≤ 7.0 mm, and target lesion length of ≥ 40 mm and ≤ 150 mm. Major exclusion criteria were previous bypass surgery or stenting in the target SFA or distally, angiographic evidence of acute thrombus, subjects with acute or chronic renal dysfunction or estimated glomerular filtration rate <30 mL/min, severe calcification or excessive tortuosity at the target lesion (determined by the operator), and subjects unable to tolerate anticoagulation therapy or antiplatelet therapy.

Preprocedural evaluation. The preprocedural evaluations included physical examination, medical history including peripheral arterial disease risk factors, medications, vital signs, complete blood count with platelet count, electrolyte panel, Doppler ultrasound (of the target limb), QoL questions (36-Item Short Form Health Survey, Walking Impairment Questionnaire), ABI, Rutherford classification, and angiography. These were assessed and performed within 30 days before the procedure. On the basis of the preprocedural angiogram, the investigator confirmed intraoperative criteria, including lesion morphology, assessment of inflow disease, and runoff vessels.

End points. The primary safety end point was defined as freedom from major adverse events (MAEs) within 30 days of the procedure that included target lesion revascularization (TLR), amputation of the treated limb, and death. The primary efficacy end point was defined as primary stent patency rate at 12 months by core laboratory-read duplex ultrasound (DUS). Patency was defined by a peak systolic velocity ratio (PSVR) <2.5 and absence of TLR through 12 months after the procedure. Secondary efficacy end points included the following: (1) technical success (defined as successful delivery of the stent with adequate lesion coverage); (2) procedural success (attainment of $<30\%$ residual stenosis of the target lesion and absence of periprocedural complications defined as death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in the target limb, or thrombosis of the target vessel); (3) ABI; (4) clinical success (relief or improvement of baseline symptoms as measured by the Rutherford category for chronic limb ischemia) at 30 days compared with baseline or sustained Rutherford category (without increase of one or more in the Rutherford category) at 12 months after the procedure compared with 30-day Rutherford classification; (5) clinically driven TLR (defined as $>50\%$ stenosis with worsening symptoms or $>70\%$ stenosis without symptoms); (6) patency of the target vessel based on DUS (as determined by the PSVR <2.5 and absence of TLR) through 12 months after the procedure; and (7) QoL measurement (36-Item Short Form Health Survey and the Walking Impairment Questionnaire) and adverse events. Detailed analyses of these secondary end points will be published in a separate manuscript.

Study organization. The OSPREY study was sponsored by Terumo Corporation. All the data were verified with the source document to ensure reliability of the data. The Clinical Events Committee (CEC) is composed of physicians who are interventional or noninterventional cardiologists not participating in this study and who are not affiliated with Terumo Corporation. All data were adjudicated by the CEC. Evaluation and analysis of all angiograms and simple radiographs were performed by the Beth Israel Deaconess Medical Center Angiographic Core Laboratory (Boston, Mass), and evaluation of the DUS images was performed by Vascular Ultrasound Core Laboratory (Boston, Mass). These core laboratories were independent from Terumo Corporation. Clinlogix, LLC (Ambler, Pa) and PAREXEL (Shatin New Territories, Hong Kong) were involved as Clinical Research Organizations in the United States, Taiwan, and South Korea. Clinlogix (United States), PAREXEL (Taiwan and Korea), and Terumo (Japan) were responsible for site management and source document verification of all data in each country. NAMSA (Minneapolis, Minn) was responsible for statistical analysis of this study.

Statistical analysis. Statistical analysis included summary statistics of mean, standard deviation, standard error, median, and range for continuous parameters and frequency and percentage for categorical parameters. Regional differences were compared with the χ^2 test or Welch t-test. Statistical significance was defined as $P < .05$; there were no adjustments for multiplicity. Kaplan-Meier estimates for 12-month patency and freedom from TLR are given at 360 days after the procedure. Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC). To analyze whether regional difference exists, subanalyses were performed comparing U.S. and Asian (Japan, Taiwan, and South Korea) subgroups.

RESULTS

Patient and lesion background. The OSPREY study enrolled a total of 261 subjects who underwent SFA stenting with the Misago stent between April 2010 and July 2012. Baseline characteristics of the patients are shown in Table I. The mean age of the patients was 69.3 $\pm$ 10.0 years, and 64.8% of the cohort was male. Approximately 91% of patients presented with claudication (Rutherford category 2-3) and 9% with critical limb ischemia (Rutherford category 4-6); the mean ABI was 0.7 $\pm$ 0.1. Regional breakdown of the subjects is as follows: 201 from the United States; 50 from Japan; and 10 additional subjects from Taiwan and South Korea. Preprocedure risk factors included diabetes mellitus (47.9%),

Table I. Baseline characteristics of patients

No. of patients	261
Age, years, mean ± SD	69.3 ± 10.0
Gender, male	64.8 (169/261)
Race/ethnicity	
White	69.0 (180/261)
Asian	23.0 (60/261)
Black	6.9 (18/261)
Hispanic	1.1 (3/261)
Previous vascular interventions	35.2 (92/261)
Diabetes mellitus	47.9 (125/261)
Arterial hypertension treated with medication	85.1 (222/261)
Hyperlipidemia	87.0 (227/261)
Smoking history	
Yes, current	42.1 (110/261)
Yes, previous	40.6 (106/261)
No	15.7 (41/261)
Unknown	1.5 (4/261)
Amputations	1.1 (3/261)
Rutherford classification	
0	0.00 (0/261)
1	0.00 (0/261)
2	48.30 (126/261)
3	47.10 (123/261)
4	4.60 (12/261)
5	0.00 (0/261)
6	0.00 (0/261)
ABI, mean ± SD	0.7 ± 0.1

ABI, Ankle-brachial index; *SD,* standard deviation.
Values are reported as % (n/N) unless otherwise indicated.

Table II. Baseline characteristics of lesions

Location	
Left	49.0 (128/261)
Right	51.0 (133/261)
Arterial segment	
Proximal SFA	12.3 (32/261)
Middle SFA	53.6 (140/261)
Distal SFA	33.3 (87/261)
Other	0.8 (2/261)
Lesion length, mm	83.8 ± 41.3
Reference vessel diameter, mm	5.1 ± 1.0
Minimum lumen diameter, mm	1.1 ± 0.9
Eccentricity	
Concentric	59.8 (156/261)
Eccentric	40.2 (105/261)
Calcification	
None	33.3 (87/261)
Moderate	35.2 (92/261)
Severe	31.4 (82/261)
Ulceration	20.7 (54/261)
Aneurysmal	1.1 (3/261)
Preprocedural TIMI flow[a]	
0	24.1 (63/261)
1	1.9 (5/261)
2	0.8 (2/261)
3	67.8 (177/261)
NA	5.4 (14/261)
TASC II classification	
A	55.6 (145/261)
B	37.5 (98/261)
C	6.9 (18/261)
D	0.0 (0/261)
Inflow tract stenosis	
<50%	60.9 (159/261)
>50%	8.8 (23/261)
NA	30.3 (79/261)
Distal runoff vessels	
1	27.2 (71/261)
2	32.2 (84/261)
3	20.3 (53/261)
NA	13.4 (35/261)

NA, Not available; *SFA,* superficial femoral artery; *TASC II,* TransAtlantic Inter-Society Consensus II.
Continuous data are presented as mean ± standard deviation, and categorical data are presented as % (n/N).
[a]Thrombolysis in Myocardial Infarction (TIMI) 0 flow refers to the absence of any antegrade flow beyond the lesion. TIMI 1 flow is faint antegrade blood flow beyond the lesion, with incomplete filling of the distal vasculature. TIMI 2 flow is delayed or sluggish antegrade flow with complete filling of the distal vasculature. TIMI 3 is normal flow.

hypertension (85.1%), hyperlipidemia (87.0%), and smoking history (82.7%). Baseline characteristics of the lesions are shown in Table II. The mean lesion length was 83.8 ± 41.3 mm, mean reference vessel diameter was 5.1± 1.0 mm, 31.4% had severe calcified lesion, and total occlusion was encountered in 24.1%.

Patient follow-up. Follow-up data were available for 240 patients (92.0%) at 12 months. The 12-month DUS data were available for 189 patients because 23 patients had DUS performed outside of the window period and 28 patients had no PSVR values (Fig 1).

Efficacy and safety results. The primary safety and efficacy end points are summarized in Table III. The freedom from MAEs at 30 days was 99.2%, and Kaplan-Meier survival estimate of primary patency at 12 months was 82.9% (Fig 2). The secondary efficacy and safety end points are summarized in Table IV. Clinically driven TLR through 12 months was 13.0%. MAEs within 30 days of the procedure were as follows: TLR, 2 of 261 (0.8%); amputation, 0 of 261 (0.0%); and death, 0 of 261 (0.0%). MAEs through 12 months were noted in 42 of 261 subjects (16.1%), including TLR in 34 (13.0%), amputation in 0 (0.0%), and death in 9 (3.4%). The cause of death in the nine patients was cardiac in 3, pulmonary in 2, lung cancer in 1, psychiatric in 1, septic shock in 1, and death of unknown cause in 1. These deaths were reviewed by the independent CEC and were determined not to be related to the Misago stent or the placement procedure. Three stents were reported as fractured by the investigator. However, one stent fracture was noted to have occurred secondary to an atherectomy procedure that was performed for the treatment of recurrent stenosis. As a result, stent fracture evidenced by plain radiography was present in two of 383 stents (0.5%) evaluated at 12 months. Thrombosis of the target vessel was observed in 1 of 261 (0.4%). Any device-related adverse event was noted in 51 of 261 subjects (19.5%).

Regional subanalysis. Subanalysis was performed to evaluate the presence or absence of regional differences in terms of characteristics of the patients and lesions as well as in outcome. When patient and lesion background was analyzed, there were no statistically significant differences between the United States and Asia, except rate of

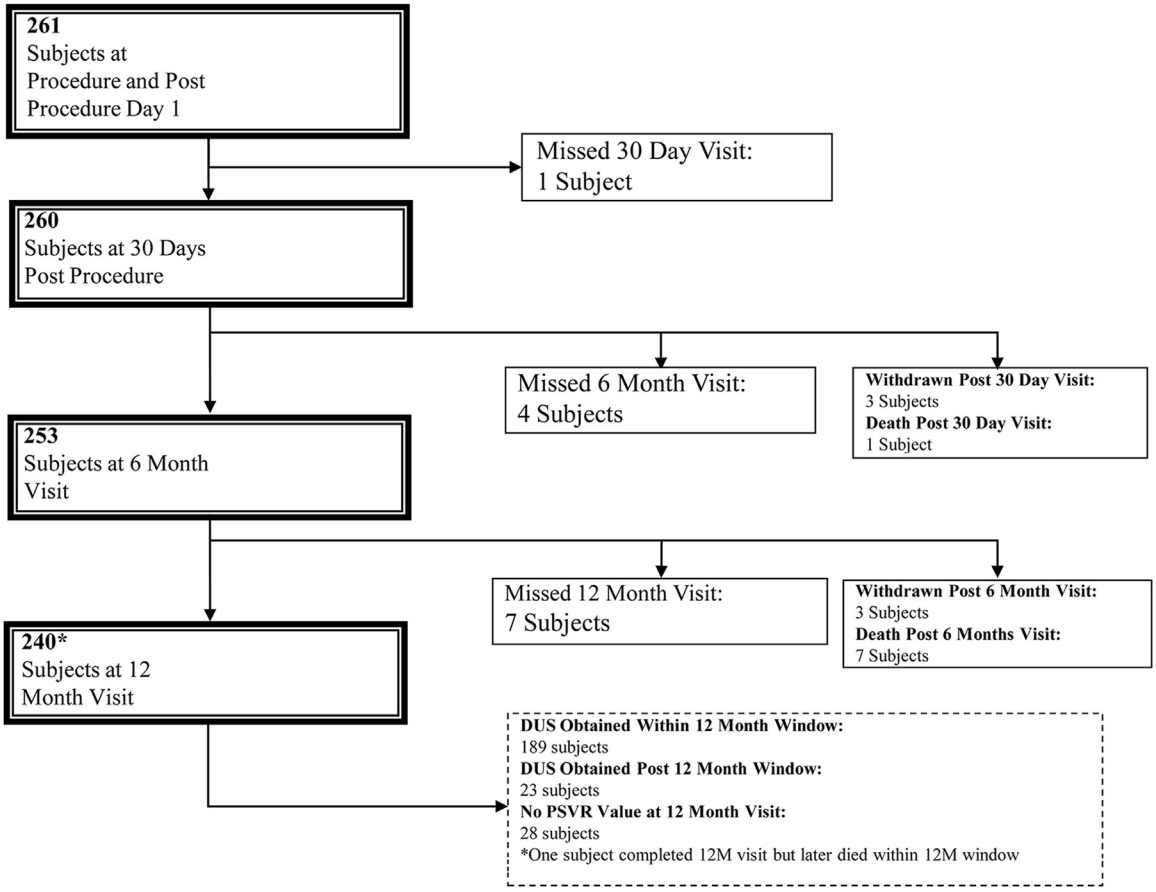

Fig 1. Flow chart of subject accountability. *DUS,* Duplex ultrasound; *PSVR,* peak systolic velocity ratio.

Table III. Primary safety and efficacy outcomes

	% (n/N)	*95% CL*
Primary safety end point		
Freedom from MAEs at 30 days	99.2 (259/261)	96.2, 100.0
Primary efficacy end point		
Primary patency at 12 months (flat rate)	69.9 (158/226)	63.6, 75.5
TLR through 12 months	13.0 (34/261)	9.4, 17.7
Primary patency at 12-month follow-up (Kaplan-Meier point estimate)	82.90	

CL, Confidence limit; *MAEs,* major adverse events; *TLR,* target lesion revascularization.

hyperlipidemia (United States, 92.0%; Asia, 70.0%; $P < .001$) and preprocedural Rutherford category (United States, 2.6 ± 0.6; Asia, 2.4 ± 0.6; $P = .033$; Table V). One-year outcome showed absence of significant difference between the United States and Asia for clinically driven TLR (United States, 13.4%; Asia, 11.7%; $P = .829$), stent fracture rate (United States, 0.9%; Asia, 0.0%; $P = 1.000$), and stent thrombosis rate (United States, 0.5%; Asia, 0.0%; $P = 1.000$; Table VI).

DISCUSSION

First-generation nitinol stent trials reported high fracture rates (10%-20%).[11,12] However, clinical trials using second-generation stents that had improved design have shown lower fracture rates ranging between 0.0% and 2.0%.[13-15] This is a meaningful advancement because stent fracture has been shown to be a significant risk factor for recurrent stenosis or reocclusion.[3,4] The Misago stent embraced the spineless linkage design because the concentration of mechanical stress occurred at the linkage point.[7] The advantage of this design in terms of stent durability was confirmed by preclinical bench testing. The Misago stent did not fracture even when 650,000-cycle stress was loaded, whereas other stents fractured after 60,000 cycles.[7] In addition, the rapid exchange system for stent delivery has been shown to reduce radiation exposure time, facilitates more rapid device exchanges, and allows more accurate stent deployment.

OSPREY 1-year results showed a patency rate of 82.9% and TLR of 13.0% despite the fact that the mean lesion length was >80 mm. These results appear favorable compared with recently approved bare-metal stents in the United States. The mean lesion lengths of the OSPREY trial, the STROLL study[13] (S.M.A.R.T. Vascular Stent System; Cordis Corp, Fremont, Calif), and the Complete SE

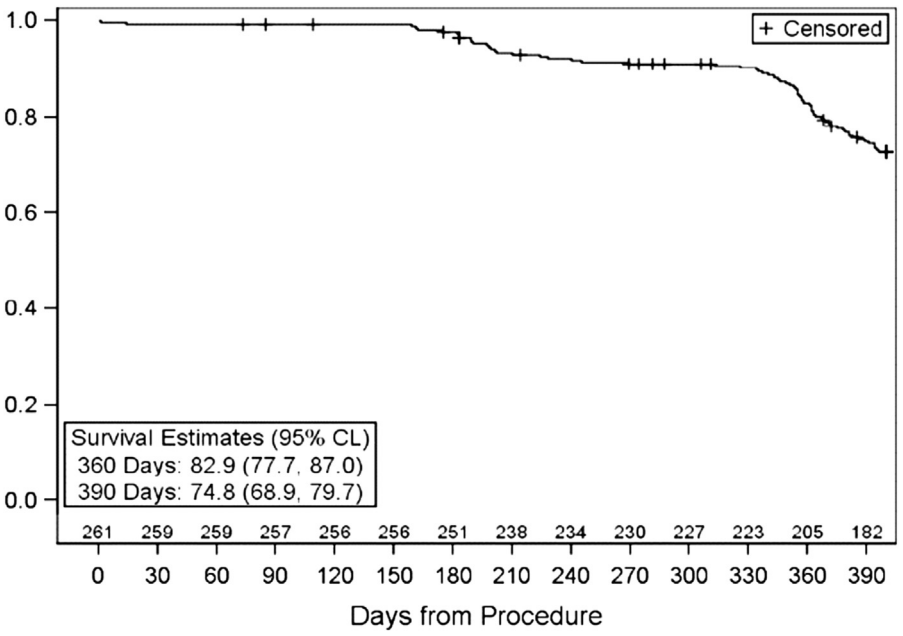

Fig 2. Kaplan-Meier primary patency within 12 months. Primary patency was considered lost if the stent occluded, target lesion revascularization (TLR) was met, or peak systolic velocity ratio (PSVR) ≥2.5 m/s was met. *CL*, Confidence limits.

multicenter trial[14] (Complete SE SFA stent; Medtronic Vascular, Santa Rosa, Calif) were 83.8 ± 41.3 mm, 77.3 ± 35.3 mm, and 60.7 ± 37.6 mm, respectively. TLRs were 13.0%, 12.6%, and 8.4%; primary patency rates were 82.9%, 81.7%, and 72.6%; and stent fracture rates were 0.5%, 2.0%, and 0.0%, respectively. Despite the fact that the OSPREY trial enrolled patients with longer lesions, the 12-month outcomes are comparable to if not better than those of other SFA stents. Zilver PTX (Cook Medical, Bloomington, Ind) is the only approved drug-eluting stent (DES) in United States for the SFA. The Zilver PTX randomized controlled trial (RCT)[15] had a mean lesion length of 65 ± 40 mm, 1-year TLR of 9.5%, primary patency rate of 83.1%, and stent fracture rate of 0.9%. Compared with the OSPREY trial, the lesion length of the Zilver PTX RCT was significantly shorter ($P < .001$) and 1-year outcomes were similar, keeping in mind that the PSVR cutoff for primary patency in the Zilver trial was <2.0. In the coronary domain, late stent thrombosis (LST) after DES implantation is of major concern,[16] and it is well known that the predictor of LST is the ratio of uncovered to total stent strut area.[17] Several investigators have reported that the uncovered (unhealed) region is observed frequently in patients with SFA treated with DES.[18] The 1-year thrombosis rate was 0.5% in the OSPREY trial and 2.6% in the Zilver PTX RCT. It is suggested that the DES in SFA also carries LST risk, and long-term dual antiplatelet therapy may be necessary in these patients.

The OSPREY study was part of the Harmonization By Doing (HBD) initiative, which represents an international effort to develop global clinical trials and to address regulatory barriers that may delay timely device approvals. The OSPREY study was selected as one of the two pilot projects intended to shorten the gap between product approvals by the medical regulatory boards within the United States (U.S. Food and Drug Administration) and Japan (Pharmaceuticals and Medical Devices Agency). The OSPREY study was planned to simultaneously confirm the safety and efficacy in U.S. and Japanese populations. The HBD initiative was first launched as a pilot project in 2003 and was publicly announced at the Japanese Circulation Society Meeting in March 2004. The primary goal of this initiative was to streamline the regulatory process for device approval, resulting in the introduction of novel and potentially lifesaving devices for patients in a timely fashion. HBD represents an effort to unite regulatory board approvals in the two countries. This combined effort could result in more robust clinical trial data and decrease the lag time between U.S. and Japanese regulatory approval as well as create an improved atmosphere of academic collaboration among major academic institutions in both countries, resulting in improved patient outcomes. Under this HBD initiative, OSPREY enrolled in the United States and in Asian countries, and about a quarter of the study population was Asian. In SFA disease, it is controversial whether cultural and racial difference between Western and Eastern populations may provide different results. However, this study and others have not detected regional differences.[19,20] OSPREY enrolled 201 U.S. patients and 60 Asian patients in a prospective manner. The results showed no significant differences between the two cohorts, and thus the OSPREY study

Table IV. Secondary outcomes

		95% CL
Technical success	100.0 (261/261)	98.3, 100.0
Successful delivery of stent at lesion site	100.0 (261/261)	98.3, 100.0
Stent deployed in lesion with adequate lesion coverage	100.0 (261/261)	98.3, 100.0
Procedural success	93.5 (244/261)	89.8, 96.0
ABI change from baseline to 30 days	0.3 ± 0.2	
ABI change from 30 days to 12 months	−0.1 ± 0.2	
Rutherford class sustained at 12 months from 30 days	80.2 (190/237)	74.6, 84.8
Clinically driven TLR through 12 months	13.0 (34/261)	9.4, 17.7
MAEs through 12 months	16.1 (42/261)	12.1, 21.1
TLR through 12 months	13.0 (34/261)	9.4, 17.7
Amputation through 12 months	0.0 (0/261)	0.0, 1.7
Deaths through 12 months	3.4 (9/261)	1.7, 6.5
Stent fracture through 12 months	0.5 (2/383)	0.0, 1.8
Thrombosis of target vessel	0.4 (1/261)	0.0, 2.4
Any device-related adverse event	19.5 (51/261)	15.2, 24.8
SF-36 change from baseline to 30 days	5.31 ± 8.44	
SF-36 change from 30 days to 12 months	3.60 ± 9.39	
WIQ change from baseline to 30 days	28.58 ± 32.31	
WIQ change from 30 days to 12 months	26.65 ± 36.89	

ABI, Ankle-brachial index; *CL,* confidence limit; *MAEs,* major adverse events; *SF-36,* 36-Item Short Form Health Survey; *TLR,* target lesion revascularization; *WIQ,* Walking Impairment Questionnaire.
Continuous data are presented as mean ± standard deviation, and categorical data are presented as % (n/N).

Table V. Regional subanalysis of patient background and lesion characteristics

	United States	*Asia*	P *value*
Diabetes mellitus	43.8 (88/201)	61.7 (37/60)	.018[a]
Hypertension treated with medication	87.6 (176/201)	76.7 (46/60)	.081[a]
Hyperlipidemia	92.0 (185/201)	70.0 (42/60)	.000[a]
Smoking history	85.6 (172/201)	73.3 (44/60)	.033[a]
Rutherford score	2.6 ± 0.6	2.4 ± 0.6	.025[b]
ABI	0.7 ± 0.2	0.7 ± 0.1	1.000[b]
Lesion length, mm	84.9 ± 41.9	80.2 ± 39.6	.428[b]

ABI, Ankle-brachial index.
Continuous data are presented as mean ± standard deviation, and categorical data are presented as % (n/N).
[a]χ^2 test.
[b]Welch *t*-test.

confirms the absence of regional difference and supports the rationale of multinational study of the SFA lesion, recognizing that the number of Asian patients was relatively small and the U.S. patients were not homogeneous. As a result of this HBD, the Misago stent gained approval in Japan and the United States on January 14, 2015 (December 6, 2012, for bailout stenting), and May 22, 2015, respectively. When one considers the fact that approval for the first stent graft for abdominal aortic aneurysm and for the first stent for the SFA in Japan was 8 years and 5 years behind U.S. approval, the effectiveness of the HBD in minimizing the device lag problem is obvious. Furthermore, the Misago stent is the first "made in Japan" Food and Drug Administration class III device to gain approval in the United States, and this was made possible only through this HBD effort, proving the merit of this scheme.

Table VI. Regional subanalysis of 12-month results

	United States	*Asia*	P *value*
Clinically driven TLR	13.4 (27/201)	11.7 (7/60)	.829[a]
Stent fracture	1.7 (3/178)	0.0 (0/56)	1.000[a]
Stent thrombosis	0.5 (1/201)	0.0 (0/60)	1.000[a]

TLR, Target lesion revascularization.
Values are reported as % (n/N).
[a]χ^2 test.

CONCLUSIONS

OSPREY 12-month results showed satisfactory outcome of the Misago stent for the treatment of SFA lesions up to 140 mm and appear to be comparable to DES experience. In addition, the lack of difference in outcome among races supports the value of international SFA stent trials.

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AUTHOR CONTRIBUTIONS

Conception and design: TO
Analysis and interpretation: TO
Data collection: TO, JA, HY, YK, MJ, JP, GP
Writing the article: TO, YK
Critical revision of the article: TO, JA, HY, YK, MJ, JP, GP
Final approval of the article: TO, JA, HY, YK, MJ, JP, GP
Statistical analysis: TO
Obtained funding: TO
Overall responsibility: TO

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APPENDIX (online only).

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