The Harmonization By Doing Initiative and the OSPREY Trial

An update on the evaluation of the Misago stent as part of the Harmonization By Doing regulatory collaboration between the United States and Japan.

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The methods of treating superficial femoral artery (SFA) disease have evolved during the past 20 years, from bypass surgery to angioplasty and, more recently, the placement of stents and use of other devices in appropriate candidates. Risk factor modification and exercise therapy remain mainstays of care, but in many patients, additional procedures are needed. Improvements in technology continue to enhance our ability to treat these patients, and importantly, advancements are also being made in our means of evaluating the devices and methods used in this challenging anatomy.

Just as interventionists have honed their techniques and industry has worked to provide devices that are better suited for treating SFA disease, clinical investigators and national regulatory bodies have also worked to enhance the clinical trials by which treatment modalities are tested. The OSPREY (Occlusive/Stenotic Peripheral Artery Revascularization Study) trial, part of the international Harmonization By Doing (HBD) initiative, is one such effort, evaluating the use of the Misago stent system (Terumo Interventional Systems, Somerset, NJ) in the SFA. This article presents the goals of the HBD initiative and that of the OSPREY trial, as well as the design characteristics and experience to date using the Misago stent.

THE HBD INITIATIVE

The HBD initiative represents an international effort to develop global clinical trials and address regulatory barriers that may delay timely device approvals.[1] This undertaking has been achieved through a cooperative process between the United States and Japan. Current regulatory participants in this endeavor include the US Food and Drug Administration, Japan's Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labor, and Welfare, as well as its review agency, the Pharmaceutical and Medical Device Agency. Additional participants are the Duke Clinical Research Institute, and various members of the Japanese academic community and the United States/Japanese medical device industry.

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The HBD initiative was first launched as a pilot project in 2003 and was publicly announced at the Japan Circulatory Society meeting in March 2004. A think tank meeting held in Tokyo in December 2005 introduced the tenets of the HBD initiative, which included building a robust clinical database by pooling the information from various countries, analyzing clinical practices and device use to assess what differences may serve as possible obstacles for futures studies, and clarifying basic rules of study development and implementation that will lead to better international collaboration.

Simply stated, the main goal of this initiative is to streamline the regulatory process for device approval, thereby resulting in the introduction of novel and

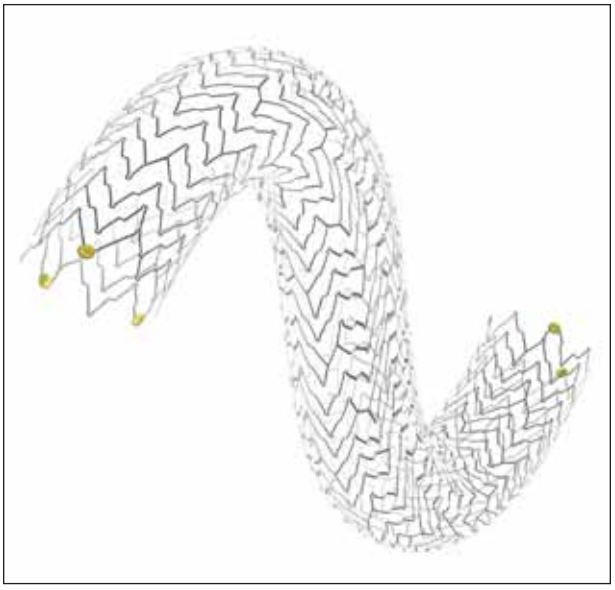
potentially life-saving devices for patients in a timely fashion. By developing a parallel model for study design (with approvals by different regulatory bodies, which have been previously mentioned), the possibility of reducing study redundancies and costs, as well as time delays in sequential trials, is greatly enhanced.

The United States and Japanese regulatory bodies share a number of similar concerns when structuring and implementing clinical trials. Although there are divergences in clinical practice between the two countries (eg, lack of clopidogrel use in patients with peripheral vascular disease in Japan), there has been a firm recognition that to bring forth novel and innovative treatments in a timely fashion, the study of various populations will be needed, as this method could increase the sample size population quite rapidly. This combined effort could not only result in more robust clinical trial data and decrease the lag time between United States and Japanese regulatory approval, but it could also create an improved atmosphere of academic collaboration among major academic sites in these countries, hopefully resulting in improved patient outcomes.

THE OSPREY TRIAL

Investigation of the Misago stent in the United States and Japan has recently begun with the start of the OSPREY trial.[2,3] This trial is unique because it will be simultaneously enrolling patients in the United States and in Japan. Referred to as "Medical Device Collaborative Consultation and Review of Premarketing Applications" under the larger HBD initiative, this trial was selected as one of two pilot projects that is intended to shorten the gap between product approvals in both countries' medical regulatory boards. The global principal investigator of the OSPREY trial is Takao Ohki, MD, who is with the Jikei University School of Medicine in Tokyo; the United States principal investigator is J. Fritz Angle, MD, who is with the University of Virginia in Charlottesville, Virginia.

In the United States, OSPREY is a single-arm, multicenter, nonrandomized, prospective clinical trial studying the treatment of atherosclerotic stenoses and occlusions of the SFA. Inclusion criteria include symptomatic leg ischemia without tissue loss by Rutherford classification (category 2, 3, or 4), a resting ankle-brachial index (ABI) of < 0.9, or abnormal exercise ABI. De novo lesion(s) of the SFA with > 50% stenosis or occlusions that require treatment, and a total lesion length of > 40 and < 150 mm of the above-the-knee SFA in one limb are included. The target lesion should be treatable with no more than two overlapping stents, limiting the stent overlap to up to 10 mm (by visual estimate). All lesions must be at least 3 cm above the knee joint and at least 2 cm distal to the origin of the profunda artery. Reference vessel diameter should be > 4 and < 7 mm, with a target lesion length of > 40 and < 150 mm.



(Courtesy of Terumo Interventional Systems.)

Figure 1. The Misago stent. The Misago stent system is limited to investigational use only in the United States.

In Japan, there are two arms of the study: 50 patients receiving the Misago stent and 50 patients receiving solely percutaneous transluminal angioplasty. In the United States, the primary endpoints are primary stent patency at 1 year, as determined by duplex ultrasound or angiography, and freedom from major adverse events within 30 days of the procedure, which would result in target lesion revascularization (TLR) or amputation of the treated limb. The study will include up to 350 patients—a maximum of 250 patients in up to 30 centers in the United States and 100 patients in Japan.

THE MISAGO STENT

The Misago stent system includes an extremely flexible self-expanding nitinol stent that is delivered in a unique fashion. The delivery system for this stent is via a rapid-exchange (RX)/monorail unit rather than the typical over-the-wire system that is used by other currently available nitinol stents. Use of an RX system for stent delivery has been shown to reduce radiation exposure times and quicken device exchanges, namely with the use of shorter guidewires and by enabling a single-operator method of device placement/removal.[4,5] The Misago stent comprises a 0.035-inch, 0.89-mm RX system with six radiopaque markers. The stent design

is nitinol alloy based with eight cells plus a double-link connector for 6-, 7-, and 8-mm-sized stents. The strut thickness is approximately 0.185 mm (Figure 1).

Results of the Misago stent in clinical use were recently published.[6] The MISAGO 1 clinical trial enrolled 55 patients undergoing endovascular intervention of totally occluded or stenotic lesions in the SFA or popliteal arteries and were treated with the implantation of 81 stents in five European centers. The primary endpoint was the rate of restenosis at 6 months, as assessed by duplex sonography. Two-thirds of the patients were men, with an average age of 68 years. Nearly 60% of patients were smokers, and approximately one-third had diabetes. Ischemic symptoms were documented in all patients, and the average lesion length was 85 ± 50 mm. Almost two-thirds of these lesions were totally occluded, and approximately 38% were classified as TransAtlantic Inter-Society Consensus C or D. The technical success rate was 100%, whereas the procedural success rate was 98.2% without death, myocardial infarction, stroke, or major bleeding.

At 6-month follow-up, the restenosis rate was 8.5%, with two patients undergoing target vessel revascularization and one stent fracture observed. Additionally at 6 months follow-up, the mean ABI improved from 0.7 at baseline to 0.95, and the Rutherford classification showed an overall improvement of 72%.

Preliminary results of the MISAGO 2 registry have also been recently announced.[7] This registry enrolled 744 patients undergoing percutaneous intervention of totally occluded or stenotic lesions in the SFA or popliteal arteries in 79 European centers. A total of 754 lesions were treated with 916 stents, with the primary endpoint being TLR at 6 and 12 months. Two-thirds of the patients were men, 60% were smokers, and nearly one-third were diabetic. The average lesion length was 64 ± 38 mm, with approximately 37% of the lesions being totally occluded. The event-free survival rate was > 90%, with freedom from TLR being approximately 97% at 6 months. The mean ABIs showed an improvement of 0.1 or more in 73% of patients, and the Rutherford classification improved or remained stable in 97% of patients. Stent fractures were found in approximately 2% of patients.

The E-MISAGO study, which is a prospective, nonrandomized, multicenter, observational study to further support the safety and efficacy of the Misago peripheral self-expanding stent system in real-world patients, is ongoing in Europe.[8] The target number of patients to be enrolled is 2,000, thereby creating the largest real-world registry of data for this specific type of device.

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CONCLUSION

Peripheral vascular stent technology continues to evolve. Given the worldwide burden of peripheral arterial disease, it is of no surprise that innovative methods to treat this entity are constantly being developed. The Misago stent offers a novel method of delivery with a flexible frame and could potentially be a valuable tool in the clinician's armamentarium in treating this disease. The OSPREY trial represents not only a major clinical trial to determine the effectiveness of the Misago stent, but it also represents an effort to unite regulatory board approvals in two countries, which could possibly facilitate dissemination and utilization of these clinical trial results to the clinician on a much quicker basis. ■

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