Design Strategies for Global Clinical Trials of Endovascular Devices for Critical Limb Ischemia (CLI)
— A Joint USA-Japanese Perspective —

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For more than 10 years, the Harmonization by Doing (HBD) program, a joint effort by members from academia, industry and regulators from the United States of America (USA) and Japan, has been working to increase timely regulatory approval for cardiovascular devices through the development of practical global clinical trial paradigms. Consistent with this mission and in recognition of the increasing global public health effects of critical limb ischemia (CLI), academic and government experts from the USA and Japan have developed a basic framework of global clinical trials for endovascular devices for CLI. Despite differences in medical and regulatory environments and complex patient populations in both countries, we developed a pathway for the effective design and conduct of global CLI device studies by utilizing common study design elements such as patients' characteristics and study endpoints, and minimizing the effect of important clinical differences. Some of the key recommendations for conducting global CLI device studies are: including patients on dialysis; using a composite primary endpoint for effectiveness that includes 6-month post-procedure therapeutic success and target vessel patency; and using a 30-day primary safety endpoint of perioperative death and major adverse limb events. The proposed approach will be uniquely beneficial in facilitating both the initiation and interpretation of CLI studies and accelerating worldwide CLI device development and innovation.

Key Words: Critical limb ischemia; Endovascular devices; Global clinical trials; Harmonization by Doing

Introduction

1. Characteristics of Critical Limb Ischemia (CLI)
CLI encompasses the most advanced clinical stages of peripheral arterial disease (PAD),* in which patients present with rest pain, ulceration, or gangrene due to chronic ischemia of the lower extremities. Even after revascularization, CLI is generally associated with significant mortality as well as a high rate of amputation. While the number of CLI patients has been continually growing worldwide, outcome measures with conventional medical management of CLI patients have not been systematically defined. Surgical revascularization has historically been considered to be the first-line treatment in these patients.1 However, patients with CLI are often poor candidates for surgical revascularization because: (1) they are elderly, (2) they have limited activities of daily living, (3) their autologous venous conduits are frequently inadequate or have often been previously harvested for coronary artery bypass graft surgery, and/or (4) general anesthesia poses an excessive health risk due to multiple comorbid conditions such as cardiovascular, pulmonary, or renal disease.1 There have been continuous efforts to develop and refine less invasive endovascular devices as a reasonable alternative to surgery. In most

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current practices in the U.S. and Japan, endovascular therapy has emerged as a first-line therapy for PAD patients.\textsuperscript{2,3} The scope of this paper is limited to PAD due to atherosclerosis obliterans, although vasculitis such as Buerger’s disease and collagen disease-related vasculitis may also cause CLI.

2. Background Information on CLI Devices

The goal of using percutaneous endovascular devices to treat CLI is to improve clinical outcomes by relieving limb ischemia while minimizing systemic stressors. However, it is difficult to set an appropriate endpoint because the clinical outcomes of CLI patients are influenced significantly by their comorbid disorders and adjuvant treatments (such as wound care). The presence of various anatomic lesion types, leading to the potential use of multiple different but often complementary devices, further adds to the complexity of treatment evaluation. In addition, there is insufficient evidence characterizing the relationship between the duration of patency needing to be shown for the treated lesion(s) and the overall clinical benefit.

To accelerate the development of endovascular devices to treat lower-limb disease, objective performance goals (OPGs) for use in clinical studies have been proposed by academia in the USA. One set of OPGs has been proposed for femoropopliteal bare metal stents in patients with symptomatic PAD (VIVA criteria\textsuperscript{4}), and another is for catheter-based treatment of CLI.\textsuperscript{5} As randomized, actively controlled clinical trials have traditionally been challenging to conduct in this disease area, both proposals were intended to accelerate trials for vascular device evaluation and approval by facilitating the conduct of single-arm trials using comparators based on the clinical results of previously conducted randomized controlled trials (RCTs) of surgery and endovascular treatments (mainly percutaneous transluminal angioplasty [PTA]).\textsuperscript{6} Based on these proposals, multiple clinical trials have been conducted to support approval from the US Food and Drug Administration (USFDA) for marketing of femoropopliteal stents indicated for treatment of claudication.\textsuperscript{7,8}

3. Current Efforts in Japan

Compared with the USA, there are differences in the environment for CLI treatment in Japan where there is a higher prevalence of diabetes mellitus and patients with endstage kidney disease (ESKD) requiring dialysis.\textsuperscript{9,10} The differences in patient comorbidities are likely related to the different medical and healthcare environments, and social customs that include longer walking distances and different sitting styles. Because of prevalent cultural views in Japan, patients tend to avoid limb amputation, allowing tissue loss and pain to progress. Moreover, because many Japanese CLI patients have comorbid conditions such as ESKD requiring dialysis, they may die from other causes even if the culprit arteries are successfully revascularized.\textsuperscript{11} If a primary endpoint is amputation-free survival (AFS), the patients who have successful revascularization but subsequently die from a comorbidity will be considered as treatment failures. In contrast, if a patient survives an unsuccessful endovascular treatment or refuses amputation even if such treatment is recommended, such cases are considered as “successes”. Therefore, there is concern that it may be difficult to properly evaluate and compare the performance and effectiveness of CLI devices using AFS as the primary endpoint when considering Japanese patients with CLI.

Based on this situation in Japan, a working group consisting of members from industry and academia, together with regulatory experts was launched in 2011 as part of the Japan Endovascular Treatment Conference (JET) with the mission to promote the development of CLI devices. The evaluation methodology for CLI devices has been underway since then. This working group has discussed the situation in Japan based primarily on the published results of the OLIVE registry,\textsuperscript{9} which is a registry dedicated to the outcomes of CLI treatments in Japan, and studied an appropriate endpoint for CLI devices in Japan. This study has been included in the development project of Japan’s Ministry of Health, Labour, and Welfare (MHLW) as part of the “Guidance for the Evaluation of Emerging Technology Medical Devices” in 2013,\textsuperscript{11} and guidance for the evaluation of CLI devices in Japan has been published. The novel aspect of this guidance is the inclusion of wound healing in the composite endpoint, which is considered as a widely acceptable endpoint in Japan because wound healing is a significant indication of amputation avoidance. A discussion aimed at the development of OPGs for wound healing also began. However, in order to accelerate development, the group concluded that it would be appropriate to conduct randomized, controlled clinical studies comparing any new endovascular therapy to PTA, as there were no consistent evaluation criteria for wound healing at that time. Subsequent to this discussion, the Society for Vascular Surgery published a proposed system for risk stratification of CLI based on wounds, ischemia, and foot infection (WII).\textsuperscript{12} Although the WII scheme was introduced relatively recently and therefore has not yet been incorporated into many clinical trials to date, it potentially can provide a sufficiently standardized and objective method for assessing wound healing over time in CLI device studies.

Building on these successful efforts, as well as previous USA-Japanese regulatory and clinical collaborations, here we describe a paradigm for evaluating new CLI devices in an international clinical trial. Use of this approach can facilitate rapid collection of clinical data relevant to the global CLI population, while taking into account important geography-dependent patient populations and clinical practice considerations.

4. Harmonization by Doing (HBD)

The HBD initiative was established by regulatory, industry, and academic members from the USA and Japan in December 2003, including the USFDA and MHLW/Japanese Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) (reorganized into the Pharmaceuticals and Medical Devices Agency [PMDA] in 2004) which are responsible for pre-market review and regulation of medical devices in their respective countries.\textsuperscript{13} The purpose of HBD activities is to promote the harmonization of evaluation and regulation of medical devices in both countries. HBD was named after its “by doing” policy that encourages members to identify important issues in these areas and converge on harmonized ways to address them. Of the 4 working groups originally organized under the HBD scheme, Working Group 1 (WG1) has focused on designing and conducting global clinical trials of cardiovascular medical devices. The ultimate goal of WG1 is to eliminate “device-lag,” or the delay that can exist in gaining cardiovascular device approval in Japan after the device has already been approved and in use in the USA (and Europe).
The CLI-SWG project has resulted in important conclusions because (1) agreement on appropriate evaluations for these studies has now been reached through open discussions by medical experts in the field of peripheral vascular intervention in both the USA and Japan, and (2) regulators in both countries participated in the discussion, with the potential of these studies to support eventual device approval in mind. Given this type of input, we believe this paradigm will greatly help CLI device developers to plan global clinical trials and incorporate international regulatory and development strategies.

### Proposed Essential Principles for Global Clinical Trials for CLI Devices

Considering the differences in the medical environments of the USA and Japan as described, the proposal for the basic concepts for global clinical trials is illustrated in Figures 1-3. The details are described below.

1. **Outline of Clinical Trials**
   a. **Target Devices**
      standalone endovascular devices that can treat CLI (e.g., uncoated PTA, bare metal stent [BMS], DES, drug-coated balloon [DCB]) are proposed as the index

| Table. Main Differences Between the USA and Japan in the Medical Environments for CLI to Be Taken Into Account When Conducting Global Clinical Trials for CLI Devices |
|---------------------------------------------------------------|
| USA | Japan |
| Predominant patients based on Rutherford classification | Category 4 | Category 5 |
| Ratio of dialysis patients in CLI population | ~10% | ~50% |
| Major amputation | More frequent | Less frequent |
| Principal evaluation method for vessel patency | Duplex ultrasonography | Angiography |
| Wound care provider | Many different specialists | Plastic surgeons |

**Figure 1.** Proposal for global clinical trial of standalone endovascular treatment devices for critical limb ischemia (CLI). Drug-coated balloon (DCB), drug-eluting stent (DES) and bare metal stent (BMS), etc., are proposed as the target devices. We also propose that CLI patients in categories 4 and 5 of the Rutherford classification (“R4” and “R5”) be studied, including those on dialysis, as target patients. The appropriate study design is a randomized controlled study of the target devices, with standard treatment, for example, balloon angioplasty (PTA), as the control. Treatment-assist devices should be evaluated by specific protocols. Factors which affect the study results (e.g., Rutherford classifications, dialysis, body mass index, etc.) shall be assigned.
device categories.

b. Target Vessels
Femoropopliteal and below the knee (BTK) arteries (anterior tibial artery, posterior tibial artery and peroneal artery) are proposed as the target arteries, as they are the most common arteries treated for CLI in both the USA and Japan. We acknowledge that recently physicians have also undertaken revascularization of pedal arch arteries, typically above the ankle, to improve distal perfusion and wound healing resulting in limb salvage.

c. Target Patients
The aim of CLI therapy is to increase arterial blood flow to ischemic areas and improve clinical outcomes. Therefore, we should exclude some particular patient subgroups that are associated with high mortality and limb loss even with improved perfusion. In this context, patients with Rutherford 6 disease (“R6”; likewise “R4” and “R5” for Rutherford categories 4 and 5,
respectively, hereinafter), who have widespread necrosis that includes heel wounds or uncontrollable wound infections, are not considered as appropriate subjects for evaluation of an index device. With this consideration, we propose the target population suitable for clinical trials should be R4 and R5 CLI patients.

In addition, because 50% of the patients with CLI were on hemodialysis in the OLIVE registry in Japan,9 and significant PAD is present in approximately one-third of hemodialysis-dependent patients in the USA10 even though dialysis patients account for less than 10% of CLI patients in that country,9,10 patients on dialysis need to be studied in order to most accurately evaluate real-world clinical scenarios. In order to establish the safety and the effectiveness of the CLI device, assessing outcomes in this cohort as a separate variable is appropriate.

d. Study Design
A RCT of the target device with standard treatment (e.g., PTA) serving as the control is currently appropriate. A practical and well-reasoned control is important to account for known and unknown covariates related to patient characteristics and clinical practice.

2. Primary Endpoints (Figure 2)
   a. Effectiveness
As the purpose of the clinical study is to evaluate the clinical effectiveness of a specific endovascular therapy, assessment of both therapeutic success and vessel patency is appropriate as the composite primary endpoint.

“The Healing of Target Wound” for R5 patients and “Relief of Ischemic Pain” for R4 patients, which define “Therapeutic Success,” and freedom from unplanned major amputation, are considered as part of the composite endpoint for clinical outcomes. Healing of the target wound and relief of ischemic pain are respectively defined as complete epithelialization of the target wound and as mitigation of ischemic pain (measured by the Visual Analog Scale [VAS]) without an increase of analgesics.15

Angiography is considered to be the most reliable method for evaluating vessel patency. However, considering the differences between the USA and Japan in medical practice patterns and the clinical conditions of CLI patients, it will be difficult to mandate angiography in all cases. Duplex ultrasonography (DUS) is a preferable evaluation method because of its ability to measure vessel patency non-invasively and repeatedly. However, it is anticipated that evaluation by DUS may not sufficiently evaluate patency in certain cases, particularly in BTK vessels with highly calcified lesions, and in centers where skilled ultrasound technologists or modern ultrasound technologies are unavailable. In such cases, angiography should be considered if the DUS is inconclusive in order to sufficiently evaluate the patency of the target lesion. The CL-SWG considers that the assessment of clinically driven TLR (target lesion revascularization) will be a valid evaluation of vessel patency. Clinically driven TLR is defined as TLR driven by either recurrence of symptoms or a decrease in perfusion pressure in the lower limb, where restenosis is confirmed by angiography during the TLR procedure.

Recurrence of symptoms includes delayed healing or worsening of the target wound for R5 patients, and an increase of pain or increased analgesics for R4 patients. Objective assessment of these symptoms, through evaluation of digitally photographed wounds analyzed by a central digital photometric laboratory or the intensity of the pain using the VAS, is very important.15

b. Evaluation Period of Primary Effectiveness
Six months is the appropriate time for evaluation of the primary effectiveness endpoint for CLI device studies. Although many clinical trials in the past, including those for femoropopliteal stents, had primary endpoints that were evaluated at 12 months, and the relationship between effectiveness and long-term clinical prognosis in the lower extremities has not been fully established at a time earlier than 12 months, we believe that results at 12 months may be subject to investigator bias or confounding caused by other factors in CLI patients. With this consideration in mind, we suggest that objective assessments occur at 6 and 12 months, with the hope that 12-month data will confirm that the 6-month time points are acceptable for evaluating CLI devices and will also provide valuable information regarding the durability of the treatment effect. If possible, it is desirable to observe even longer-term follow-up (>12 months) to further assess the durability of treatment.

c. Safety
With respect to the assessment of safety associated with the intervention, CLI-SWG considers that perioperative death (POD) and major adverse limb events (MALE), such as unplanned major amputation or use of surgical bypass, within 30 days after the treatment should be included.5

3. Other Considerations
It is necessary to evaluate AFS and MALE, which have been included in other clinical studies in the past, as secondary endpoints. Other endpoints, such as vessel patency, time to complete wound healing, perfusion pressure in the lower limb, quality of life (QOL), and major adverse cardiac and cerebrovascular event (MACCE), should be considered as appropriate. Either DUS or angiography can be used to determine vessel patency, keeping in mind their respective limitations. In order to minimize the variation in DUS evaluations, utilization of a central imaging core laboratory and standardized procedures is desirable. A wound core laboratory is also desirable for evaluating wounds.

Discussion
In order to develop the design strategy for global clinical trials of CLI devices, CLI-SWG had in-depth discussions based on clinical data. Several points raised during the CLI-SWG discussions include the following.

1. Patients With ESKD Requiring Dialysis
Approximately 50% of the CLI patient population in Japan requires dialysis, whereas dialysis patients account for less than 10% of the CLI population in the USA.9,10 Considering the possibility of selection bias that might arise with enrolling dialysis patients, the Japanese experts were reluctant to enroll dialysis patients in global clinical trials. Meanwhile, the US experts considered that if the patients on dialysis were not enrolled, almost 50% of the Japanese patients would miss the opportunity of receiving such treatment. Furthermore, the population of US patients on dialysis is increasing. Therefore, the group agreed that it would be better to enroll these patients with certain
considerations provided in the proposed essential principles (e.g., uniform assignment of the dialysis patients to each cohort, or application of a stratified analysis).

2. Evaluation Period
With respect to the evaluation period for the primary effectiveness endpoints, most of the US members considered that 12 months would be appropriate, whereas the Japanese members recommended 6 months. Many Japanese experts were concerned that it might be difficult to properly interpret the results at 12 months when evaluating the performance of the target device. If the primary endpoint is set at 12 months, because of the severity of CLI, many unrelated comorbidities and complications caused by comorbidity are expected to occur, and these events (including patient deaths) would make interpretation of the primary endpoint data more difficult. Furthermore, most of the adverse events and the vast majority of wound healing in Japan occur before 6 months. Because of these factors, as well as the typical comorbidities of CLI patients, the group agreed that 6 months would be appropriate for current studies. At the same time, the group recommended collecting data at 12 months or longer, if possible, to aid in confirming 6 months as the optimal time point for evaluation in the future.

3. Selection and Identification of Target Vessels
In patients with CLI, there may be multiple potential vessels and lesions contributing to the observed ischemia. As a result, it is important to identify the culprit lesion(s) among them. The “angiosome” concept is regarded as a promising strategy for detecting the relationship between the location of tissue loss and the lesions contributing to the observed ischemia. As the CLI-SWG did not reach a consensus on whether sufficient evidence exists to establish a unified method for identifying the culprit lesion and correlating its treatment with relief of clinical symptoms, such identification methods are left to the judgment of the investigators in each country for the time being. The CLI-SWG intends to discuss this matter again, when sufficient data have been accumulated.

4. Perfusion Evaluation Modality
Differences in methodology for quantitative evaluation of blood flow was also raised as an issue. Skin perfusion pressure (SPP) measurement is widely used in Japan, whereas other methods, such as transcutaneous oxygen pressure (TcpO2) measurement, are prevalent in the USA. Each medical facility likely adopts different modalities for end-organ perfusion analysis. Standardization of objective assessments of limb perfusion remains an unanswered question. We propose hemodynamics be evaluated by any modality and it is planned to review the outcomes of various modalities in the future.

Significance and Conclusions
In today’s global marketplace, the clinical and economic impact of designing and conducting a global clinical trial has grown and must increase even further to provide patients worldwide with early and simultaneous access to promising innovative medical devices. The CLI-SWG believes that the proposed harmonization scheme will directly help CLI device manufacturers formulate development and regulatory strategies that will lead to improved and timely patient access to safe and effective CLI devices that are important to public health. Moreover, a unique achievement of the CLI-SWG group is that we developed a novel important clinical study paradigm that specifically considered the similarities and difference in patient characteristics and clinical care in multiple countries. Although each CLI device study may vary according to factors such as the device design, intended use, and regulatory requirements, we believe that this program will better enable stakeholders to prospectively collect data globally to facilitate evaluation of CLI devices, an approach that was once unimaginable. This proactive approach will also be advantageous in reducing the complexity of pooling and analyzing retrospectively collected data from a variety of sources and of comparing data across pre-market trials and from post-market surveillance. In addition, adopting the proposed approach will aid the formulation of OPGs for CLI treatment success endpoints that reflect current real-world needs, and allow for further refinement of the CLI study design paradigm as clinical evidence from completed studies regarding appropriate CLI treatment endpoints and outcomes becomes available. Furthermore, we believe that this collaborative approach can not only create an environment for accelerating international CLI device development, but also serve as a model for facilitating innovation in other cardiovascular areas in the USA and Japan in a similar way. Finally, through USA-Japan joint clinical trials as HBD WG1 activities, the regulators in both USA and Japan have enhanced their mutual understanding of their respective medical device development/approval processes and developed a fruitful working relationship. CLI is an extremely complex disease, and its evaluation may be affected by confounding factors that can provide challenges to the evaluation of CLI devices. As a result, we recognize that there may still be lessons to be learned regarding optimal endpoints and time points for CLI studies, including the appropriateness of a 6-month primary endpoint, strategies for identifying culprit lesions, and gaining consensus on optimal methods for evaluating vessel patency and wound healing. Although there are still some issues left unresolved, sponsors can refer to the basic concepts presented by the CLI-SWG when beginning to design clinical trials of CLI devices, taking into account the characteristics and development status of their own devices. We hope the harmonious relationship and continued discussion between the USA and Japan will promote the development of new CLI treatment strategies.

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