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Proceedings from the Society of Interventional Radiology Research Consensus Panel on Critical Limb Ischemia

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Background

In the United States, it is estimated that 5–12 million people have peripheral arterial disease (PAD) (1). The prevalence of PAD increases with age and is estimated to afflict 4.3% of the population over 40 years of age and 14.5% of those over 70 (2). Depending on the severity and extent of the disease, patients may be asymptomatic or present with clinical symptoms including atypical leg pain, classic intermittent claudication, acute limb ischemia, or chronic critical limb ischemia. The incidence of critical limb ischemia (CLI) is 500–1000 patients per million in the western world [2]. The natural history of patients with CLI is poor (25% mortality and 30% amputation rate at 1 year) (3–5). Patients with critical limb ischemia (CLI) have advanced atherosclerosis involving all cardiovascular beds and thus have 5-year mortality greater than patients with symptomatic coronary arterial disease. Although the precise mechanisms associated with these high mortality and amputation rates is not known, individuals with CLI are known to suffer from a increased rates of comorbidities, including poorly controlled atherosclerosis risk factors (such as smoking, diabetes, hypertension and hypercholesterolemia), advanced chronic kidney disease, and coronary artery disease (6).

Increasingly, endovascular therapy (e.g. angioplasty, atherectomy or stent placement) for patients with CLI has become the first line of treatment, while open surgical revascularization is reserved for patients who are either unsuitable for endovascular management, whose anticipated lifespan is longer than two years, or whose limb symptoms progress despite prior endovascular intervention (3, 7–10). Recently, the bypass vs. angioplasty in severe ischemia of the leg (BASIL) trial compared endovascular treatment to surgical bypass and demonstrated that endovascular revascularization may confer advantages compared to surgery for patients whose life expectancy is less than 2-years (11). The surgical technique is well developed; however, the same cannot be said for endovascular therapies, which are often more varied (8, 12–16). With the introduction of new disruptive technologies such as drug eluting stents, drug coated balloons, bioabsorbable stents, atherectomy, cell based therapies, therapeutic angiogenesis, and nanotechnologies, has made the selection of individuals therapies more challenging, as the current CLI comparative effectiveness evidence base is weak (17–26). In addition, new percutaneous techniques are being developed such as transpedal access, SAFARI (Subintimal Antegrade Flossing using Antegrade and Retrograde Intervention) and below the ankle (pedal) and plantar-pedal loop angioplasty (12, 15, 16). The goal of this paper is to discuss the proceedings from SIR Foundation Research Consensus Panel (RCP) for the development of a research agenda for CLI.

Methods

Panel Membership

On May 7, 2012, the SIR Foundation assembled a research consensus panel (RCP) for the development of a research agenda for CLI. The panel membership included a (i) a multidisciplinary group of expert panelists, (ii) representatives from governmental agencies, and (iii) representatives from industries involved in the peripheral arterial field. There were eleven expert panelists including three interventional radiologists, three vascular medicine internists, three interventional cardiologists, and two vascular surgeons. Government agencies included the Food and Drug Administration and the Agency for Healthcare Research and Quality. Industry representatives came from major companies involved in the production and/or distribution in the United States of products for peripheral vascular therapies.

Agenda Methodology

Unlike prior SIR research consensus panels, a prior topic was selected to help focus the discussion. The topic for this RCP was the development of a registry for the endovascular management of patients with CLI. This topic was chosen based on input from the SIR peripheral artery disease service line and the SIR sponsored lower extremity arterial revascularization (LEARN) meeting in September 2011. Six focused topics were selected prior to the meeting for presentation by selected RCP faculty. Presentation topics are shown in table 1. Panelists were also asked to include in their presentations a discussion of gaps in the current knowledge base, and recommendations for basic science and clinical research questions or projects that need further study. Specifically, panelists were asked to (i) define the most important clinical questions that could realistically be answered through pivotal multi-institutional clinical trials or registries, (ii) describe the most promising future directions that merit preclinical or early clinical exploration in the endovascular registry for critical limb ischemia, and (iii) outline the critical alliances that must be developed to advance the prioritized research and how the SIR Foundation can best support these initiatives. Afterwards, a round-robin discussion was held to examine important research questions and trial design, potential opportunities for future research studies or sub-studies within a CLI registry, and to consolidate similar or redundant ideas into succinct focused

topics relevant for a CLI registry. Thereafter, invited comments from government and industry representatives were heard.

What endovascular therapies should be included in a CLI registry?

Extensive discussion focused on which endovascular technologies that should be included in a CLI registry. All currently available technologies in the United States such as chronic total occlusion (CTO) recanalization wires and catheters, reentry devices, drug eluting stents, bare metal stents, covered stent grafts, atherectomy, and embolic protection devices were recommended for inclusion in the registry. The panel favored creation of a “real world registry” that would allow for evaluation of all available technologies in order to capture baseline and outcome status of the widest group of patients with CLI, and to evaluate the variable device-based preferences of the endovascular physicians.

What can we learn from heart registries?

Coronary registries have been established as an important clinical research tool for over two decades. The original registry started with National Cardiovascular Data registry (NCDR) CathPCI registry in 1998 (27). The NCDR was established with a priori-defined goals. These goals included the definition of common data elements that would be useful to determine and model hospital-based clinical outcomes, would be able to provide procedural details of invasive cardiac procedures, including operator and hospital characteristics, and would facilitate capture of real world practice outcomes. For example the CathPCI registry has 1400 participants with eleven million records and has successfully contributed to the publication of 61 manuscripts and 142 abstracts. Other examples of successful cardiac disease registries include the implantable cardioverter defibrillator (ICD), Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION), and others. Such registries have provided data that have informed current endovascular clinical practice. For example, the NCDR registry included the observation of that use of the VasoSeal (Datascope Corp., Fairfield, NJ), a femoral artery closure device was associated with a higher risk of local vascular adverse events compared to manual compression techniques (28). These data resulted in the removal of the VasoSeal from the market.

What disruptive technologies are coming?

According to Christenson, emerging technologies may be classified as “sustaining” or “disruptive”: the former device fit within existing design and care paradigms and usually represent evolutionary technology that are more readily incorporated into existing service systems, while the latter devices entirely change the value proposition (29). CLI, characterized by ischemic rest pain, ulceration or gangrene represents a cardiovascular disease for which current-device based treatment strategies provide limited clinical benefit or non-durable outcomes (1). The desire by patients, physicians and payors to achieve major future improvements in these outcomes could favor the emergence of disruptive technologies to assure that a new value proposition – complete and reliable resolution of severe leg ischemic symptoms – can be achieved (29). Several categories of developing technologies have the potential to provide disruptive changes to existing treatment. Broadly stated, these include procedural techniques, interventional devices, and biological modifications that allow cellular and functional restoration.

Recent publications describe new endovascular techniques as subintimal recanalization of infrapopliteal arteries, trans-collateral revascularization, combined antegrade and transpedal retrograde procedures, and plantar-pedal loop reconstructions (12, 15, 16). Currently, these techniques have two problems: a paucity of dedicated catheter systems, and a consequent inherent variability in technique and lack of reproducibility that prevents generalization to all patients at risk. Plantar-pedal loop revascularization perhaps represents the most

promising of these strategies in serving an unmet need and allowing an extension of interventional management to patients with otherwise non-reconstructible, calcaneal or forefoot ischemia (30).

Infrapopliteal drug-eluting stents, drug-eluting balloons, and bioabsorbable stents are evolving platforms that potentially add patency (and time for clinical resolution) to enhance existing technical strategies (19–24). Early data suggests that these devices may be readily deployable in the relatively near future, with promising incremental improvements in maintenance of arterial patency and achievement of wound healing (31). Furthermore, while overall limb salvage may not be affected, there is the potential to reduce the hazards and costs related to secondary [re] interventions as a result of loss of anatomic or clinical patency (19, 24).

The most powerful disruptive technologies will be related to the integration of biological or pharmacologic therapies that alter CLI biology (gene therapy, growth factors, angiogenic factors), afford small vessel reconstitution (endothelial seeding or progenitor cells), or result in plaque modification either enhancing the effects of interventions or altering the cellular response to intervention (25). Although not yet commercially feasible, these horizon technologies will fundamentally challenge value propositions for patients with CLI.

Primary and Secondary Outcomes for CLI Trials and Registries

The goals of treatment in CLI are preservation of a functional limb in a surviving patient, relief of pain, healing of wounds, and improvement in related quality of life. In the current treatment paradigm, these goals are most commonly achieved by effective revascularization of the limb. CLI patients present a high burden of atherosclerosis, and are at increased risk for cardiovascular events and mortality. Moreover, the clinical symptoms of CLI are rarely resolved in complete or durable fashion by a single intervention. Therefore an important secondary goal is to minimize the magnitude and frequency of invasive treatments, both to reduce their attendant morbidity/costs and to maximize symptom-free survival for the patient. Important challenges in CLI study design include an inadequate clinical staging system, inconsistent definitions of cohorts and endpoints in the literature (reflecting lack of consensus), the impact of evolving technologies on practice, itinerant versus longitudinal care patterns, lack of equipoise across various specialists and disciplines, and practical limitations of turf and economics.

In any study design, the choice of primary and secondary endpoints should reflect the goals of treatment of the population, while also testing the primary hypothesis of the interventions being compared. For example, comparison of a new bioengineered vascular graft to a conventional prosthetic graft in a CLI population should focus primarily on freedom from graft failure, since this most directly tests the performance of the new construct. However once a new device has been shown to maintain patency that is either non-inferior or superior to an existing therapy then trials designed for FDA approval would also require clinically relevant endpoints such as amputation and wound-free survival. While patient reported outcomes such as function and quality of life measures are critical and sorely needed in the CLI arena, clinical trials must be primarily designed around hard, objective endpoints that are clinically compelling and readily adjudicated. An additional, and important consideration concerns the primary approach to summarizing and comparing the selected outcome measures between groups. The most common method in clinical trials is a time-to-first-event analysis. However the recrudescence rate and chronicity of CLI are such that time-integrated approaches would likely be far more meaningful to capture the complete patient experience.

In the area of surgical versus endovascular revascularization for CLI, only a single RCT—the BASIL trial—has been completed to provide a relevant example (11). Amputation-free survival was the primary and overall survival the key secondary endpoint. Other RCTs testing drug or biological therapies in CLI have followed suit (18, 26). These endpoints are obviously of fundamental importance in CLI, however they are fairly insensitive to the effectiveness of limb revascularization and are challenging to power. They also fail to capture many of the key clinical outcomes in the CLI patient as described above. In 2009, the Society for Vascular Surgery convened a working group to examine existing datasets on revascularization for CLI, to suggest Objective Performance Goals and future clinical trial designs. The recommendations of this group, and the summary of data from which it is derived, can be reviewed in a published manuscript and at <http://www.criticallimb.org> (32).

The following endpoints were recommended for any CLI study:

- Major limb amputation and overall survival
- Reinterventions-further sub classified as major or minor
 - Major reintervention = amputation, new bypass procedure, thrombolysis/thrombectomy, or major open graft revision (anything beyond simple patch angioplasty). These were defined as Major Adverse Limb Events (MALE)
- Hemodynamic failure-defined by a combination of clinical and imaging criteria
 - Reintervention, amputation, or stenosis (RAS)
- Clinical failure-defined by failure to improve in clinical stage (eg Rutherford score)
- Time to complete wound healing for patients with non-healing ulcer as the CLI criterion

Among these endpoints, the appropriate ordering for any given trial should again consider the presumed mechanism of the treatment being tested, and its relevant control. For comparison of revascularization techniques, MALE-free survival and hemodynamic failure (RAS) are highly relevant choices as primary endpoints, with AFS as a key secondary endpoint. In addition, all studies should uniformly report on the total number and types of reinterventions, all treatment-related complications (major and minor), and rehospitalizations. Follow-up should be for a minimum of one year. Clinical state, hemodynamic status, wound status, limb function and QoL should be recorded at each study interval.

Medical Management for Critical Limb Ischemia

Patients with critical limb ischemia (CLI) have a very high risk of mortality and limb loss as well as significant morbidity from ischemic pain, decreased ambulation and ischemic ulcers that need chronic wound care. Therefore the medical approach to CLI begins with an overall assessment of the patient's cardiovascular risk and appropriate management of those risk factors. Once accomplished, medical therapies might be considered to address lower extremity manifestations of CLI. Key to this discussion is whether medical therapy is effective in decreasing mortality, preventing limb loss, healing ischemic wounds and relieving ischemic pain without the need for narcotics. The best-studied drug class, going back to several decades, is the prostaglandin medications as summarized in a Cochrane collaboration review (33). This meta-analysis reviewed 532 trials in CLI of which 20 had moderate quality and 8 had good quality. In the placebo controlled trials with good quality, there was a significant benefit on relieving rest pain, healing ischemic ulcers, but not reducing the risk of amputation or mortality. Similar results were found with the various

sub-classes of prostaglandin medications. Recently, a large randomized trial studied PGE1 in 383 randomized patients presenting with ischemic rest pain or ischemic ulceration that had no options for revascularization (34). The medication was administered intravenously for five days per week for a total of eight weeks. The primary endpoint was death or amputation at six months and the trial was terminated prematurely due to futility. Recent evidence on aggressive management of CLI with prostaglandins is inconclusive.

A number of angiogenic therapies have been attempted culminating in a large phase III trial of an angiogenic agent NV1FGF (26). This trial enrolled 525 patients with ischemic ulcers unsuitable for revascularization, conducted in 30 countries, 171 sites and took over 19 months to recruit. The primary endpoint was time to amputation or death and this occurred in 33.2% of patients randomized to placebo, 37.1% patients randomized to FGF. Thus, there was no evidence of benefit for this agent.

A final option would be cellular-based therapies. Perhaps most encouraging is the publication of the results of a Phase II study of bone marrow and expanded multicellular therapy (17). This study enrolled 86 patients with ischemic ulcers and no option for revascularization with the primary endpoint of time to treatment failure. This was defined as death, major amputation, doubling of wound size or new gangrene. In this study the primary endpoint was statistically positive in favor of treatment, but amputation-free survival did not reach significance, but had a favorable trend.

In summary, pharmacologic and biologic therapies have been disappointing for CLI however cellular therapies do hold promise, but are early in their development. Based on this review there are currently no approved medical therapies to treat the limb manifestations of critical limb ischemia.

What frequency of visits should the patient after an endovascular treatment has to assess patency?

Duplex ultrasonography (DUS) is the optimal modality to assess patency following endovascular intervention for aortoiliac and femoropopliteal artery disease. DUS is inexpensive, non-invasive, has no contraindications, and can be used in a serial manner in patients who have undergone endovascular intervention. DUS is the surveillance standard following surgical revascularization in patients with CLI (35). However, the accuracy of DUS to assess the infrapopliteal arteries has been reported to be inferior to surveillance of proximal arteries (36). In a recent prospective comparison of DUS to contrast arteriography (CA) in 169 patients with PAD and intermittent claudication (IC) (42) or critical limb ischemia (CLI) (127), there was no difference in accuracy¹. Interestingly, DUS was superior to CA ($p<0.001$) in identifying potential distal crural artery revascularization targets, while CA was superior to DUS in identifying proximal crural artery lesions. Due to depth of insonation and bony interference, DUS faced the greatest technical challenges in assessing the tibioperoneal trunk and peroneal artery.

In one prospective series of 40 limbs with CLI requiring surgical revascularization, DUS was as accurate as CA to identify the target crural artery for the distal anastomosis(37). The limitation of DUS in infrapopliteal arteries is largely due to lack of appropriate training and experience (38). Unfortunately, there have been no prospective series demonstrating the accuracy of DUS following endovascular intervention of the infrapopliteal arteries. In a recent prospective randomized trial of a drug-eluting stent vs. a bare metal stent in infrapopliteal arteries, DUS was used as a method of determining patency at 6 months following randomization, with CA at 12 months (39). The correlation between the two modalities was not reported, and <50% of patients underwent both imaging modalities.

Some investigators have even used duplex ultrasonography to guide endovascular intervention (40).

Contrast-enhanced magnetic resonance arteriography (CE-MRA) has demonstrated efficacy in determining the presence, location, and severity of PAD. In a meta-analysis of 32 clinical trials comparing MRA to CA, the sensitivity and specificity to identify infrapopliteal PAD was 92% and 93% respectively (41). There have been no prospective studies validating the role of CE-MRA following infrapopliteal endovascular intervention. As a surveillance modality for CLI interventions, MRA faces significant deterrents: risk of gadolinium – induced nephrogenic systemic fibrosis; claustrophobia; metal artifact from stent deployment; incompatibility with AICD and pacing devices; and excessive cost.

In a meta-analysis of computerized tomographic arteriography (CTA) for PAD, the sensitivity and specificity in infrapopliteal arteries is 95% and 91% respectively (42). Overstaging occurred in 8% of segments, and understaging in 15%. Despite the fact that no objective data has demonstrated the role of CTA following endovascular intervention for CLI, this modality offers some promise as a non-invasive strategy in infrapopliteal artery disease. However, the need for significant external beam radiation, iodinated contrast administration, and cost makes this an unappealing modality for serial examinations.

Given the limitations of all technologies, the optimal, cost-effective strategy for surveillance following endovascular intervention would include:

- a. Trained vascular technologists performing arterial DUS of the infrapopliteal arteries in conjunction with known physiologic assessments of distal perfusion (toe pressure, toe waveform, skin perfusion pressure, etc). Discrepancy between arterial segment patency and hemodynamic success metrics should prompt further investigation, such as CA. In addition, a percentage of all enrolled patients may benefit from CA examination as well.
- b. In non-stent based therapies (drug-coated balloons, atherectomy, bioresorbable stents), a percentage of all enrolled patients receive CA, with DUS in the entire patient cohort.
- c. When DUS is non-diagnostic, CA, CTA, or MRA may be used.

There is a need for prospective evaluation of DUS, CTA and MRA in this patient population.

Discussion

Patients with critical limb ischemia have multiple comorbidities with different presentations (1). Patients may present with prior conservative wound management and healed wounds (43–45). Other patients can present and need an endovascular or surgical treatment in order to heal their wounds. Therefore, the panel decided because of these different presentations, a goal should be to collect broadly inclusive site-reported data on all therapies (device, drug, surgery, technique) and clinical conditions (limb status, comorbidities). Due to variability in the severity of CLI at presentation, stratification of registry outcomes should be considered to include those patients with different Rutherford stages. For example, an important measurable outcome for a patient with ischemic rest pain in the absence of ulceration would be resolution of pain (45). In contrast, for a patient with pedal gangrene and inevitable amputation, a determination of the ability to maintain a functional amputation (e.g. transmetatarsal) would be more beneficial (45).

There were several objectives to a CLI registry, which were agreed upon (table). These areas of consensus reflected perceived current deficiencies in data collection and reporting that would allow data extrapolation to specific populations. An attempt should be made to recognize performance characteristics, hazards and deficiencies of existing devices for subsequent device engineering modifications. There should be an attempt to establish risk stratified outcomes data and create performance goals. Importantly, a registry should be able to provide preliminary data for subsequent RCT's focused on definable at-risk populations with reasonable treatment comparators and best-fit endpoints. Separately, it would be beneficial to identify populations for which no good solution exists to stimulate [orphan] therapeutic development. Finally, a registry should be hypothesis generating, identifying future directions and unmet needs that merit pre-clinical or early clinical exploration, consistent with the inherently evolving nature of medical research.

There is recognized value to clinicians, physical scientists and medical industry to the raw data collectable in a broad based registry. Principal amongst this is angiographic data. An analysis of the angiograms collected during a large-scale registry has potential implications for device engineering, systems controls and future device development. Data regarding patterns of disease including vessel caliber, tapering, collaterals, calcification characteristics, lesion lengths and runoff status would be useful for device development dedicated for treatment of what is the frequent complex patterns of disease inherent with CLI. Furthermore, as technical strategies and operator familiarity and comfort extend CLI treatment to below ankle interventions including plantar-pedal loop therapy, there is a clear need for technology generation to facilitate recanalization and revascularization within distal vascular beds. Integral to this may be a better conceptual understanding of angiosomes on a more microscopic level than currently discussed, with the goal of optimizing perfusion or allowing targeted delivery of therapeutics to ischemic tissue.

The information collected from a CLI registry may also benefit the future design of pivotal trials to evaluate either device performance characteristics or clinical outcomes of varying treatment strategies. The development and validation of streamlined and CLI disease-specific outcomes measures this could potentially assure the development of lean and cost effective protocols for future industry or physician initiated studies of CLI treatment. In addition to such parameters as non-invasive imaging, hemodynamics, and perfusion measurements, it may be possible to refine or redevelop new measures of wound healing (45). Several companies are developing wound imaging software, which allows for photographic recording and staging of ischemic wounds by measuring such parameters as wound depth, color, exudate, granulation, and size (46, 47). While time to complete wound healing has traditionally been utilized as the most robust measure of CLI treatment efficacy, there may be value in creating normative healing curves – also called wound trajectories – to allow an earlier assessment of treatment effect (47). This approach has been used with some success for traumatic injuries (47).

Regardless of the measurement tools used, data collection from a CLI registry could provide preliminary data that is necessary for the statistical design of future CLI trials. There is an opportunity to collect effect size for specific outcomes measures that would allow sample size determination and more streamlined protocol design. This is of inherent importance for CLI research in which there is otherwise a paucity of coherent information to guide future trial planning.

Finally, the CLI RCP recognized the need for critical alliances to assure the ideal conduct and universal recognition of data generated from a CLI registry. While there is need for a lead organization, it is equally important to assure multi-society support to assure uniform clinical support, garner support from industry for access to device data for device evaluation,

and assure input from AHRQ and independent health assessors (private, state, federal) to allow health quality and cost effectiveness outcomes.

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Table 1

Selected Presentation Topics

What endovascular therapies should be included in a CLI registry?
What can we learn from coronary registries?
What disruptive endovascular technologies are coming?
What should the primary and secondary outcomes be?
What is the best medical therapy for the patient with CLI?
What frequency of visits should the patient after an endovascular treatment have to assess patency?

CLI = critical limb ischemia.

Table 2

General Needs of a CLI Registry

<ul style="list-style-type: none">• Create a revised classification system for CLI based upon clinical and angiographic patterns of presentation.• Incorporate process measures for data collection of medical therapy with the purpose of improving quality adherence to medical guidelines by incorporating goals and compliance with medical therapy targets such as LDL, BP, and HgA1c into registry CRFs.• Identify patterns of care as delineated by unique patient populations (including socioeconomic status), regional variations, and practice structure or specialty.• Collect a broad spectrum of outcome measures to evaluate suitable and reproducible surrogates (eg, SPP, TcPO₂) for patency (for which direct measure is costly) that may be used in subsequent trials<ul style="list-style-type: none">– Document wound healing using established or well-described metrics.– Collect perfusion and hemodynamic data including SPP, TcPO₂, and vascular indices.– Validate noninvasive and angio assessment of CLI.– Include quality of life measure.• Measure costs of differential therapies and strategies including multidevice strategies.

BP = blood pressure, CLI = critical limb ischemia, CRF = chronic renal failure, HgA1c = hemoglobin A1c, LDL = low-density lipoprotein, SPP = skin perfusion pressure, TcPO₂ = transcutaneous partial oxygen.