Bare Nitinol Stenting of Tibial Arteries in CLI Patients

An interim look the VIVA I/XCELL trial.

BY KRISHNA ROCHA-SINGH, MD, FACC, FSCAI, ON BEHALF OF VIVA PHYSICIANS, INC.

Peripheral arterial disease (PAD) of the lower extremities affects approximately 25 million Americans annually.[1-3] The spectrum of clinical symptoms in these patients ranges from reproducible leg discomfort with ambulation (intermittent claudication), to severe pain at rest, to skin ulceration and gangrene leading to amputation (critical limb ischemia [CLI]). The diabetic population is particularly prone to the most severe manifestations of PAD, with markedly increased amputation rates[4] and mortality rates after amputation.[5] Although femorotibial surgical bypass has been a standard of care for many years, it is not widely utilized due to patient comorbidities that make surgery a prohibitive risk, lack of available quality venous conduits, and a limited physician pool capable of performing the operation. Importantly, these surgical procedures are associated with perioperative mortality rates of 2% to 5% and morbidity rates of 10% to 30%[6-8] at 1 year. Limb salvage rates and 1-year patency rate with a surgical approach vary depending on the nature of the operation, but generally range from 95% in the best-case scenario to 50% to 70% with prosthetic grafts.[9-11] The cumulative effect of these limitations is that primary amputation is often the default surgical option.

Given these limitations, less-invasive endovascular approaches to limb salvage in this population have been sought. Led by advances in technologies and techniques, this approach has gradually gained acceptance across the subspecialties. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) Trial concluded that in patients presenting with severe limb ischemia due to infrainguinal occlusive atherosclerosis, lower-limb bypass and balloon angioplasty were associated with broadly similar outcomes in terms of amputation-free survival.[11] These results have further focused efforts toward defining less-invasive endovascular therapies. Single-center reports and prospective registry data of balloon angioplasty, cryoplasty, and excisional atherectomy have demonstrated that percutaneous interventions may offer a safe alternative to surgical intervention, with encouraging limb salvage rates.[12-16] However, endovascular approaches to CLI are not without limitations.

It is well understood that angioplasty and other interventional techniques have limited patency, due in part to residual plaque burden, vascular recoil, and dissection. Twenty percent of patients randomized to receive balloon angioplasty in the BASIL trial were judged to be immediate technical failures.[11] A potential solution to these shortcomings may be found in the application of small-vessel, self-expanding stents. Regrettably, there are no currently FDA-approved endovascular therapies specifically targeting CLI patients, and data defining the effectiveness, safety, durability, and impact on quality of life are lacking.

Figure 1. The Xpert Biliary Stent (Abbott Vascular). Available deployment diameters range from 3 mm to 6 mm, and lengths range from 20 mm to 60 mm.

TABLE 1. BASELINE CLINICAL CHARACTERISTICS

	n (%)
Patient number	58
Mean age (y)	76
Men	31 (53%)
Women	27 (47%)
History of smoking	53 (51%)
Diabetes	41 (71%)
Chronic renal insufficiency	15 (26%)
Hypertension	49 (84%)
Rutherford class 4	12 (21%)
Rutherford class 5	35 (60%)
Rutherford class 6	11 (19%)

TABLE 2. BASELINE ANATOMIC DATA

	%
Runoff vessels:	
One vessel	73%
Two vessels	25%
Three vessels	2%
Lesion type:	
De novo	100%
Mean stented length	7 cm

THE VIVA I/XCELL TRIAL

In January 2006, VIVA Physicians, Inc. (VPI) met with the FDA's Center for Device and Radiological Health staff to discuss the clinical challenges associated with the care of CLI patients, potential trial designs, and study endpoints to best define the safety and effectiveness of infrapopliteal nitinol stents and regulatory issues. As a result of those discussions, the VIVA I/XCELL trial became the largest US prospective, multicenter registry of patients with CLI to evaluate an infrapopliteal stent, the Xpert self-expanding nitinol stent (Abbott Vascular, Santa Clara, CA) (Figure 1). The criteria for inclusion included (1) patients with chronic CLI in Rutherford classes 4, 5, and 6, (2) a stenosis >50%, or occlusion of the tibial vessel with a diameter 2 mm to 5 mm with (3) a total estimated stented length ≤15 cm.

The XCELL trial is a phase 1 feasibility study, and the data will be used to define appropriate primary and secondary endpoints and assess event rates to power a pivotal trial of this endovascular treatment strategy for treating infrapopliteal atherosclerosis in CLI patients. Importantly, this trial incorporates independent hemodynamic, angiographic, and photomorphometric wound-healing core labs and a Data and Safety Monitoring Board. The primary study endpoint of 12-month amputation-free survival and secondary endpoints of angiographically defined stent restenosis rates, stent fracture assessment, and rate and extent of ulcer wound healing will be determined. Recruitment is ongoing with the goal to enroll 140 patients at ≤15 US sites. Pre-enrollment evaluation will include a baseline noninvasive assessment of limb perfusion (eg, ankle-brachial indices/thigh-brachial indices, baseline pulse plethysmography, pulse volume recording, and/or transcutaneous pulse oximetry), in addition to baseline quality-of-life and pain assessments, and an angiogram to document baseline angiographic status with follow-up visits at 30 days, 3 months, 6 months, and 12 months.

INTERIM DATA

As the XCELL trial approaches its enrollment midpoint, the challenges of treating the CLI cohort are evident (Tables 1 and 2). Currently, 59 patients have met entry criteria with the majority (79%) in Rutherford class 5 or 6 and diabetic (71%), with single-vessel runoff (73%);

the mean stented vessel length was 7 cm. Assessment of 6-month angiographic stent patency, 12-month major amputation-free survival, wound-healing rates, and stent-fracture assessment is presently underway.

FUTURE DIRECTIONS

The development of new endovascular technologies for use in infrapopliteal arteries must directly confront several challenges. The CLI patient frequently presents with long segments of stenotic and/or occlusive disease, often in densely calcified, small-caliber arteries with frequently compromised in-flow and runoff. Further complicating this strategy, these patients are typically elderly with multiple comorbidities (heart failure, renal insufficiency, and poor nutrition). Clearly, technological advances in low-profile, high-pressure angioplasty balloon designs (.014-inch and .018-inch platforms) available in long lengths (10 cm to 15 cm), combined with specialized coated extra-support wires, have greatly improved the acute procedural success of infrapopliteal revascularization procedures. The addition of the Cutting Balloon (Boston Scientific Corporation, Natick, MA), sculpting balloon (AngioSculpt, AngioScore Inc., Fremont, CA), cryoplasty balloon (PolarCath, Boston Scientific Corporation), laser atherectomy (Spectranetics Corporation, Colorado Springs, CO), and excisional atherectomy (FoxHollow Technologies, Redwood City, CA) represent potentially important adjuncts to our armamentarium.

Although these technologies have established their safety in improving acute procedural success and vessel luminal diameter and have achieved satisfactory limb salvage rates, no device has proven its superiority or cost-effectiveness over the more-established and less-expensive balloon angioplasty. Recently, encouraging preliminary data from several European single-center and multicenter registry trials of drug-eluting steel stents (Cypher, Cordis Corporation, a Johnson & Johnson Corporation, Miami, FL), nitinol stents (Xpert, Abbott Vascular), and bioabsorbable metal stents (AMS, Biotronik GmbH & Co., Berlin, Germany) in CLI patients have been reported. Clearly, these initial results must be confirmed by larger randomized multicenter trials with appropriate long-term follow-up and adjudicated effectiveness and safety endpoints.

CONCLUSION

In the US, the regulatory pathway for device approval of vascular stents requires demonstration of safety and effectiveness via a premarket approval (PMA) process.[17] This demonstration must be derived from clinical trial data specific to the proposed labeling and indications and for the intended patient. Generally, this provision has required that the device sponsor perform a randomized clinical trial against an established standard of care to ascertain the requisite safety and efficacy. However, the FDA Modernization Act of 1997[18] subsequently required the FDA to consider a "least burdensome method" of evaluation that is likely to result in device approval and thereby consider nonrandomized trial designs. In keeping with this, the agency recently agreed that the superficial femoral artery balloon angioplasty performance metrics were an appropriate comparator for single-arm trials of bare nitinol stents.[19] Presently, VPI is collaborating with the FDA on the development of below-the-knee surgical performance goals for CLI patients, which may provide a potential option for future vascular device approval in this challenging patient cohort. ■

This article was written on behalf of VPI members Gary Ansel, MD; Michael Dake, MD; Tony Das, MD; Michael Jaff, DO; James Joye, DO; John Laird, Jr, MD; Jon Matsumura, MD; Kenneth Rosenfield, MD; and Timothy Sullivan, MD.

Krishna Rocha-Singh, MD, FACC, FSCAI, is Medical Director, Prairie Vascular Institute, in Springfield, Illinois. He has disclosed that he is a consultant for Boston Scientific Corporation, Cordis Corporation, ev3 Inc., and Medtronic Corporation and receives research funds from Abbott Vascular, Inc. Dr. Rocha-Singh may be reached at (217) 788-0706; ksingh@prairieheart.com.

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