Interim Results From the VIVA I: Xcell Trial

Bare-nitinol stenting of tibial arteries and wound-healing assessment in critical limb ischemia patients.

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The global economic and social burden of critical limb ischemia (CLI) is substantial and growing. An estimated quarter-million major and minor lower extremity amputations are performed in the US and Europe yearly due to CLI.[1-5] In the US, amputation rates have increased over the past 2 decades from 19 to 30 per 100,000 patient years primarily due to advancing age and the diabetes epidemic.[6]

Revascularization of CLI patients is particularly challenging because the anatomic disease is frequently multilevel (aortoiliac, femoropopliteal, and/or infrapopliteal) and involves multiple tibial vessels; relatively few patients present with simple, focal stenotic disease with adequate distal runoff.[7,8] The rate of multivessel long occlusive disease (>10 cm) is even higher in diabetic patients. In a consecutive series by Graziani et al of more than 400 diabetic CLI patients undergoing peripheral angiography, 36% of patients were noted to have either two occluded tibial arteries and/or multiple stenoses of tibioperoneal and/or femoropopliteal vessels.[9]

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, a 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%[1] at 1 year. Limb salvage rates and 1-year patency 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. The cumulative effect of these limitations is that primary amputation is increasingly the default surgical option.

Recently, Romiti et al published a meta-analysis based on 30 peer-reviewed articles published between 2000 and 2006, which analyzed the midterm outcomes after tibial angioplasty in CLI patients and compared the clinical outcomes with a meta-analysis of popliteal-to-distal vein bypass graft.[10] Notably, whereas primary and secondary vessel patency favored bypass surgery over percutaneous transluminal angioplasty at time points between 1 and 36 months, the amputation-free survival rate and quality-of-life assessments for comparable patient cohorts were identical. The conclusions of this meta-analysis were similar to those of the BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial;[11] this randomized prospective 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. These reports and other single-center studies and prospective registries 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]

Led by advances in technologies and techniques, an endovascular-first approach in appropriate patients has gradually gained acceptance across the subspecialties. Given the comparable 12-month amputation-free survival rates in patients treated with either a surgical or endovascular approach, a focus on other potentially clinically rele-

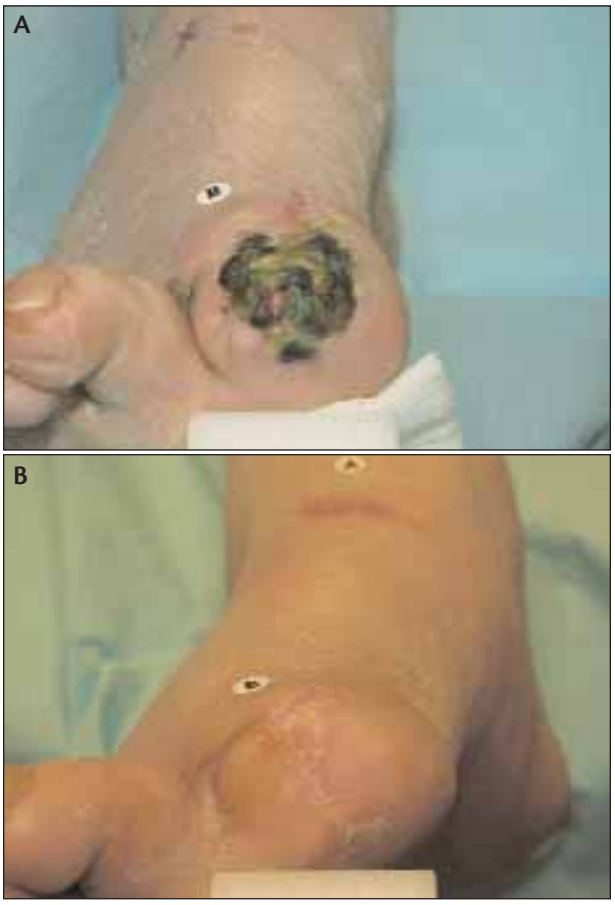

Figure 1. Seventy-two-year-old man presented with a non-healing first toe amputation site; a transmetatarsal amputation was contemplated (A). Six-month follow-up wound assessment after successful stenting of a long anterior tibial segment of disease (B). The 6-month follow-up angiogram confirmed vessel patency.

vant endpoints that may distinguish the effectiveness of these modalities' revascularization strategies has emerged. In this regard, the rate and completeness of ischemic wound healing (ie, tissue perfusion) has evolved into an important reflection of effectiveness of these two modalities. However, given the evolving enthusiasm for the endovascular-first approach, it should be noted that significant limitations persist. It is well understood that angioplasty and other interventional techniques have limited patency due in part to residual plaque burden, vascular recoil, and dissection. Indeed, 20% of patients randomized to receive balloon angioplasty in the BASIL trial were judged to be immediate technical failures.[11] Additionally, clinical patency after tibial percutaneous transluminal angioplasty, particularly in long lesions, has been poor. Although the duration of vessel patency may be sufficient to promote wound healing, the longer-term effect on recurrent wound

TABLE 1. BASELINE CLINICAL CHARACTERISTICS

Clinical Characteristics	Patients (n=113)
Age (mean±SD)	75.22±9.19
Men	60 (53.1%)
Women	53 (46.9%)
Diabetes mellitus	76 (67.3%)
Chronic renal insufficiency	26 (23%)
History of smoking	61 (54%)
Hypertension	99 (87.6%)
Rutherford criteria:	
4	21 (18.6%)
5	76 (67.3%)
6	16 (14.2%)

TABLE 2. BASELINE ANGIOGRAPHIC CHARACTERISTICS

Angiographic Characteristics	Patients (n=113)
Tibial runoff vessels:	
1	70 (61.9%)
2	40 (35.4%)
3	3 (2.7%)
Stented length, cm (mean±SD)	7.56±4.18

formation in the event of vessel renarrowing or restenosis is unclear. Although the recent commercial availability of a paclitaxel-eluting balloon (In.Pact Amphirion; Invatec, S.p.A., Roncadelle, Italy) and the announcement of several European trials[17] evaluating their effectiveness as an adjunct to tibial angioplasty in CLI patients holds potential promise, their availability in the US is not imminent. In the interim, one potential solution to these shortcomings may be found in the application of small-vessel, self-expanding stents. Regrettably, there are no endovascular therapies specifically targeting CLI patients that are currently approved by the Food and Drug Administration, and data defining the effectiveness, safety, and impact on wound healing and quality of life are lacking.

THE XCELL TRIAL BACKGROUND

In January 2006, the VIVA Physicians met with the Food and Drug Administration's Center for Devices and Radiological Health (CDRH) 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 chronic limb ischemia to evaluate

TABLE 3. CHANGE IN WOUND AREA (cm^2) FROM BASELINE THROUGH 6-MONTH FOLLOW-UP IN 46 OF 147 ISCHEMIC WOUNDS STUDIED

Healing Wounds (46 of 147)	Wounds n (%)	Baseline Area (cm^2) Mean±SD (n=44)[a]	Healing Area (cm^2) Mean±SD (n=46)
Healing before or at 3 months	29 (19.7)	6.46±13.13	3.9±7.28
Healing at 6 months	17 (11.6)	8.14±6.41	4.26±5.18
Total healing wounds	46 (31.3)		

[a]Missing baseline calculation on two patients.

TABLE 4. PERCENTAGE OF WOUNDS HEALED FROM BASELINE AREA (cm^2) THROUGH 6-MONTH FOLLOW-UP

Healing/Healed Wounds Through 6 Months[a]	Wounds (n=147) n (%)
100% healed, n (%)	62 (42.2)
75%–99% healed, n (%)	9 (6.1)
50%–74% healed, n (%)	13 (8.8)
25%–49% healed, n (%)	9 (6.1)
24% healed, n (%)	13 (8.8)

[a]Unable to calculate percent healed on two patients due to missing baseline area calculation.

an infrapopliteal stent, the Xpert self-expanding nitinol stent (Abbott Vascular, Santa Clara, CA). The criteria for inclusion included (1) patients with chronic CLI in Rutherford classes 4, 5, and 6, (2) an isolated stenosis >50%, or occlusion of the tibial vessel with a diameter 2 to 5 mm, with (3) a total estimated stented length ≤15 cm. 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 is paired with the secondary endpoints of angiographically defined in-stent restenosis rates, stent fracture assessment, and rate and extent of wound healing (Figure 1). Pre-enrollment evaluation includes a baseline noninvasive assessment of limb perfusion (eg, ankle-brachial and toe-brachial indexes, baseline photoplethysmography [PPG], pulse volume recordings [PVR], and/or transcutaneous pulse oximetry [$TcPO_2$]), in addition to baseline quality-of-life and pain assessments and an angiogram to document patients' baseline angiographic status with follow-up visits at 30 days, 3, 6, and 12 months. At the present time, 114 patients have been enrolled at 12 enrolling US sites. As a phase 1 feasibility study, data from the Xcell trial will be used to define appropriate primary and secondary clinical endpoints, assess event rates, and power pivotal trials of endovascular treatment strategies for treating infrapopliteal atherosclerosis in CLI patients.

INTERIM DATA

As enrollment in the Xcell trial nears conclusion, the challenges of treating CLI patients have become evident (Tables 1 and 2). Thus far, 114 patients have met entry criteria with the majority in Rutherford class 5 or 6 (81.5%) and diabetic (67%), with single-vessel runoff (62%); the mean stented vessel length was 7.6 cm. The 12-month amputation-free survival rate of this challenging cohort thus far is an encouraging 91.2%. Of particular interest, the adjudicated wound-healing core lab data have established that 42.2% of wounds noted at study enrollment were completely healed by the 6-month follow-up, while an additional 48.3% were ≥75% healed; only 8.2% of the wounds worsened during follow-up (Tables 3 and 4). This trial will also provide important new insights into the association among the durability of the wound-related artery stent patency, the rate of wound healing, and the associated quality of life of these patients after intervention.

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 inflow and pedal runoff. Further complicating this strategy is that 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- and .018-inch platforms) available in long lengths (10–22 cm), combined with specialized, coated extra-support wires and vascular approaches, have greatly improved the acute procedural success. The addition of the cutting balloon (Boston Scientific Corporation, Natick, MA), sculpting balloon (AngioSculpt, Inc., Fremont, CA), cryoplasty balloon (PolarCath; Boston Scientific Corporation), laser atherectomy (Spectranetics Corporation, Colorado Springs, CO), exci-

sional atherectomy (ev3 Inc, Plymouth, MN), orbital atherectomy (Cardiovascular Systems, Inc., St. Paul, MN), and extractional atherectomy (Jetstream Catheter; Pathway Medical Technologies, Kirkland, WA) all represent potentially important adjuncts to our armamentarium. Although most of these technologies have established their safety in improving acute procedural success and vessel luminal diameter and have achieved satisfactory 12-month limb salvage rates, no device has proven its superiority or cost-effectiveness over the more-established and less-expensive balloon angioplasty.

Recently, several device companies have announced the initiation of large prospective registries to assess the effectiveness of their marketed products. Invatec recently announced its intent to conduct a large multicenter, randomized controlled trial of its paclitaxel-eluting balloon (In.Pact Amphirion) compared to balloon angioplasty; enrollment of more than 375 CLI patients is anticipated to commence in mid-2009 and will include both angiographic and wound-healing core labs to independently adjudicate primary and secondary study endpoints.

Encouraging preliminary data from several European single-center and multicenter registry trials of drug-eluting steel stents (Cypher stent, Cordis Corporation, Warren, NJ) and nitinol stents (Xpert stent) in CLI patients have recently been announced and more are planned. Ev3 Inc. will soon announce enrollment in a large international prospective registry of 800 patients with Rutherford class 1 through 6 symptoms to be treated with their FoxHollow excisional atherectomy device as a stand-alone therapy. The DEFINITIVE LE trial will feature an independent Duplex ultrasound core laboratory to adjudicate the primary study endpoints of 12-month vessel patency in claudicants and an angiographic core to assess procedural success.

Clinicians and payers alike await the results of these important clinical trials to help assist them in important clinical decision making in this challenging patient population. ■

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