JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 12, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.08.008

EDITORIAL COMMENT

Missing the Forest for the Trees?

Drug-Eluting Balloon Treatment for Infrapopliteal Disease*

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The treatment of patients with infrapopliteal disease has become common in our clinical practice as the number of patients with symptomatic peripheral arterial disease skyrockets, affecting 12% to 29% of the elderly and as many as 8 to 10 million Americans (1,2). Contemporary data suggest that >10% of these patients have critical limb ischemia (CLI), defined as rest pain, nonhealing wounds, or gangrene (3). Historically, treatments for CLI have yielded poor results. At 1 year, 25% of patients will be dead, 30% will have undergone amputation, and only 45% will remain alive with both limbs (4,5). Given the high comorbidity burden of patients with CLI and their increased risk of complications with open surgery, endovascular therapy has been advocated as the preferred treatment (6).

The foundation for an endovascular first strategy emanated from the BASIL (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) (7) randomized controlled trial published 10 years ago, which demonstrated similar amputation-free survival in patients with CLI suitable for both lower extremity bypass and endovascular therapy with higher short-term morbidity with surgery. Since that large seminal randomized controlled trial comparing 2 different therapies for CLI, there has been an explosion of smaller single-center, single-arm studies confirming the procedural success and safety of different interventional devices with universally high limb salvage rates. Even CLI patients who are not suitable for revascularization, "no option patients," enrolled in gene and cell therapy trials have 1-year limb salvage rates of >75% to 80% (8–10). Furthermore, primary patency or binary restenosis has not been associated with hard outcomes such as limb salvage or quality of life metrics (11–13).

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In this issue of *JACC: Cardiovascular Interventions*, Zeller et al. (14) studied 76 patients with stenosis, restenosis, or occlusion of the infrapopliteal arteries excluding in-stent restenosis suffering from claudication (n = 16) or critical limb ischemia (n = 60), and they assessed the safety and performance of the Passeo-18 Lux paclitaxel coated drug-eluting balloon (DEB) versus the uncoated Passeo-18 balloon catheter (both Biotronik, Berlin, Germany). Using this multicenter randomized controlled trial, they contributed 3 main findings to the existing published reports.

1. The primary safety endpoint consisting of mortality, major amputation, treatment thrombosis, and target vessel revascularization was not statistically different between DEB and plain balloon angioplasty (PTA) at 6 months (0% vs. 8.3%, p = 0.239).
2. Patency loss on 6-month angiography between DEB and PTA groups was high (20.3% vs. 26.6%), approaching 50% in both groups and not statistically different at 1 year (50.8% vs. 45.6%).
3. Despite the loss of patency and high target lesion revascularization rates at 12 months between DEB and PTA (24% vs. 27.3%), limb salvage rates were high (96.7% vs. 94.1%) in both groups.

Zeller et al. (14) should be congratulated for the BIOLUX P-II (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries) prospective, multicenter, randomized controlled trial with independent clinical event adjudication and angiographic core lab for a study designed to determine the superiority of 1 device versus PTA alone. These studies are considered the "crème de le crème" of clinical research, allowing clinicians to compare treatments directly to one another minimizing the effects of confounding on cause and effect. These studies are in the minority compared to single-arm, single-center device trials or prospective device registries, which can confirm safety but not comparative effectiveness. Our expectations as clinicians in 2015 should be an investment in trials to demonstrate the comparative safety and effectiveness of different devices, and we should no longer settle for single-arm device trials of safety. Unfortunately for paclitaxel DEB, this study joins others in failing to meet criteria for superiority versus PTA alone for angiographic and hard clinical endpoints and supports the supposition of high restenosis rates but high limb salvage rates with plain old balloon angioplasty alone (15,16).

There are many deficiencies in the clinical research design of studies in the treatment of CLI that must be addressed moving forward. Most importantly, we must come to consensus regarding the relevant endpoints and their definitions in CLI trials. This deficiency has been overtly recognized in the medical community by Conte et al. (17) in their suggested objective performance goals and clinical trial design statement published in 2009 to evaluate catheter-based treatment of CLI. They advocate for a primary efficacy endpoint defined as 30-day death and major adverse limb event (amputation or major reintervention) occurring within 1 year adopted in part by the study by Zeller et al. (14). Efforts to harmonize and solidify relevant clinical trial and registry data elements and definitions in the evaluation and treatment for peripheral arterial disease were recently addressed by the U.S. Food and Drug Administration with multiple stakeholders and culminated in the release of consensus definitions from the Peripheral Academic Research Consortium (18). This document advocates for a consistent use of definitions and nomenclature across clinical trials in the peripheral arterial disease space for more efficient regulatory evaluation and best practice guidelines to inform clinical decisions.

However, one must ask, have we lost the forest for the trees? With limb salvage rates at 1 year exceeding 85% in most CLI trials evaluating all types of treatments, such as PTA (cryoplasty, cutting balloons, scoring balloons), drug-eluting stents for focal tibial disease, atherectomy, ablation, cell therapy, and no-option control patients is limb-salvage really the endgame? We are well aware of the difficult lifestyle of our patients with CLI who come to our appointments in their wheelchairs often propelled by caregivers just after their biweekly wound care appointment. Up to 70% of CLI patients are on analgesia with continued pain that is hard to suppress and have quality-of-life scores worse than cancer, chronic heart failure, and chronic kidney disease (19). The Institute of Medicine envisioned a more patient-centered health care system focused on the patient's functional status and health-related quality of life (defined as the patient's perceived physical, emotional, and social well-being and function). Treatment of CLI should be focused on improving health status in addition to limb preservation, which is a refreshingly easy metric to achieve in contemporary CLI programs. Disease-specific questionnaires such as the Peripheral Artery Questionnaire and the Walking Impairment Questionnaire are just a few of the validated tools in assessing functional status and quality of life in patients with lower extremity claudication; however, CLI-specific instruments that incorporate wound care domains may be more comprehensive (20). Most would agree that wound care is at least as important to wound healing and limb salvage as blood flow is, yet efforts to standardize the care of wounds in clinical practice or clinical trials has been lacking. Current classification schemes such as the Fontaine stages and Rutherford categories are insufficient to capture the extent and severity of nonhealing wounds. Perhaps the Society for Vascular Surgery Lower Extremity Threatened limb classification system, which has been designed to better define the disease burden based on the degree of ischemia, wound extent, gangrene, and infection, will allow better quantification of wound severity and allow measures of wound healing as an endpoint in future trials of CLI care (21). Although vessel patency and limb salvage are logical and laudable endpoints to consider, until we routinely include measures of wound healing and quality of life to these trials, we will continue to miss the forest for the trees in our patients with CLI.

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KEY WORDS critical limb ischemia, drug-coated balloon, drug-eluting balloon, peripheral artery disease