What Is the Correct Endpoint?

Discerning endpoints for clinical trials in endovascular therapy for infrainguinal arterial disease.

BY MICHAEL R. JAFF, DO

As interest in minimally invasive therapy for patients with peripheral arterial disease increases, decisions regarding optimal therapy must be based on the strongest evidence available. Unfortunately, published series of infrainguinal intervention are few and far between, with different inclusion and exclusion criteria and different endpoint definitions. For interventionists to decide the optimal treatment for their patients, comparative patient populations and endpoints must be used.

In searching for the highest level of modern literature in infrainguinal endovascular therapy, one need not look further than the recent prospective randomized trial of percutaneous transluminal angioplasty (PTA) versus nitinol self-expanding stents in the superficial femoral artery by Schillinger et al.[1] In this study, patients with advanced intermittent claudication, ischemic rest pain, or nonhealing ischemic ulcers were randomized, with a primary endpoint of patency of the treated segment as determined by contrast or computed tomographic arteriography at 6 months after enrollment. Restenosis was defined as >50% stenosis of the treated segment, including 10 mm at the proximal and distal aspects. All other factors, including patency at 12 months (as determined by duplex ultrasonography), clinical outcomes (treadmill walking distance), and stent fractures were secondary endpoints. In this series, restenosis at 6 months was 25% in the stent group and 50% in the PTA group (P=.02).

The patency benefit of stenting in this trial has persisted at 24 months, as measured by duplex ultrasonography.[2] It is interesting to note that the initial benefit of exercise tolerance of the stent group at 12 months was lost at 24 months.

TABLE 1. DEFINITION OF GRAFT PATENCY*

- Anatomic patency by arteriography, duplex ultrasonography, magnetic resonance arteriography (theoretically, computed tomographic arteriography)
- Maintenance of arterial pressure obtained immediately postprocedure (ie, change in ankle-brachial index [ABI] ≤ .1 when compared to baseline postprocedure)
- Maintenance of pulse volume waveform distal to the site of revascularization when compared to postprocedure waveform

**Adapted from Rutherford et al.*[3]

INCONSISTENT DEFINITIONS

It remains curious that there are inconsistencies in definitions of patency or clinical benefits. More than 20 years ago, Rutherford et al described the anatomic and clinical standards against which all vascular reconstructions should be compared.[3] Patency was defined by one of several standards (Table 1). Clinical improvement was defined by a grading scale (Table 2). However, many investigators have not adopted these definitions for endovascular interventions.

Without formal definitions, the reader may be misled by the reported outcomes. For example, *clinical patency* is a term used quite often in abstracts and national meetings. This term refers only to the clinical outcome of the patient without providing any real information on the success and patency of the intervention. For example, if a patient is being treated for disabling intermittent claudication with a femoropopliteal bypass graft or femoropopliteal endovascular intervention and has complete resolution of symptoms, there is no doubt that the patient has responded well to the intervention. However,

TABLE 2. DEFINITION OF CLINICAL IMPROVEMENT*

- +3: Markedly improved: Symptoms completely resolved or markedly improved; ABI >.9
- +2: Moderately improved: Single category of improvement with at least .1 increase in ABI, but not normal
- +1: Minimally improved: .1 increase in ABI or one category of clinical improvement
- No change
- -1: Mildly worse: .1 decrease in ABI or one category of clinical deterioration
- -2: Moderately worse: One category worse or an unexpected minor amputation
- -3: Markedly worse: More than one category worse or an unexpected major amputation

**Adapted from Rutherford et al.*[3]

if the patient has a worsening absolute claudication time after 6 months, this may be due to:

- failure of the intervention;
- development of inflow or outflow lesions with patency of the treated segment;
- concurrent nonvascular limb symptoms (eg, neurogenic, arthritic).

Therefore, clinical patency alone is insufficient to provide useful data to determine the appropriateness of therapy.

In addition, providing only anatomic patency results without describing clinical outcomes is insufficient. A patient treated for critical limb ischemia and a nonhealing ulceration undergoes infrapopliteal intervention for limb salvage. Describing longitudinal patency data over the next 6 months is unimportant without a description of the ischemic ulcer size, rate of healing, and, ultimately, amputation. Combining clinical endpoints with anatomic patency is expected.

MEANINGFUL ENDPOINTS

Hirsch best describes these important endpoints in an editorial accompanying the initial Schillinger report.[4] He challenges future peripheral arterial disease trials to contain meaningful clinical endpoints, including:

- treadmill exercise testing and quality-of-life questionnaires for patients treated for intermittent claudication;
- complete wound healing, resolution of pain, and limb salvage in patients treated for critical limb ischemia;
- comparative device trials must include relevant patient outcomes and health and economic parameters.

Yancey and coauthors, who studied the role of directional atherectomy in patients with TASC C lesions, provided an example of such meaningful endpoints.[5] Eighteen procedures were performed in 17 limbs, resulting in initial resolution of symptoms in 12 of 17 limbs. The investigators also reported complete hemodynamic and patency data. This report provides readers with a true understanding of the role of directional atherectomy in these patients. The problem, of course, is the small cohort and short follow-up time.

Recent reports of performance criteria for femoropopliteal PTA compared an historical group of patients in published series with the PTA "arms" of randomized trials of other devices that resulted in device approval by the FDA.[6] In the article, the investigators note, "The difficulty in achieving consensus on appropriate endovascular treatment strategies in patients with debilitating claudication is perpetuated, in part, by the nonconformity in patient study cohorts, definition of safety, inclusion/exclusion criteria, clinical and hemodynamic endpoints, follow-up duration, and choice of quality-of-life instruments." The appendices of the article define procedural, clinical, and anatomic endpoints.

Finally, a European consensus group provided an extensive list of definitions and endpoints, including a series of clinical, anatomic, and hemodynamic parameters, which are useful in endovascular device trials.[7]

CONCLUSION

Comparison of one treatment to another is only successful if similar patient and lesion cohorts are studied, primary and secondary endpoints are identical and the definitions are clear, and reports include meaningful clinical endpoints, such as quality of life and wound healing. ■

Michael R. Jaff, DO, is Medical Director, Vascular Ultrasound Core Laboratory at Massachusetts General Hospital in Boston, Massachusetts. Dr. Jaff may be reached at (617) 726-3784; mjaff@partners.org.

1. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006;354:1879-1888.
2. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting [published online ahead of print May 14 2007]. Circulation. http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.688341v1. Accessed May 16, 2007.
3. Rutherford RB, Flanigan DP, Gupta SK, et al. Suggested standards for reports dealing with lower extremity ischemia. J Vasc Surg. 1986;4:80-94.
4. Hirsch AT. Treatment of peripheral arterial disease—extending "intervention" to "therapeutic choice." N Engl J Med. 2006;354:1944-1947.
5. Yancey AE, Minion DJ, Rodriguez C, et al. Peripheral atherectomy in TransAtlantic InterSociety Consensus type C femoropopliteal lesions for limb salvage. J Vasc Surg. 2006;44:503-509.
6. Rocha-Singh K, Jaff MR, Crabtree TR, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Cath Cardiovasc Intevent. 2007;69:910-919.
7. Diehm N, Baumgartner I, Jaff MR, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischemia of lower limb arteries. Eur Heart J. 2007;28:798-805.