Therapy for Peripheral Artery Disease: Gaps in Treating Patients With Claudication

Ryan J. Mays, PhD, MPH; Judith G. Regensteiner, PhD, FAHA

Peripheral artery disease (PAD) is estimated to affect up to 29% of people ≥50 years of age in the United States and >200 million people worldwide. Diagnosis of PAD is associated with an increased risk of adverse medical events and premature mortality from cardiovascular disease. The classic symptom of PAD, intermittent claudication (IC), is characterized by exertional leg pain that resolves with rest and is estimated to affect up to 35% of PAD patients ≥50 years of age. Patients with PAD and IC have impaired walking ability, poor functional outcomes, and a reduced quality of life resulting at least in part from the leg pain experienced. Thus, PAD with IC is a significant international healthcare concern with an adverse impact on patients resulting from systemic atherosclerosis and IC symptoms. Few pharmacological therapy options are available to treat PAD symptoms. The most efficacious option currently to improve IC is supervised walking exercise. However, this treatment is not widely available despite strong evidence of its efficacy. In contrast, options that are more readily available to provide symptom relief for IC include invasive treatments such as endovascular therapy and surgical procedures.

In this issue of Circulation, Nordanstig and colleagues present their results of a comparison of invasive and noninvasive treatments in a prospective, single-center, randomized, clinical trial of patients with stable IC symptoms. The aim of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) trial was to compare outcomes for PAD patients receiving peripheral revascularization in combination with noninvasive therapy with outcomes in patients who received only noninvasive medical therapy. The noninvasive therapy included the provision of educational materials and medical management of the systemic atherosclerosis, prescription of cilostazol (100 mg twice daily), and general advice to walk at least 30 minutes at least 3 times per week with the use of Nordic poles encouraged. The exercise program was reinforced at 3 and 6 months. A key point of difference from other trials was that the primary outcome of the IRONIC trial was health-related quality of life (HRQOL) rather than treadmill walking ability or other objective measurements that have often been used as primary outcomes in previous trials for PAD patients with IC. The primary end point was assessed before and after 1 year of treatment with 2 well-validated HRQOL questionnaires. The results were positive, demonstrating greater improvements in HRQOL in the patients treated with invasive therapy than those treated with the noninvasive therapy alone. In thinking about the IRONIC trial, 2 key points of discussion arise that have implications for future directions in research for PAD patients with IC.

Quality of Life as a Primary Outcome in PAD With IC

The IRONIC trial used several innovative elements in the study design. Prominent among them was the use of HRQOL as the primary end point. The use of patient-reported outcomes as a primary end point in a clinical trial raises some questions that must be addressed, however. Whether HRQOL is the correct primary end point for a study depends largely on the goals of the study and the lens through which the results will be viewed. Most peripheral revascularization trials have used primary outcomes such as loss of primary patency and need for reintervention rather than patient-reported outcomes specifically. Exercise training studies in PAD have most often used treadmill walking time or distance as the primary outcome. Perception of an objective measure such as a change in hemodynamics may be of great importance to the investigator or to a clinician, given its relationship to IC symptoms. However, a patient may judge the benefit of an intervention by effects on HRQOL, which is composed of many dimensions and not just leg symptoms. The concept of HRQOL as a primary outcome has clearly been adopted by Nordanstig et al in the IRONIC trial; thus, their approach is fairly novel. Several trials have demonstrated that endovascular therapy and surgical procedures improve quality of life significantly in PAD patients, and the present study adds to this existing knowledge base by casting a broad net to evaluate outcomes in a standard hospital setting where patients present with varying morphology and location of peripheral arterial lesions. Nevertheless, the integration of quality of life as a tool to measure the clinical success of any intervention has yet to occur in standard clinical practice and remains largely an academic pursuit. Beyond a patient’s anecdotally conveyed HRQOL discussed with the healthcare provider regarding
the results of a therapy, it is clear that such HRQOL metrics have not been implemented on a consistent basis in clinical settings. Additionally, the use and interpretation of the most appropriate aspects of HRQOL are important for determining the best treatment options in PAD.

**Lack of Easy Access to Exercise Training for PAD Patients With IC**

In addition to the question of the usefulness of HRQOL as a primary end point, results of the IRONIC trial highlighted an already well-known area of weakness in the treatment of PAD with IC: the relative dearth of effective noninvasive treatments for IC. Only 1 drug, cilostazol, has been approved by the US Food and Drug Administration as an effective treatment for IC. However, it is less efficacious than supervised walking exercise and is contraindicated in patients with heart failure. Supervised walking exercise to improve walking in patients with IC has been rated *Class IA* by the American College of Cardiology/American Heart Association guidelines for the treatment of IC in PAD. There is an abundance of evidence to support this conclusion. However, supervised exercise continues to be largely unavailable to most patients, as is pointed out by the authors of the IRONIC trial. Many issues have precluded the widespread use of this efficacious therapy. Likely factors include the lack of third-party reimbursement, habitual lifelong sedentary behavior, patients’ disinterest in exercise as a result of leg pain during walking, and compliance issues caused by the need for travel to clinics several times per week over an extended period of time. Prior unsupervised exercise programs, consisting mostly of general advice to exercise with little follow-up provided, have largely been ineffective, rated by the American College of Cardiology/American Heart Association PAD management guidelines as *Class Ib* with a *Level of Evidence, B*. The reason may be that general advice to exercise at home will typically fail to improve walking ability, in part because PAD patients must make a concerted effort to change their behavior, which is challenging given that they have typically been sedentary for much or all of their lives. Recently, however, a number of unsupervised exercise trials in community settings have proved to be more successful. The reason for the success of these trials may be that some elements of supervised exercise programs were included such as training, monitoring, and coaching of patients. Including some of the successful parts of supervised walking training in the community setting may be the appropriate next step for noninvasive therapy that includes exercise training as a way to improve outcomes.

**Call for Research**

The results of the IRONIC trial add to the existing knowledge base on revascularization as a treatment that clearly can improve blood flow and thereby reduce IC. In addition, the IRONIC trial raises some important questions that can point to important research directions in vascular medicine. Invasive procedures lead to improved patient satisfaction and better walking performance outcomes compared with a noninvasive medical therapeutic approach including general exercise advice. So what is wrong with noninvasive therapy options, specifically exercise training for PAD? The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study used supervised exercise training as a comparator to invasive therapy with the result that both treatments proved effective with regard to HRQOL and walking ability. However, the problem is that supervised exercise is not easily available for the reasons mentioned earlier, and programs that can be carried out in the home or community setting have been unsuccessful until recently. Until reimbursement is available for supervised walking exercise (and a resolution to other barriers for program participation), researchers and healthcare providers alike need to continue to perform research on developing exercise programs that can be used in community settings. A PAD patient’s assessment of how his or her quality of life is affected by both the disease and its treatment is also very important. The call for and use of patient-centered outcomes is beginning to proliferate in medicine. The practice of using HRQOL in clinical settings may be one of the next seminal steps in research to treat IC resulting from PAD. More research is clearly needed in this area because there are currently many quality of life instruments in the PAD published literature, making the decisions of which tools to use and when to use these measures as primary or secondary outcomes more difficult.

**Disclosures**

Dr Mays is supported by grant K01 HL115534 from the National Institutes of Health and the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr Regensteiner reports no conflicts.

**References**

Therapy for Peripheral Artery Disease: Gaps in Treating Patients With Claudication
Ryan J. Mays and Judith G. Regensteiner

Circulation. 2014;130:929-931; originally published online August 5, 2014;
doi: 10.1161/CIRCULATIONAHA.114.011990

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/130/12/929

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/