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

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Introduction

Peripheral artery disease (PAD) is estimated to affect up to 29% of people 50 years of age in the US¹ and over 200 million people worldwide.² Diagnosis of PAD is associated with an increased risk of adverse medical events and premature mortality from cardiovascular disease.^{3,4} 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 and older.^{5,6} Patients with PAD and IC have impaired walking ability and poor functional outcomes as well as a reduced quality of life due at least in part to the leg pain experienced.⁷ Thus, PAD with IC is a significant international healthcare concern with adverse impact on patients resulting from the systemic atherosclerosis and the symptom of IC. There are few pharmacological therapy options 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 the 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.⁸

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In this issue of *Circulation*, Nordanstig and colleagues⁹ present their results comparing invasive vs. non-invasive treatments in a prospective, single-center randomized clinical trial in 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 non-invasive therapy to outcomes in patients who only received non-invasive medical therapy. The non-invasive 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 use of Nordic poles being 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 which have often been used as primary outcomes in prior trials for PAD with IC patients. The primary endpoint was assessed pre and post 1-year of treatment using two well-validated HRQOL questionnaires.^{10,11} The results were positive, demonstrating greater improvements in HRQOL in the patients treated with invasive therapy than the non-invasive therapy alone. In thinking about the IRONIC trial, two key points of discussion arise which 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 endpoint. The use of patient-reported outcomes as a primary endpoint in a clinical trial raises some questions that must be addressed, however. Whether HRQOL is the correct primary endpoint for a study largely depends on the goals of the study and the lens through which the results will be viewed.¹² Most peripheral revascularization trials have utilized primary outcomes such as loss of primary patency, and need for re-intervention rather than patient-reported outcomes specifically.¹³ 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.^{14,15} The concept of HRQOL as a primary outcome has clearly been adopted by Nordanstig et al⁹ in the IRONIC trial and their approach is thus fairly novel. Several trials have demonstrated that endovascular therapy and surgical procedures improve quality of life significantly in PAD patients,¹⁶⁻¹⁸ and the current 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 individual, anecdotally conveyed HRQOL discussed with their respective 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.¹⁹ 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 with IC

In addition to the question of the usefulness of HRQOL as a primary endpoint, 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 non-invasive treatments for IC. Only one drug, cilostazol, has been approved by the 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 those with IC has been rated IA by the ACC/AHA guidelines for the treatment of IC in PAD. There is an abundance of evidence to support this conclusion.^{8,20} However, supervised exercise continues to be largely unavailable to most patients, as is pointed out by the authors of the IRONIC trial.⁹ Many issues have precluded the widespread use of this efficacious therapy. Likely factors include the lack of third-party reimbursement, habitual lifelong sedentary behavior, disinterest in exercise by patients due to leg pain during walking, and compliance issues due to the need for travel to clinics several times per week over an extended period of time. Prior unsupervised exercise programs, mostly consisting of general advice to exercise with little follow-up provided, have been largely ineffective, rated by the ACC/AHA PAD management guidelines as IIb with an evidence level of B.⁸ This may be because 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 they have typically been sedentary for much or all of their lives.²¹ However, recently a number of unsupervised exercise trials in community settings have proven to be more successful.^{22,23} 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 for patients. Including some of the successful parts of supervised walking training in the community setting may be the appropriate next step for non-invasive 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 regarding revascularization as a treatment which clearly can improve blood flow and thereby reduce IC.²⁴ 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 when compared to a non-invasive medical therapeutic approach including general exercise advice. So what is wrong with non-invasive therapy options, specifically exercise training for PAD? The CLaudication: Exercise Vs. Endoluminal Revascularization (CLEVER) study did use supervised exercise training as a comparator to invasive therapy with the result that both treatments proved effective with regard to HRQOL as well as walking ability.¹⁶ However, the problem is that supervised exercise is not easily available for the reasons mentioned earlier and programs which can be carried out in the home and/or community settings have also been unsuccessful until recently. Until reimbursement is available for supervised

walking exercise (as well as a resolution to other barriers for program participation), researchers and healthcare providers alike need to continue to perform research on developing exercise programs which can be used in community settings. A PAD patient's assessment of how their 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.¹² 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 as there are currently many quality of life instruments in the PAD published literature,¹⁹ making the decision of which tools to utilize more difficult, in addition to the question of when to use these measures as primary or secondary outcomes.

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