Lessons Learned from Recent Randomized Clinical Trials for Intermittent Claudication

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It is well recognized that lower extremity peripheral arterial disease (PAD) is highly prevalent and results in significant cardiovascular mortality akin to cardiovascular disease. Among patients with PAD there is a broad range of clinical manifestations, with a third of patients having typical intermittent claudication (IC). The symptoms of lower extremity PAD, even in a stable nonlimb threatening form, result in measurable reductions in quality of life (QOL) and physical functioning, including mobility loss. The morbidity from PAD and relatively high rate of vascular procedures performed in symptomatic patients has resulted in health economic costs that are greater than ischemic heart disease and stroke. Moreover, the number of catheter-based interventions for PAD has increased in recent years, likely due to multiple factors, including disease recognition, development of endovascular devices, and a shift from open surgical procedures and performance of procedures by 3 disciples of medicine: interventional cardiology, interventional radiology, and vascular surgery.

One of the major unresolved issues is how should outcomes be measured? Is it enough to improve QOL or do we need to demonstrate reductions in cardiovascular morbidity and mortality to justify the cost of invasive therapies? In 2007, over 2 million physician office visits were related to PAD; therefore, performing clinical trials to study the treatment of PAD should be relatively straightforward, but unfortunately this has not been the case. Randomized clinical trials in PAD are uncommon and notoriously slow to enroll. This may be due to restrictive enrollment criteria, or to an unfounded belief of lack of clinical equipoise between randomized treatments that bias physicians and patients. That the pace of research in the field is slow is reflected in the fact that from the PAD guidelines in 2005 to the update in 2011, which included clinical trials and new data believed to impact patient care through December 2010, not a single new study resulted in a change in the recommended treatment for IC.

Since the publication of the updated PAD guidelines, however, 2 randomized clinical trials examining treatment strategies for IC in patients on optimal medical therapy have been reported. The focuses of the trials were exercise therapy and endovascular revascularization. The studies add to our understanding of the relative benefits of these therapies in IC and highlight the ongoing challenge in performing randomized clinical trials in this population. Although the trials were small, the lessons we learned from them are big.

The first study, published in Circulation, is the 6-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. This trial was designed to compare 3 therapies previously shown to be effective in the treatment of IC: optimal medical care (OMC), alone or in combination with supervised exercise or stent revascularization. Patients were randomized in a 1:2:2 fashion. The study initially had a fourth arm of stent therapy and supervised exercise, but unfortunately this was halted due to slow recruitment. The study was restricted to patients with aortoiliac disease, although concomitant treatment of femoral-popliteal disease was allowed. All arms included OMC, which consisted of guideline-driven management of PAD, including cilostazol. Patients in the OMC group alone also received instructions for self-directed exercise programs. The supervised exercise program consisted of 26 weeks of exercise 3 times a week for 1 hour, a regimen expected to improve walking ability based on prior studies. The stent arm had revascularization carried out for all hemodynamically significant aortoiliac stenosis. The mean lesion length was 3.9 cm, and 38% of patients had treatment of total occlusions. No patients received additional infrainguinal revascularization.

In the 6-month analysis there were 20 patients in the OMC arm, 38 in the supervised exercise, and 41 in the stenting arm. Baseline characteristics were similar in the groups. Despite the small sample size, several differences in outcomes for the treatment arms emerged. As expected, the ankle brachial index (ABI) significantly improved in the stent arm by 0.29 from a baseline of 0.66. The ABI was unchanged in the OMC and supervised exercise arms. The primary end point was a change in peak walking time on a graded treadmill test. Patients in the supervised exercise and stent arms had greater gains compared with the OMC group, with patients in the supervised exercise arm achieving the greatest benefit. With respect to the secondary end points, including QOL, functional status, and free living step activity, supervised exercise and stent therapy were superior to OMC, but with stent therapy achieving a greater extent of improvement compared with supervised exercise. The trial suggests there is a role for both supervised exercise and stent therapy in patients with aortoiliac disease and IC, but did not examine whether combination therapy offered additional benefit.
The second randomized clinical trial in patients with IC recently was published by Mazari et al. In this trial, 178 patients with persistent IC due to unilateral femoral-popliteal artery disease on OMC were randomized to percutaneous transluminal angioplasty (PTA), supervised exercise, or a combination of PTA and supervised exercise. Endovascular treatment of the femoral-popliteal disease was restricted to PTA, and no adjunctive devices, including stents, were used. The lesions were relatively simple: Trans Atlantic Inter-Society Consensus type A or B in 84% of patients. The supervised exercise program was 3 times a week for 12 weeks, and included closed circuit training and brisk walking. The 1-year analysis included 46 patients in the supervised exercise group, 50 in the PTA group, and 47 in the combined PTA and supervised exercise group. The baseline characteristics among the treatment groups were well matched. The primary outcome measures were maximum walking distance (up to a maximum of 5 minutes on a treadmill) and QOL. Patients in all 3 groups had statistically significant improvements in maximum walking distance and in QOL. There were no differences, however, at 1 year in maximum walking distance or QOL indicators between the 3 treatment arms. In this trial, PTA outcomes were examined by duplex ultrasound, and in the subset of patients that had 1-year follow-up, restenosis was identified in 69% and 60% of the PTA and PTA plus supervised exercise groups, respectively. Clinically driven repeat intervention was performed in 9 patients in the PTA group. In contrast, none of the patients in the PTA plus supervised exercise group required repeat intervention. The trial suggests that PTA, supervised exercise, or the combination are equally effective in the treatment of IC from femoral-popliteal disease in terms of QOL, but that combination therapy may result in a more sustained clinical benefit.

There are several lessons to be learned from these PAD trials. First, although the randomized controlled trial is regarded as the gold standard for epidemiological research, this approach often has limitations. As exemplified by these trials, strict inclusion and exclusion criteria result in narrowly-defined patient populations that do not reflect the totality of treated patients in practice. For example, CLEVER initially planned to enroll 252 patients: 999 were screened, 183 consented, and only 119 randomized at 22 sites over more than a 3-year period. The study was halted early without achieving prespecified stopping rules do to slow enrollment. In the study by Mazari, 1157 patients were screened over a 6-year period in a single center; 178 (15%) were randomized and 145 completed 1-year follow-up. The reasons for exclusion were primarily inappropriate anatomic criteria and insufficient symptomatology on medical therapy. Only 153 decline to participate. Although anatomic limitations in PAD trials can be justified on differential responses to medical or revascularization therapy, they introduce significant challenges to patient eligibility and trial recruitment and necessitate multiple studies to encompass the full cadre of patients with symptomatic nonlimb threatening lower extremity symptoms. These studies support the development of large well-designed registry studies examining the treatment of IC to complement the knowledge gained from randomized trials.

While registry studies are plagued with confounding, they offer an opportunity to examine clinical, anatomic, and procedural variables associated with specific outcomes that cannot be done in small trials. This can be accomplished if appropriate end points are measured.

What are the end points that should be evaluated in trials of IC? Another lesson learned from the 2 randomized trials is the importance of obtaining multiple outcome measures and the use of disease specific instruments, including objective measures of exercise performance, community walking, QOL, and functional status. For clinical trials to succeed, treatment, testing, and evaluation protocols should reflect what occurs in clinical practice. If measures used to compare the efficacy of competing treatment approaches are felt to be arbitrary, practitioners will question the generalizability of the results to their patients. In the case of PAD, more objective measures of disease related physical limitations needs to be incorporated into clinical practice, such as the Walking Impairment Questionnaire and Peripheral Artery Questionnaire, rather than fewer incorporated into clinical trials. Evidence for this recommendation includes poor correlation between physician and patient assessment of the impact of IC on the patient’s QOL, poor correlation between ABI and self-reported level of disability, and poor correlation between objective measures, such as treadmill walking distance and QOL. Similar to prior studies, discordance was observed between treadmill performance, free step activity, and QOL measures in the treatment arms of CLEVER. The greater improvement in QOL in the stent arm may reflect the gratification of symptom relief, as 43% of the stent group were free of IC at 6 months, compared with 21% of the supervised exercise group. Both studies show that the benefits of supervised exercise and endovascular revascularization overlap, but are not the same. It is probable that the therapies are complementary and that a combination of supervised exercise to improve cardiovascular fitness combined with endovascular revascularization to promote better well-being and functional status in daily life is the best combination for patients with IC, but this needs to be examined in larger trials.

Lastly, what possible changes will be made to the PAD guidelines and medical coverage based on the results of these trials? It is likely that supervised exercise will remain a class I indication and the initial recommended treatment modality in IC. Hopefully these trials will push Medicare and insurance coverage for these services. The CLEVER trial provides evidence that an unsupervised exercise program is not effective for aortoiliac disease, so it is unlikely it will move up from a class IIb recommendation. Cilostazol has a class I indication for symptom improvement and increasing walking distance; this recommendation is supported by several trials, and the present trials should not influence this recommendation. Although OMC, including cilostazol, did not improve outcomes in CLEVER, the small number of patients and universal treatment with cilostazol limit the ability to determine the effectiveness of the drug for IC. The recommendation for endovascular procedures in selected individuals with IC that do not respond adequately to exercise or pharmacological therapy is unlikely to change from a class I recommendation. The wording, however, may more strongly sug-
gest that patients must fail a supervised exercise program prior to invasive strategies. The guidelines need to remain broad because the findings in these 2 small studies may not apply to less motivated patients, those with less favorable anatomy, and those with more significant comorbidities.

Despite all we have learned from these 2 trials, we need a greater commitment by clinicians, researchers, and funding agencies to further study the optimal therapy to reduce the morbidity and mortality associated with IC in a cost-effective way. Until that time, physicians will continue to individualize therapy for their patients, and treatment opportunities are likely to be missed.

Disclosures

None.

References


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