Priority Updates from the Research Literature from the Family Physicians Inquiries Network

PURLs®

Ramipril for claudication?

This ACE inhibitor can help patients with peripheral artery disease walk longer while remaining pain free.

Luke A. Stephens, MD, MSPH; Nina Rogers, MD; James J. Stevermer, MD, MSPH
Department of Family and Community Medicine, University of Missouri, Columbia (Drs. Stephens and Stevermer); Department of Family Medicine, University of Chicago (Dr. Rogers)

PURLs EDITOR
Anne Mounsey, MD
Department of Family Medicine, University of North Carolina at Chapel Hill

PRACTICE CHANGER

Consider prescribing ramipril for patients who have intermittent claudication.[1]

STRENGTH OF RECOMMENDATION

A: Based on a high-quality placebo-controlled randomized controlled trial (RCT) consistent with prior RCTs.

Ahimastos AA, Walker PJ, Askew C, et al. Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. *JAMA*. 2013;309:453-460.

ILLUSTRATIVE CASE

A 63-year-old man presents with pain in both legs, which starts with activity and resolves with rest. He has a resting blood pressure of 135/77 mm Hg consistent with past measurements, and an ankle-brachial index (ABI) <0.90, which is consistent with peripheral artery disease (PAD). His daily medications are 81 mg aspirin, 25 mg hydrochlorothiazide, and 40 mg simvastatin. What additional agent could be added for his symptoms?

PAD, defined as an ABI <0.9, affects approximately 5% of Americans older than 40 years. About two-thirds of those with PAD are asymptomatic; the remaining third suffer from intermittent claudication (IC).[2]

Exercise and smoking cessation are effective at reducing IC symptoms, as well as the long-term cardiovascular event risk associated with PAD.[3] But even with these lifestyle changes, patients with PAD are often troubled by persistent symptoms.

Few evidence-based treatments for IC

Compared with placebo, the antiplatelet agents indobufen and picotamide have been shown to improve pain-free walking distance (PFWD).[4] So have cilostazol[5] and naftidrofuryl,[6] as well as lipid-lowering agents.[7]

In a pilot study of 40 patients, 10 mg ramipril was shown to improve pain-free walking time (PFWT) at 24 weeks by 227 seconds (95% confidence interval [CI]=175-278; *P*<.001). That represents a 164% increase from baseline, vs no change in PFWT at 24 weeks for the placebo group.[8] A recent small (N=33), double-blinded RCT found similar improvements in maximum treadmill walking distance, PFWD, and patient-reported walking distance at 24 weeks with ramipril compared with placebo.[9]

In the HOPE study, a subsection of patients who were older than 55 years and had PAD were treated with a daily target dose of 10 mg ramipril for a mean of 4.5 years. Compared with placebo, ramipril reduced the primary outcome—cardiovascular mortality, myocardial infarction (MI), or stroke—by 25% (risk ratio=0.75; 95% CI, 0.61-0.92).[10]

In the study reported on here, Ahimastos et al took a closer look at ramipril.

STUDY SUMMARY

Patients on ramipril can walk longer pain free

The authors conducted a double-blind, randomized placebo-controlled trial evaluating the effectiveness of 10 mg/d ramipril for the improvement of maximum walk time (MWT) and PFWT in patients with PAD.[1] Eligible patients had an ABI <0.9 in at least one leg and a history of IC in at least one leg, with stable claudication symptoms and a stable medi-

INSTANT POLL

Have you found ACE inhibitors useful in treating patients with peripheral artery disease (PAD)?

- ☐ *Yes, ACE inhibitors help many patients with PAD stay active and pain free.*
- ☐ *Occasionally; I only prescribe them for patients with comorbidities for which ACE inhibitors are indicated.*
- ☐ *Rarely; I prefer not to add an ACE inhibitor to an already long list of medications.*
- ☐ *No. I do not prescribe ACE inhibitors for PAD.*

jfponline.com

cal regimen for 6 months or more. Exclusion criteria included a resting blood pressure >160/100 mm Hg; use of ACE inhibitors, angiotensin II receptor blockers, potassium sparing diuretics, or potassium supplements in the past 6 months; serum creatinine >2.3 mg/dL; renal artery stenosis; previous coronary or lower extremity revascularization procedure; MI in the past 3 months; major surgery planned for the following year; critical limb ischemia; or any condition other than PAD limiting walking ability.

In total, 212 patients underwent randomization, and either took 10 mg/d ramipril or placebo for 24 weeks. The participants had similar baseline characteristics. Most were male (83.5%), with a mean age of 65.5 years; 33.5% were current smokers; 50% had hypertension; and 24.1% had type 2 diabetes.

Primary outcomes—PFWT and MWT—improved in the ramipril group. Compared with the placebo group, those in the ramipril group had a mean PFWT increase of 75 seconds (95% CI, 60-89; *P*<.001) and a 255-second increase in MWT (95% CI, 215-295; *P*<.001), a 52% and 107% increase from baseline, respectively. Most secondary measures (including the Walking Impairment Questionnaire median distance score, the speed score, and the stair-climbing score) also improved significantly, relative to the placebo group. However, ABI did not change significantly in either group.

Ramipril not only reduces cardiovascular mortality, MI, and stroke in patients with PAD, but is effective in improving patient-oriented outcomes such as duration of walking without developing intermittent claudication.

WHAT'S NEW

Evidence that ramipril improves patient-oriented outcomes

Ramipril not only reduces cardiovascular mortality, MI, and stroke in patients with PAD,[10] but is effective in improving patient-oriented outcomes such as duration of walking without developing IC.

CAVEATS

Would ramipril help less stable patients?

Inclusion criteria used by Ahimastos et al limit the generalizability of this study to patients with stable symptoms for 6 months or more. Similarly, because the study lasted for 24 weeks, it is not known whether ramipril's benefits for patients with claudication would continue indefinitely. Also of note: The ABI did not improve in the treatment cohort at the end of this 24-week period, and the authors did not report objective outcomes such as revascularization or mortality.

CHALLENGES TO IMPLEMENTATION

Monitoring, adverse effects may present problems

Use of ACE inhibitors requires monitoring of renal function and serum potassium. In addition, ACE inhibitors can induce a chronic cough that often limits their use in those affected; 6.6% of the treatment group withdrew from this study due to persistent cough.[1] JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

References

1. Ahimastos AA, Walker PJ, Askew C, et al. Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. *JAMA*. 2013;309:453-460.
2. Centers for Disease Control and Prevention. Lower extremity disease among persons aged ≥40 years with and without diabetes—United States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2005;54:1158-1160.
3. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev.* 2008;(4):CD000990.
4. Wong PF, Chong LY, Mikhailidis DP, et al. Antiplatelet agents for intermittent claudication. *Cochrane Database Syst Rev.* 2011;(11):CD001272.
5. Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev.* 2008;(1):CD003748.
6. de Backer TL, Vander Stichele R, Lehert P, et al. Naftidrofuryl for intermittent claudication. *Cochrane Database Syst Rev.* 2012;(12):CD001368.
7. Aung PP, Maxwell HG, Jepson RG, et al. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev.* 2007;(4):CD000123.
8. Ahimastos AA, Lawler A, Reid CM, et al. Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med.* 2006;144:660-664.
9. Shahin Y, Cockcroft JR, Chetter IC. Randomized clinical trial of angiotensin-converting enzyme inhibitor, ramipril, in patients with intermittent claudication. *Br J Surg.* 2013;100:1154-1163.
10. Ostergren J, Sleight P, Dagenais G, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J.* 2004;25:17-24.