

# Brief Communication: Ramipril Markedly Improves Walking Ability in Patients with Peripheral Arterial Disease

## A Randomized Trial

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**Background:** Peripheral arterial disease (PAD) affects up to 12% of adults older than 50 years of age. Conventional therapies have only modest effects in improving symptoms.

**Objective:** To examine the effects of angiotensin-converting enzyme inhibition on walking ability in patients with PAD.

**Design:** Randomized, double-blind, placebo-controlled trial initiated in March 2003 and completed in January 2005.

**Setting:** The Alfred Hospital, Melbourne, Australia.

**Participants:** 40 older adults with symptomatic PAD and no history of diabetes or hypertension.

**Intervention:** 10 mg of ramipril ( $n = 20$ ) or placebo ( $n = 20$ ) once daily for 24 weeks. All patients completed the trial.

**Measurements:** Pain-free and maximum walking time were recorded during a standard treadmill test, and the standard Walking Impairment Questionnaire was administered.

**Results:** After adjustment for the baseline pain-free walking time, mean pain-free walking time after ramipril treatment was 227 sec-

onds (95% CI, 175 seconds to 278 seconds;  $P < 0.001$ ) longer than that after placebo treatment. Similarly, maximum walking time improved by 451 seconds in the ramipril group (CI, 367 seconds to 536 seconds;  $P < 0.001$ ) but did not change in the placebo group. Ramipril improved the Walking Impairment Questionnaire median distance score from 5% (range, 1% to 39%) to 21% (range, 12% to 58%;  $P < 0.001$ ), speed score from 3% (range, 3% to 39%) to 18% (range, 8% to 50%;  $P < 0.001$ ), and stair-climbing score from 17% (range, 4% to 80%) to 67% (range, 38% to 88%;  $P < 0.001$ ). No adverse events were reported.

**Limitations:** The sample size is modest, and the strict inclusion criteria limit the applicability of the results to patients with claudication and infrainguinal disease and those without diabetes.

**Conclusion:** Ramipril improved pain-free and maximum walking time in some adults with symptomatic PAD.

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Peripheral arterial disease (PAD) is a common disorder, with 12% of adults older than 50 years of age having an ankle-brachial index (ABI) that is diagnostic of PAD ( $<0.9$ ) (1). Approximately one third of these patients experience intermittent claudication during walking, limiting normal activities. Medical treatments to improve walking distance are limited. The angiotensin-converting enzyme (ACE) inhibitor ramipril reduced cardiovascular morbidity and mortality compared with placebo in patients with established atherosclerotic disease, including PAD, in the Heart Outcomes Prevention Evaluation (HOPE) study (2). This effect seemed to be independent of blood pressure reduction (3) and may relate to the known benefits of ACE inhibitors on both coronary and brachial endothelial function (4). No previous controlled studies have investigated the effect of ACE inhibitors on symptoms of intermittent claudication. Given the positive effects of ramipril in the HOPE trial and its convenient once-daily dosing formulation, we hypothesized that therapy with ramipril would improve intermittent claudication symptoms. We aimed to examine the effect of 6-month ramipril therapy on walking distance and claudication pain in a defined group of patients with claudication due to infrainguinal PAD by using a double-blind, randomized, placebo-controlled design.

## METHODS

We screened 152 patients with PAD from general practice clinics in the Melbourne, Australia, metropolitan area (Figure 1). Of them, 40 patients (mean age, 66 years [SD, 4]) were recruited and completed the trial. All patients gave written informed consent to participate in the study. The Ethics Committee of the Alfred Hospital, Melbourne, Australia, approved the study, and we performed the study in accordance with the Declaration of Helsinki 2000. All participants had an ABI less than 0.9 at rest in at least 1 leg; had a history of intermittent claudication (unilateral or bilateral), which was stable for 6 months; had evidence of superficial femoral artery stenosis or occlusion on duplex ultrasonography; had blood pressure of 160/90

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mm Hg or less; had a stable medication regimen for at least 6 months; and had not previously been treated with ACE inhibitors. We excluded patients with limiting coronary artery disease, renal failure, history of hypertension, or type 2 diabetes mellitus.

Computer-generated numbers specified the allocation sequence. A tamper-proof randomization process generated by the hospital research center randomly assigned participants into blocks of 10 to receive either ramipril (Tritace, Aventis Pharma Pty. Ltd., Macquarie Park, Australia, 10 mg once daily for 24 weeks) or placebo (10 mg once daily for 24 weeks) in a parallel-group, double-blind design. Both investigators and patients were blinded to drug assignment. Furthermore, investigators did not have access to baseline data when they performed follow-up measurements and patients were not asked which treatment they thought they were receiving. No patient assigned to placebo crossed over to ramipril during the trial or vice versa.

We advised participants to maintain all aspects of their lifestyle throughout the trial and requested them to refrain from exercise, smoking, and caffeine for 24 hours before all testing. On the morning of testing, patients rested in a supine position for 15 minutes in a quiet room before the measurements. We assessed blood pressure, ABI, walking distance, duplex ultrasounds of leg arteries, and the Walking Impairment Questionnaire (WIQ) scores before and after both interventions. We advised patients about potential side effects and requested that they report any adverse event to the study coordinator.

### Context

Few therapies substantially reduce symptoms and improve exercise performance in patients with peripheral arterial disease (PAD).

### Contribution

In this double-blind trial, investigators randomly assigned 40 older adults without diabetes and with symptomatic PAD to receive either ramipril or placebo, 10 mg once daily for 24 weeks. Compared with placebo, ramipril increased maximum and pain-free walking time and walking speed and distance.

### Cautions

The trial was small and involved selected patients with limited mobility and exercise tolerance.

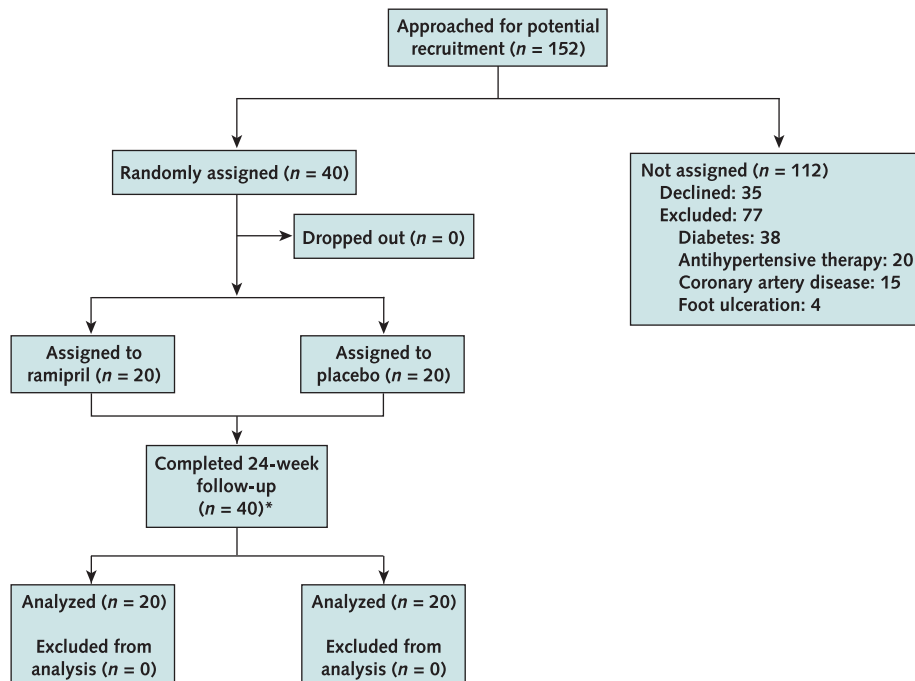
### Implications

Ramipril may improve symptoms in some patients with PAD.

—The Editors

All patients performed a treadmill exercise test at a speed of 3.2 km/h and a grade of 12% (5), and we recorded pain-free walking time (time to onset of claudication pain) and maximum walking time. In our study, all patients reached a maximal level of claudication pain that limited exercise during the graded treadmill test.

Figure 1. Flow of patients through the study.



\*Treadmill test, ankle-brachial index, Walking Impairment Questionnaire, duplex ultrasonography, and blood tests.

**Table. Baseline Characteristics\***

Variable	Placebo Group (n = 20)	Ramipril Group (n = 20)
Men, n	18	20
Age, y	67 (3)	65 (6)
BMI, kg/m <sup>2</sup>	24.4 (3)	24.3 (2.7)
Smokers, n	8	9
Brachial systolic BP, mm Hg	140 (6)	139 (5)
Brachial diastolic BP, mm Hg	89 (9)	85 (10)
Total cholesterol level		
mmol/L	5.04 (0.63)	5.08 (0.60)
mg/dL	195 (24)	196 (23)
LDL cholesterol level		
mmol/L	2.82 (0.67)	2.80 (0.61)
mg/dL	109 (26)	108 (24)
HDL cholesterol level		
mmol/L	1.37 (0.27)	1.37 (0.41)
mg/dL	52.9 (10.4)	52.9 (15.8)
Triglycerides level		
mmol/L	1.70 (0.86)	1.58 (0.80)
mg/dL	65.6 (33.2)	61.0 (30.9)
Limiting leg ABI at rest	0.54 (0.11)	0.58 (0.07)
Pain-free walking time, s	168 (33)	160 (62)
Maximum walking time, s	244 (34)	234 (81)
Median WIQ distance score (range)	6 (2–20)	5 (1–39)
Median WIQ speed score (range)	6 (3–14)	3 (3–39)
Median WIQ stair-climbing score (range)	23 (4–42)	17 (4–80)
Warfarin/aspirin, n/n	4/4	4/5
Lipid-lowering therapy, n	4	7

\* Data are means (SDs), unless otherwise indicated. ABI = ankle-brachial index; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; WIQ = Walking Impairment Questionnaire.

The WIQ was developed and validated against treadmill walking and is used to evaluate limitations in community-based walking ability (6). The WIQ assessed walking distance, speed, and stair-climbing ability, using a weighted standardized formula and returning a summary score between 0% and 100% (6, 7).

### Statistical Analyses

All analysts were blinded to treatment assignment, and an independent investigator double-checked all measurement calculations and database entries. The study was powered to detect a 180-second change in maximum walking time with ramipril, assuming a standard deviation of 250 seconds ( $\alpha = 0.05$  [2-sided]; power, 86%). We compared 24-week changes from baseline in pain-free walking time, maximum walking time, and WIQ scores between treatments by using an analysis of covariance model with terms for treatment and baseline value as the analysis end points. We log-transformed the WIQ data to achieve a normal distribution before analysis. We conducted all statistical analyses by using Stata software, version 8.2 (Stata Corp., College Station, Texas). We expressed normally distributed data as means (SDs) or 95% CIs and non-normally distributed data as medians (ranges). A *P* value less than 0.05 was deemed to be significant. No data were missing for any clinical variable measured in our study.

### Role of the Funding Sources

This work was funded by the National Health and Medical Research Council of Australia. Aventis Pharma Pty. Ltd. provided ramipril (Tritace) and matching placebo capsules but provided no other funding for the study or to the investigators. The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

### RESULTS

The ramipril and placebo groups were similar in age, other cardiovascular risk factors, medication use, and PAD severity, as evidenced by clinical symptoms (walking times), WIQ scores, and resting ABI (Table). No patient was taking cilostazol or pentoxifylline. On duplex ultrasonography, 6 of 40 patients had a superficial femoral artery occlusion (2 placebo patients and 4 ramipril patients), and the remaining patients had stenotic disease in the superficial femoral artery. Only 25% of patients were taking antiplatelet or lipid-lowering therapy. No adverse events were reported.

### Ankle-Brachial Index

Ramipril significantly increased ABI both at rest (change with placebo,  $-0.05$  mm Hg [SD, 0.04]; change with ramipril,  $0.07$  mm Hg [SD, 0.08];  $P < 0.001$ ) and after exercise (change with placebo,  $-0.04$  mm Hg [SD, 0.05]; change with ramipril,  $0.08$  mm Hg [SD, 0.14];  $P < 0.001$ ). At rest, this increase was due to reduction in brachial systolic blood pressure with ramipril treatment ( $-0.85$  mm Hg [SD, 1.57] vs.  $-5.05$  mm Hg [SD, 2.33];  $P < 0.001$ ) rather than an increase in limiting leg pressure ( $-0.75$  mm Hg [SD, 1.71] vs.  $-0.15$  mm Hg [SD, 1.27];  $P = 0.26$ ). After exercise, both a reduction in brachial pressure (change with placebo,  $0.30$  mm Hg [SD, 2.45]; change with ramipril,  $-6.80$  mm Hg [SD, 6.07];  $P < 0.001$ ) and an increase in limiting leg pressure (change with placebo,  $-5.40$  mm Hg [SD, 7.56]; change with ramipril,  $7.10$  mm Hg [SD, 4.59];  $P < 0.001$ ) contributed to the increase in ABI.

### Treadmill Test

After adjustment for the baseline pain-free walking time, mean pain-free walking time after ramipril treatment was 227 seconds (95% CI, 175 seconds to 278 seconds;  $P < 0.001$ ) longer than after placebo treatment (Figure 2). Similarly, maximum walking time significantly improved over the 24-week treatment period by 451 seconds (CI, 367 seconds to 536 seconds;  $P < 0.001$ ) in the ramipril group after adjustment for baseline values (Figure 2). The lack of change observed over the 24-week treatment period in the placebo group (change in mean walking time,  $-10$  seconds [SD, 9] [CI,  $-14$  seconds to  $-6$  seconds];  $P < 0.001$ ) may reflect both the advanced age of participants and the fact that they all had limiting infrainguinal disease, which would probably give more reproducible treadmill

data than aortoiliac disease. In addition, we asked patients to maintain all aspects of their lifestyle throughout the trial.

### Walking Impairment Questionnaire

Ramipril improved WIQ median distance score from 5% (range, 1% to 39%) to 21% (range, 12% to 58%) ( $P < 0.001$ ), speed score from 3% (range, 3% to 39%) to 18% (range, 8% to 50%) ( $P < 0.001$ ), and stair-climbing score from 17% (range, 4% to 80%) to 67% (range, 38% to 88%) ( $P < 0.001$ ).

### Duplex Ultrasonography

Volume flow was unaltered in the limiting leg at the stenotic site. However, ramipril significantly increased volume flow in the common femoral artery proximal to the site of stenosis in both the limiting leg (change with placebo,  $-0.014$  L/min [SD, 0.022]; change with ramipril,  $0.017$  L/min [SD, 0.034];  $P = 0.008$ ) and the nonlimiting leg (change with placebo,  $-0.006$  L/min [SD, 0.041]; change with ramipril,  $0.019$  L/min [SD, 0.019];  $P = 0.035$ ).

## DISCUSSION

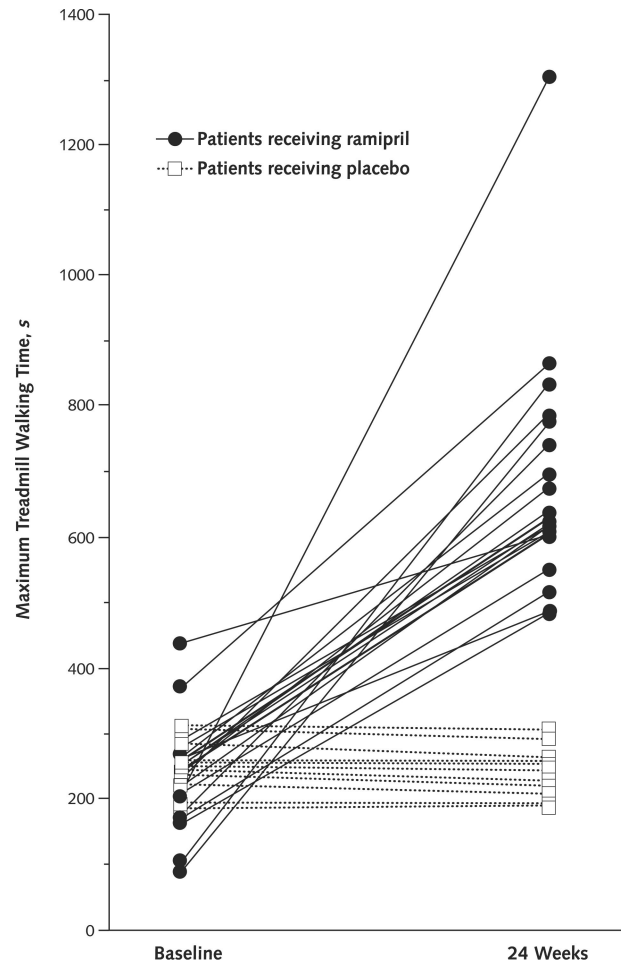
Our study shows that treatment with ramipril, an ACE inhibitor, improves walking ability in some patients with PAD. Ramipril increased treadmill-assessed pain-free walking time by a mean of 164% (range, 21% to 415%) and increased maximum walking time by a mean of 243% (range, 38% to 767%). Assuming a constant speed of 0.89 m/s (3.2 km/h), this corresponds to a clinically significant increase in walking distance of 401 meters (CI, 326 meters to 476 meters), which would appreciably affect daily functional capacity. The magnitude of this effect is greater than that reported for conventional medical therapies. For example, cilostazol and pentoxifylline improve walking times or distances by up to 80%, and exercise training results in an average 120% improvement (8–11).

Although treadmill walking tests are an objective measure of functional ability in patients with intermittent claudication, they do not address regular daily activities in the home or in the community setting. The improvements in WIQ scores were consistent with the measured improvement in pain-free walking time and maximum walking time, demonstrating that ACE inhibition improves the ability to perform normal daily activities.

Five previous studies examined the effect of ACE inhibitor therapy on walking time in patients with PAD (12–16). The intervention period in all these trials was relatively short (2 weeks to 3 months), all studies were small (10 to 23 patients), and all but 1 trial were not placebo-controlled. Our findings suggest that a longer intervention period is necessary for ACE inhibition to provide efficacy.

Angiotensin-converting enzyme inhibitor treatment improves blood flow to the lower extremities of patients with PAD (12, 13, 15). Mechanisms include vasodilatation

**Figure 2. Effect of ramipril on maximum treadmill walking times.**



Maximum walking times for each patient receiving ramipril and placebo at baseline and after the 24-week intervention are shown.

through reduction in angiotensin II, sympathetic inhibition, and improvement in endothelial function (17) through preservation of bradykinin. In addition, angiogenesis (collateral formation) and atherosclerotic regression may also contribute (18, 19). In our study, the improvement in volume flow at a nonoccluded site upstream from the site of stenosis, but not at the stenotic site, suggests that collateral flow was enhanced by ramipril, perhaps through angiogenesis.

The trial was small. We recruited patients according to tight inclusion criteria, selecting patients with limited mobility and exercise tolerance. The inclusion criteria limit the applicability of the results to patients with limiting infrainguinal disease without diabetes, who make up approximately one half of patients with claudication (20). The remarkable consistency in the placebo group data before and after intervention may be partly related to the homogeneity of the group studied. Furthermore, the WIQ

has restricted capacity to discriminate between patients with poor exercise tolerance. Our findings warrant further investigation in a larger clinical trial that includes patients with diabetes and those with aortoiliac disease and infrainguinal disease.

In conclusion, ramipril therapy for 24 weeks increased both pain-free walking time and maximum walking time by a clinically and statistically significantly greater magnitude than current therapies. While ACE inhibitor therapy reduces vascular events in patients with PAD, it is not currently specifically indicated for relief of clinical symptoms. Our data demonstrate that ramipril may have benefits beyond reduction in vascular events in this high-risk population and may substantially improve clinical symptoms and quality of life.

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