Effect of Ramipril on Walking Times and Quality of Life Among Patients With Peripheral Artery Disease and Intermittent Claudication

A Randomized Controlled Trial

Anna A. Ahimastos, PhD
Philip J. Walker, MBBS, FRACS
Christopher Askew, PhD
Anthony Leicht, PhD
Elise Pappas, BSp, ExSc
Peter Blombery, MBBS, FRACP
Christopher M. Reid, PhD
Jonathan Golledge, MBBChir, MChir
Bronwyn A. Kingwell, PhD

Importance Approximately one-third of patients with peripheral artery disease experience intermittent claudication, with consequent loss of quality of life.

Objective To determine the efficacy of ramipril for improving walking ability, patient-perceived walking performance, and quality of life in patients with claudication.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled trial conducted among 212 patients with peripheral artery disease (mean age, 65.5 [SD, 6.2] years), initiated in May 2008 and completed in August 2011 and conducted at 3 hospitals in Australia.

Intervention Patients were randomized to receive 10 mg/d of ramipril (n=106) or matching placebo (n=106) for 24 weeks.

Main Outcome Measures Maximum and pain-free walking times were recorded during a standard treadmill test. The Walking Impairment Questionnaire (WIQ) and Short-Form 36 Health Survey (SF-36) were used to assess walking ability and quality of life, respectively.

Results At 6 months, relative to placebo, ramipril was associated with a 75-second (95% CI, 60-89 seconds) increase in mean pain-free walking time ($P<.001$) and a 255-second (95% CI, 215-295 seconds) increase in maximum walking time ($P<.001$). Relative to placebo, ramipril improved the WIQ median distance score by 13.8 (Hodges-Lehmann 95% CI, 12.2-15.5), speed score by 13.3 (95% CI, 11.9-15.2), and stair climbing score by 25.2 (95% CI, 25.1-29.4) ($P<.001$ for all). The overall SF-36 median Physical Component Summary score improved by 8.2 (Hodges-Lehmann 95% CI, 3.6-11.4; $P=.02$) in the ramipril group relative to placebo. Ramipril did not affect the overall SF-36 median Mental Component Summary score.

Conclusions and Relevance Among patients with intermittent claudication, 24-week treatment with ramipril resulted in significant increases in pain-free and maximum treadmill walking times compared with placebo. This was associated with a significant increase in the physical functioning component of the SF-36 score.

Trial Registration clinicaltrials.gov Identifier: NCT00681226

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Approximately 27 million individuals in Europe and North America have peripheral artery disease (PAD).[1] Intermittent claudication occurs in approximately one-third of patients with PAD and typically presents as pain within leg muscle groups that occurs during walking but is relieved by rest.[2] Patients with intermittent claudication have significant impairment in ambulatory function, resulting in functional disability and significant lifestyle limitation.[3,4]

Treatment of these patients is aimed at reducing cardiovascular risk, increasing functional performance, and improving health-related quality of life. However, current drug treatments to improve walking distance have limited efficacy and only increase walking distance by between 12% and 60%[5-10] (the only 2 drug treatments approved by the Food and Drug Administration for use in the United States, pentoxifylline and cilostazol, increase walking distance by 15% and 25%, respectively[11]).

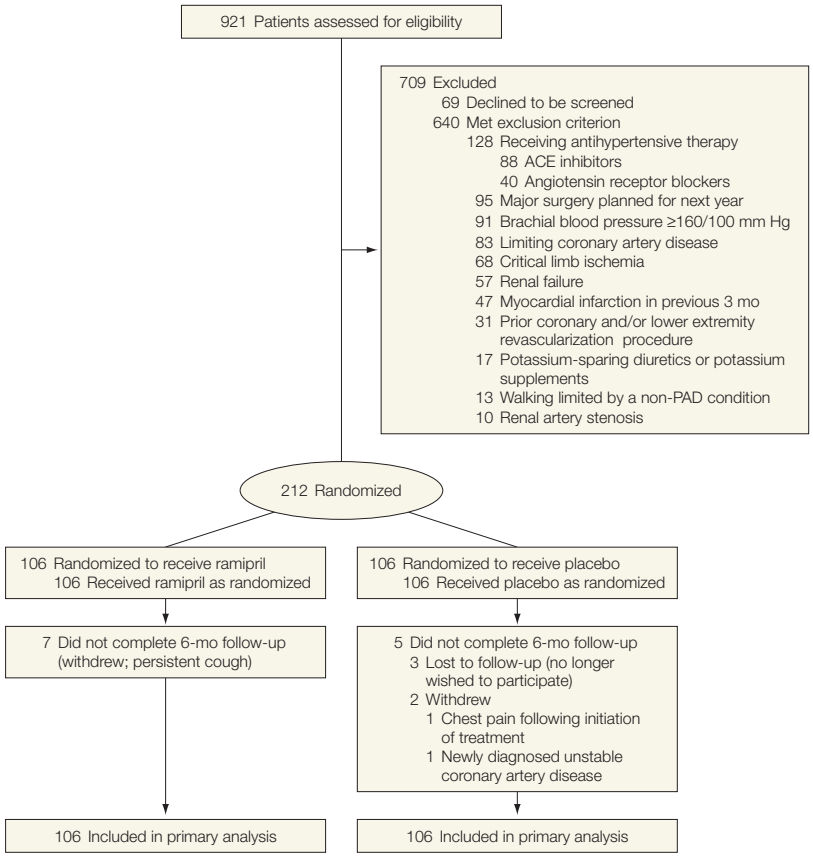
We previously reported in a pilot trial that the angiotensin-converting enzyme (ACE) inhibitor ramipril is associated with significantly increased treadmill-assessed pain-free and maximum walking time.[12] However, that trial was small, and the findings were restricted to patients with limiting infrainguinal

For editorial comment see p 487.

Author Audio Interview available at www.jama.com.

Author Affiliations: Baker IDI Heart and Diabetes Institute, Melbourne (Drs Ahimastos and Kingwell); University of Queensland School of Medicine and Royal Brisbane and Women's Hospital, Herston (Dr Walker); Queensland University of Technology, Brisbane (Dr Askew); Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville (Drs Leicht and Golledge and Ms Pappas); Alfred Hospital, Prahran (Dr Blombery); and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne (Dr Reid), Australia.
Corresponding Author: Anna A. Ahimastos, PhD, Baker IDI Heart and Diabetes Institute, PO Box 6492, St Kilda Rd Central, Melbourne, Victoria, 8008 Australia (a.ahimastos@alfred.org.au).

Figure. Study Flow



Data were imputed for the 12 patients who did not complete 6-month follow-up. ACE indicates angiotensin-converting enzyme; PAD, peripheral artery disease.

disease without diabetes, who comprise approximately one-half of all patients with claudication.[12] Other previous ACE inhibitor studies in patients with claudication have been equivocal, owing to issues including small sample size, short intervention duration, and absence of a placebo group.[12-18]

The current investigator-initiated trial was conducted to examine the association of ramipril therapy for 24 weeks on walking distance and health-related quality of life as compared with placebo in a larger, more general PAD population including patients with diabetes and patients with aortoiliac as well as infrainguinal disease.

METHODS

The institutional review boards of the participating hospitals approved the protocol. Participants provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki, Fifth Revision (2000). Data collection and interventions were performed at the Alfred Hospital (Melbourne), the Townsville Hospital (Townsville), and Royal Brisbane and Women's Hospital (Brisbane), Australia, between May 10, 2008, and August 23, 2011.

All patients were receiving usual care appropriate to their individual risk profile and symptoms, such as lipid-lowering therapy or antiplatelet therapy, and were supervised by their physicians throughout the trial. All patients also received lifestyle advice prior to commencing the trial.

Inclusion and Exclusion Criteria

The inclusion criteria were an ankle brachial index (ABI) of less than 0.90 at rest in at least 1 leg; history of intermittent claudication (unilateral or bilateral) and stable for the previous 6 months; and a stable medication regimen for at least 6 months. The exclusion criteria were resting brachial blood pressure of 160/100 mm Hg or greater; current use of either ACE inhibitors or angiotensin II receptor blockers or use of these drugs in the prior 6 months; current use of potassium-sparing diuretics or potassium supplements or use of these drugs in the prior 6 months; renal failure (serum creatinine level >2.3 mg/dL [200 μmol/L]); renal artery stenosis; previous coronary revascularization procedures, lower extremity revascularization procedures, or both; myocardial infarction in the previous 3 months; major surgery planned during the following year; critical limb ischemia and any condition other than PAD limiting walking ability, including limiting coronary artery disease, chronic obstructive pulmonary disease, and musculoskeletal conditions (assessed during physical examination and medical history performed by the study physician) (FIGURE).

Study Design, Randomization, and Masking

A tamper-proof randomization process generated by The Alfred Hospital Research Center, Melbourne, randomly assigned participants into blocks of 10 to receive either ramipril (Ramace, sanofi-aventis) (10 mg/d for 24 weeks) or matching placebo in a parallel-group, double-blind design.

All investigators, analysts, and patients were blinded to drug assignment as well as to baseline data when they performed follow-up measurements. No patient assigned to receive placebo crossed over to ramipril, or vice versa, during the trial. Medication adherence was measured by monthly pill counts.

Safety Reporting

Patients were advised about potential adverse effects and requested to re-

port any adverse event. Safety was assessed by adverse-event monitoring, blood biochemistry analysis, measurement of vital signs, physical examination (at 3 weeks, 3 months, and 6 months following initiation of treatment), and monthly telephone calls.

Outcomes

Outcomes were measured before randomization and at the 6-month follow-up. The 2 prespecified primary outcomes were pain-free walking time (time to onset of claudication pain) and maximum walking time assessed by a standard treadmill exercise test. Secondary outcomes were ABI; stenosis severity assessed by duplex ultrasounds of the lower limb arteries; patient-reported symptoms and functional status assessed by the Walking Impairment Questionnaire (WIQ); and health-related quality of life assessed by the Short-Form 36 Health Survey (SF-36).

Treadmill Test. The standard constant-load treadmill exercise test was performed at a speed of 3.2 km/h and a grade of 12%.[19] All patients underwent a single test at baseline and at follow-up. Consistent instructions were given in relation to hand support and upright walking posture. In Australia and Europe a constant-load treadmill test is the standard method for assessment of pain-free and maximum walking distance in patients with PAD. This method translates well to everyday walking ability, is reproducible,[20] and has been used in several previous studies of drug effects on claudication distance.[21] Constant-load and graded treadmill tests give comparable results in patients with claudication distances greater than 100 m, which characterized 95% of patients in our study.[22]

ABI Measurement. ABI was measured and calculated by the same investigator for all patient visits as the ratio of the highest systolic blood pressure in each ankle from the right and left posterior tibial or dorsalis pedis arteries, divided by the highest brachial systolic blood pressure.[12]

Duplex Ultrasonography. Scanning was performed by a single qualified and experienced vascular technologist, and all images were also assessed and analyzed by 2 independent experienced vascular physicians blinded to patient identity and treatment ($\kappa = 0.94$ for interobserver reliability). Peak systolic velocity in lower-limb vessel segments was measured to determine the grade of stenosis, as previously described.[23] Volume flow was calculated from the lumen cross-sectional area and the integrated mean velocity.

Patient-Reported Functional Status. The WIQ[24] is a PAD-specific measure of self-reported walking limitations with 3 domains; walking distance, walking speed, and stair climbing. Each domain is scored on a 0 to 100 scale, with higher scores indicating lesser symptoms and greater functional capacity. All patients completed the WIQ forms independently.

Health-Related Quality of Life. The SF-36 provides a comprehensive measure of the degree of disability experienced by the patient as a result of PAD[25] and is reported as 2 aggregate summary measures, the Physical Component Summary and the Mental Component Summary. All patients completed the SF-36 forms independently.

Statistical Analyses

Baseline characteristics were compared using the χ^2 test for categorical variables and 1-way analysis of variance for continuous variables. We compared 24-week changes from baseline in pain-free walking time, maximum walking time, ABI, and volumetric blood flow at the site of stenosis using an analysis of covariance model with terms for treatment and baseline values. Because of skewed distributions, differences in median values for the WIQ and SF-36 questionnaire data were compared using Kruskal-Wallis analysis of variance. Normally distributed data were expressed as means (SDs) or 95% CIs. Nonnormally distributed data were expressed as medians and interquartile ranges (IQRs) or medians with Hodges-Lehmann 95% CIs. All data were expressed as both the within-group change and the difference between the randomized groups.

To detect a 120-second change in walking time (assuming an SD of 300 seconds) and a 65-second change in pain-free walking time (assuming an SD of 161 seconds) with ramipril, 100 patients per group would provide a power of 80% at an α of .05.[12] A 2-sided *P* value less than .05 was deemed significant. For the 200 participants who completed the 6-month follow-up, no data were missing for any clinical variable measured. Analyses were performed using SPSS version 19.0 (SPSS Inc).

Multiple imputation for missing 6-month data was performed using SPSS MI syntax (version 19.0) to obtain 5 separate imputed data points. These results were combined using the Aggregate syntax to enable intention-to-treat analysis. Imputation involved regression modeling methods in which imputed values were predicted on the basis of models including age, ABI, body mass index, sex, race, smoking status, baseline outcome values, leg symptoms, and comorbid conditions.

RESULTS

Of 921 potential participants approached for recruitment into the trial, 69 declined and 640 met an exclusion criterion, leaving 212 eligible participants (mean age, 65.5 [SD, 6.2] years) (Figure). Two hundred patients completed the 6-month follow-up. Intention-to-treat analyses including all randomized patients were performed.[26] Multiple imputation was used to account for the 12 patients lost to follow-up owing to adverse events (n=2 [0.9%]), persistent cough (n=7 [0.3%]), or loss of interest (n=3 [1.4%]), before completing 6-month follow-up testing (Figure).[27,28]

The ramipril (n=106) and placebo (n=106) groups were similar for all baseline parameters (TABLE 1). One hundred seventeen patients (55.2%) were taking antiplatelet therapy, and 117 (55.2%) were taking lipid-lowering therapy. The 200 patients completing the study adhered to the study medication (100% adherence rate), according to pill-count measures. All patients continued their individually tailored medications (usual care) throughout the trial, with

Table 1. Baseline Characteristics of the Study Population[a]

Characteristic	Placebo (n = 106)	Ramipril (n = 106)	*P* Value[b]
Age, mean (SD), y	65.5 (7.1)	65.5 (5.3)	.98
Men, No. (%)	90 (84.9)	87 (82.1)	.36[c]
BMI, mean (SD)[d]	25.7 (3.4)	25.6 (3.4)	.83
Dominant lesion, No. (%)[e]			
Aortoiliac disease	29 (27.4)	33 (31.1)	.22[c]
Occlusion	11 (10.4)	19 (17.9)	.17[c]
Stenosis	18 (17.0)	14 (13.2)	.28[c]
Femoropopliteal disease	77 (72.6)	73 (68.9)	.45[c]
Occlusion	13 (12.3)	23 (21.7)	.09[c]
Stenosis	64 (60.4)	50 (47.2)	.07[c]
Diabetes mellitus	27 (25.5)	24 (22.6)	.51[c]
Hypertension	55 (51.9)	51 (48.1)	.47[c]
Smoking history, No. (%)			
Current	32 (30.2)	39 (36.8)	.19[c]
Former	44 (41.5)	41 (38.7)	.39[c]
Never	30 (28.3)	26 (24.5)	.32[c]
Brachial blood pressure, mean (SD), mm Hg			
Systolic	138 (8)	139 (7)	.70
Diastolic	83 (11)	82 (10)	.86
Lipids, mean (SD), mg/dL			
Total cholesterol	190 (32)	192 (31)	.60
HDL-C	54 (15)	54 (14)	.86
LDL-C	100 (26)	105 (25)	.18
Triglycerides	145 (62)	151 (71)	.47
Glucose, mean (SD), mg/dL	106 (27)	106 (27)	.97
Medications, No. (%)			
Antiplatelet agents	57 (53.8)	60 (56.6)	.39[c]
Aspirin	36 (34.0)	27 (25.5)	
Clopidogrel	21 (19.8)	33 (31.1)	
Cilostazol	13 (12.3)	7 (6.6)	.12[c]
Statins	56 (52.8)	61 (57.5)	.29[c]
β-Blockers	15 (14.2)	18 (17.0)	.35[c]
Limiting-leg ABI at rest, mean (SD)	0.55 (0.14)	0.57 (0.14)	.24
Pain-free walking time, mean (SD), s	144.2 (54.3)	140.3 (61.1)	.63
Maximum walking time, mean (SD), s	238.4 (70.8)	233.6 (90.7)	.67
WIQ scores, median (IQR)			
Distance[f]	6.1 (2.7-11.2)	6.3 (3.9-19.7)	.60
Speed	10.9 (6.5-17.4)	7.6 (6.5-17.4)	.62
Stair climbing	16.8 (15.3-38.7)	16.8 (15.7-37.8)	.58
SF-36 scores, median (IQR)			
Physical Component Summary[g]	35.6 (34.5-44.9)	35.6 (34.7-44.7)	.63
Mental Component Summary	47.8 (34.7-64.3)	44.1 (33.7-62.2)	.45

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SF-36, Short-Form 36 Health Survey; WIQ, Walking Impairment Questionnaire.

SI conversions: To convert total cholesterol, HDL-C, and LDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, multiply by 0.0113; and glucose values to mmol/L, multiply by 0.0555.

[a] Multiple imputation for missing 6-month data was performed in the 7 dropouts in the ramipril group and the 5 dropouts in the placebo group.

[b] By 1-way analysis of variance unless otherwise specified.

[c] By χ^2 test.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Eighteen patients (8.7%) in the ramipril group and 11 (10.4%) in the placebo group had tibial peroneal disease, but no hemodynamically significant stenosis was present.

[f] The walking distance, walking speed, and stair-climbing domains of the WIQ are scored on a 0 to 100 scale, with higher scores indicating lesser symptoms and greater functional capacity. To date, the minimum clinically important difference has not been established for the WIQ.

[g] The SF-36 questionnaire consists of 8 scaled scores that are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 (worst outcome) to 100 (best outcome) scale. The SF-36 is reported as 2 aggregate summary measures, the Physical Component Summary and the Mental Component Summary. Minimum clinically important changes in SF-36 scores are defined as those greater than 2 to 2.5 points; moderate changes are those greater than 5 points.[29]

no changes to these therapies in any patient. Six-month treatment with ramipril resulted in no significant change in any of the blood safety parameters (eTable 1, available at http://www.jama.com). Twelve patients (5.6%) reported slight dizziness following initiation of treatment (9 [8.5%] in the ramipril group and 3 [2.8%] in the placebo group). Seven patients (6.6%) in the ramipril group experienced persistent cough and withdrew from the trial (Figure). Only 2 adverse events were reported in the placebo group. One patient reported chest pain once the trial medication was initiated. Another patient experienced pronounced ST-segment depression after completing the baseline treadmill exercise test, was newly diagnosed with unstable coronary artery disease, and underwent percutaneous coronary angioplasty. These 2 patients withdrew from the study (Figure).

Treadmill Test

Relative to placebo, ramipril was associated with a 75-second (95% CI, 60 to 89 seconds) increase in mean pain-free walking time ($P<.001$) (TABLE 2). Similarly, ramipril was associated with a 255-second (215 to 295 seconds) increase in maximum walking time ($P<.001$) (Table 2). These changes were independent of the small change in blood pressure that occurred with ramipril treatment.

Blood Pressure

Relative to placebo, ramipril was associated with decreases in blood pressure (systolic: −3.1 mm Hg [95% CI, −3.8 to −2.5 mm Hg]; $P<.001$ and diastolic: −4.3 mm Hg [95% CI, −5.2 to −3.4 mm Hg]; $P<.001$). The association of ramipril with improved treadmill walking times was similar in patients with blood pressures above and below 140/90 mm Hg (eTable 2).

Ankle Brachial Index

Relative to placebo, there was a small increase in ABI following ramipril treatment, both at rest (0.10 [95% CI, 0.08 to 0.13]; $P<.001$) and after exercise (0.11 [95% CI, 0.08 to 0.14]; $P<.001$) (Table 2). At rest, this finding was at-

tributable to a greater decline in brachial systolic pressure in the ramipril group. The association between ramipril and treadmill times was similar in patients with a change in ABI above and below the median (eTable 3).

Duplex Ultrasonography

In 111 patients with femoropopliteal disease (50 receiving placebo [45%] and 61

Table 2. Primary and Secondary Outcome Measures of the Study Population[a]

Outcome Measure	No. of Participants	Value		Mean (95% CI)[b]		*P* Value[c]
		Baseline	6 mo	Within-Group Changes	Between-Group Difference	
Primary outcome measures, mean (SD)						
PFWT, s						
Placebo	106	142 (54)	156 (57)	14 (6 to 21)	75 (60 to 89)	<.001
Ramipril	106	140 (61)	229 (85)	88 (76 to 101)		
MWT, s						
Placebo	106	238 (71)	259 (80)	23 (13 to 36)	255 (215 to 295)	<.001
Ramipril	106	234 (91)	512 (235)	277 (238 to 316)		
Secondary outcome measures, limiting-leg ABI, mean (SD)						
At rest						
Placebo	106	0.55 (0.14)	0.54 (0.16)	0.00 (−0.02 to 0.02)	0.10 (0.08 to 0.13)	<.001
Ramipril	106	0.57 (0.14)	0.64 (0.13)	0.08 (0.06 to 0.09)		
Following exercise						
Placebo	106	0.43 (0.12)	0.42 (0.16)	0.00 (−0.03 to 0.18)	0.11 (0.08 to 0.14)	<.001
Ramipril	106	0.45 (0.14)	0.52 (0.14)	0.07 (0.05 to 0.09)		
WIQ scores, median (IQR)[d]						
Distance score						
Placebo	106	6.1 (2.7 to 11.2)	4.7 (2.3 to 7.4)	−1.1 (−4.2 to 0.0)	13.8 (12.2 to 15.5)	<.001[e]
Ramipril	106	6.3 (3.9 to 19.7)	16.9 (13.4 to 31.8)	9.9 (8.3 to 12.1)		
Speed						
Placebo	106	10.9 (6.5 to 17.4)	6.9 (3.3 to 10.9)	−3.3 (−4.0 to 0.0)	13.3 (11.9 to 15.2)	<.001[e]
Ramipril	106	7.6 (6.5 to 14.4)	20.1 (15.2 to 30.2)	10.9 (7.6 to 12.0)		
Stair climbing						
Placebo	106	16.8 (15.3 to 38.7)	16.7 (12.6 to 21.0)	−4.2 (−8.4 to 0.0)	25.2 (25.1 to 29.4)	<.001[e]
Ramipril	106	16.8 (15.7 to 37.8)	41.9 (31.0 to 67.1)	20.9 (16.8 to 25.2)		
SF-36 scores, median (IQR)[f]						
Physical Component Summary						
Placebo	106	31.4 (30.9 to 32.7)	32.5 (31.8 to 33.0)	0.2 (−0.4 to 1.8)	8.2 (3.6 to 11.4)	.02[e]
Ramipril	106	32.3 (30.4 to 33.1)	41.4 (32.8 to 48.6)	6.3 (0.0 to 19.0)		
Mental Component Summary						
Placebo	106	47.8 (34.7 to 64.3)	48.5 (33.2 to 66.8)	0.1 (−0.5 to 0.3)	0.5 (−0.7 to 1.1)	.74[e]
Ramipril	106	44.1 (33.7 to 62.2)	49.2 (35.1 to 62.5)	1.8 (0.0 to 3.9)		
Volume flow, limiting-leg ABI, mL/min						
Site of stenosis						
Placebo	50	602 (95)	633 (96)	31 (17 to 45)	−2 (−27 to 22)	.85
Ramipril	61	503 (140)	536 (148)	33 (14 to 53)		
Patent site						
Placebo	50	599 (118)	577 (109)	−22 (−29 to −16)	63 (55 to 71)	<.001
Ramipril	61	497 (67)	538 (72)	41 (36 to 46)		
Common femoral artery diameter, limiting leg, cm						
Site of stenosis						
Placebo	50	8.75 (0.52)	8.46 (0.53)	−0.12 (−0.15 to 0.31)	0.22 (0.12 to 0.46)	.44
Ramipril	61	6.81 (1.22)	6.43 (1.35)	0.33 (−0.02 to 0.54)		
Patent site						
Placebo	50	9.88 (0.60)	9.67 (0.60)	−0.13 (−0.18 to 0.42)	0.12 (0.01 to 0.24)	.23
Ramipril	61	8.70 (0.62)	8.86 (0.59)	0.16 (0.08 to 0.38)		

Abbreviations: ABI, ankle-brachial index; IQR, interquartile range; MWT, maximum walking time; PFWT, pain-free walking time; SF-36, Short-Form 36 Health Survey; WIQ, walking impairment questionnaire.

[a] Multiple imputation for missing 6-month data was performed in the 7 dropouts in the ramipril group and the 5 dropouts in the placebo group.

[b] Within-group changes and differences between randomized groups for the WIQ scores and SF-36 scores are median changes (Hodges-Lehmann CIs). Between-group differences are calculated from averaged differences for each patient and thus cannot be calculated from within-group mean changes.

[c] By analysis of covariance with terms for treatment and baseline values unless otherwise specified.

[d] The walking distance, walking speed, and stair climbing domains of the WIQ are scored on a 0 to 100 scale, with higher scores indicating lesser symptoms and greater functional capacity. To date, the minimum clinically important difference has not been established for the WIQ.

[e] By Kruskal-Wallis analysis of variance.

[f] The SF-36 Questionnaire consists of 8 scaled scores that are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 (worst outcome) to 100 (best outcome) scale. The SF-36 is reported as 2 aggregate summary measures, the Physical Component Summary and the Mental Component Summary. Minimum clinically important changes in SF-36 scores are those greater than 2 to 2.5 points; moderate changes are those greater than 5 points.[29]

receiving ramipril [55%]), we also determined volume flow in the common femoral artery 5 cm proximal to the site of stenosis in the leg with the lower ABI (limiting leg). Volume flow was unaltered at the stenotic site in both the placebo and the ramipril groups (Table 2). However, relative to placebo, there was a significant increase in volume flow after ramipril therapy in the common femoral artery proximal to the site of stenosis (63 mL/min [95% CI, 55 to 71 mL/min]; $P<.001$) (Table 2).

WIQ Questionnaire

Relative to placebo, ramipril was associated with improvements in WIQ scores. The median distance score improved by 13.8 (Hodges-Lehmann 95% CI, 12.2 to 15.5), the speed score by 13.3 (Hodges-Lehmann 95% CI, 11.9 to 15.2), and the stair climbing score by 25.2 (Hodges-Lehmann 95% CI, 25.1 to 29.4) ($P<.001$ for all) (Table 2).

SF-36 Survey

The overall SF-36 median Physical Component Summary score improved by 8.2 (Hodges-Lehmann 95% CI, 3.6 to 11.4; $P=.02$) in the ramipril group relative to placebo. Ramipril was not associated with change in the overall SF-36 Mental Component Summary score (Table 2).

COMMENT

Although clinical trial data substantiate the efficacy of ramipril with regard to reduction in major cardiovascular end points in patients with PAD,[30] ACE inhibition is not specifically recommended for the relief of intermittent claudication. To our knowledge, this is the first adequately powered randomized trial demonstrating that treatment with ramipril is associated with improved treadmill walking performance in patients with PAD.

Ramipril was associated with a 75-second (95% CI, 60 to 89 seconds) increase in treadmill-assessed pain-free walking time and a 255-second (95% CI, 215 to 295 seconds) increase in maximum walking time, which corresponds to a clinically significant increase in uphill walking distance of 184 m (95% CI, 155-213 m). The 77% and 123% increases in pain-free and maximum walking times, respectively, with ramipril are greater than those reported for other conventional drug therapies including pentoxifylline,[6] cilostazol,[9] dipyridamole,[5,8] ticlopidine,[5,8] beraprost,[7] iloprost,[31] naftidrofuryl,[10] and statins,[32] which are associated with increases in treadmill walking distance of no more than 60%. Of these drugs, only pentoxifilline and cilostazol are approved by the US Food and Drug Administration for treatment of walking impairment resulting from claudication, with cilostazol providing the greatest improvement (25%).[11]

The increase in WIQ scores suggests that ramipril improves patient-perceived ability to perform normal daily activities.[33] Ramipril therapy was also associated with moderate improvement in the physical health component of the SF-36 score. Importantly, these associations were additional to those achieved with standard clinical management by a general practitioner or vascular specialist. Further benefits may be achieved by adherence to lifestyle recommendations including smoking cessation and regular exercise, as well as more aggressive medical management of cardiovascular risk factors.

Some previous claudication studies have shown a change in relation to the primary outcome measure (maximum walking time, pain-free walking time, or both) ranging from −7% to 48% in patients receiving placebo.[6,31,32,34-38] In certain studies, these changes (ranging from 32%-48%) appear to have reached statistical significance, although the level of statistical significance was not explicitly reported.[6,32,37] In other studies reporting changes ranging from −7% to 24% with placebo,[31,34-36,38] statistical nonsignificance in the placebo group change could be inferred from the error terms. The inclusion of a large number of study sites, inclusion of patients with comorbid conditions such as angina pectoris, and changes in background therapy are all factors that may have contributed to greater variability in walking times in these studies. Factors contributing to the consistency and small magnitude of the increase in walking times in the placebo group of the current study include the low number of study sites (3), the recruitment of patients with stable intermittent claudication, the stability of concurrent medical therapies and lifestyle, and careful exercise testing procedures.

We previously reported greater increases in pain-free and maximum walking times with 10 mg of ramipril as compared with placebo (227 seconds and 451 seconds for pain-free and maximum walking time, respectively, with ramipril). The greater magnitude of the effects of ramipril in the previous study likely relates in part to the exclusion of patients with diabetes and aortoiliac disease. In the current study, the magnitude of the association of ramipril therapy with change in maximum walking time was greater in patients with femoropopliteal disease (286 seconds [95% CI, 280 to 293 seconds]) compared with those with aortoiliac disease (127 seconds [95% CI, 118 to 137 seconds]; $P<.001$) (eTable 4). There was no difference in the magnitude of the ramipril response in those with multi-level vs single-level disease (eTable 5). The broader inclusion criteria and larger study population make the current findings applicable to a more representative PAD population with claudication.

Mechanisms

ACE inhibitor therapy may mediate improved functional capacity through multiple mechanisms, including increased peripheral blood flow[39] and adaptations in skeletal muscle structure and function, which likely enhance production of adenosine triphosphate.[40-44] Improved blood flow may be mediated via vasodilatation through reduction in angiotensin II, sympathetic inhibition, and improvement in endothelial function through preservation of bradykinin.

In the current study, there was an increase in volume flow at a patent site proximal to the site of stenosis but no change at the stenotic site. The absence of a flow change at the downstream stenotic site suggests that ramipril caused dilation of collateral vessels between the

2 sites or perhaps even formation of new collateral vessels (angiogenesis).[45] Certain ACE inhibitors (including quinaprilat and perindopril) increase capillary density in animal models[46-49] via bradykinin accumulation, whereas ramipril therapy has been associated with increased expression of vascular endothelial growth factor in cardiac tissue.[50] However, other ACE inhibitors have no significant effects on angiogenesis in humans and animals.[46,51,52]

ACE inhibition may promote adaptive changes in skeletal muscle, which improve the efficiency of oxygen and metabolic substrate uptake and utilization. In patients with chronic heart failure, both ACE inhibition and angiotensin type I receptor blockade have been associated with increased exercise capacity and a shift of the myosin–heavy chain protein isoforms in the gastrocnemius from the type II form toward the type I, slow aerobic, fatigue-resistant isoform.[44] A shorter-duration intervention had no such effect.[43]

ACE inhibition also may have direct effects on glucose metabolism in skeletal muscle. ACE inhibition is known to enhance insulin signaling and glucose uptake into skeletal muscle,[40] which could also improve walking ability. This effect is likely mediated via reduced metabolism of bradykinin and downstream effects on nitric oxide, which increases delivery of both insulin and glucose to muscle. In addition, bradykinin directly stimulates insulin-dependent and insulin-independent glucose uptake into muscle.[41,42]

However, whether ACE inhibitors really have a beneficial effect on skeletal muscle function and ultimately physical function remains controversial. Two intervention studies have shown that ACE inhibitors improve functional capacity in patients with impaired mobility[53] or heart failure.[54] Muscle mass and strength were preserved in users of ACE inhibitors in large longitudinal cohorts including the Women's Health and Aging Study (WHAS)[55] and the Health ABC population cohort.[56] However, additional clinical trials and observational studies[57,58] have shown no associations of ACE inhibitor treatment with functional decline. Thus, there is not a consistent association between ACE inhibitor use and functional performance in patients without PAD, and further specifically designed studies are required.

Limitations

First, the beneficial associations of ramipril in the current trial may be maintained beyond 6 months, but the current study cannot address this issue. The Heart Outcomes Prevention Evaluation (HOPE)[30] showed that ramipril has beneficial effects on morbidity and mortality, supporting longer-term treatment with ramipril in patients with PAD.

Second, the inclusion and exclusion criteria were designed to select a population of patients with stable PAD in whom we could ethically administer either a placebo or an ACE inhibitor intervention and obtain follow-up data at 6 months. The population was therefore restricted to the lower end of the blood pressure spectrum and excluded patients with other major comorbid conditions and any condition other than PAD limiting walking ability. Whether the findings are generalizable to individuals with higher blood pressure or to other ethnically diverse populations is unknown.

Third, although animal studies suggest that ACE inhibitors may have favorable effects on skeletal muscle, this was not examined.

In conclusion, among patients with intermittent claudication, 24 weeks of treatment with ramipril compared with placebo was associated with significant improvement in pain-free and maximum walking times, with improvement in patient-perceived walking performance as measured by WIQ scores and the physical health aspect of quality of life.

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Study concept and design: Ahimastos, Blombery, Kingwell.
Acquisition of data: Ahimastos, Walker, Askew, Leicht, Pappas, Golledge.
Analysis and interpretation of data: Ahimastos, Walker, Askew, Blombery, Reid, Golledge, Kingwell.
Drafting of the manuscript: Ahimastos, Reid, Kingwell.
Critical revision of the manuscript for important intellectual content: Ahimastos, Walker, Askew, Leicht, Pappas, Blombery, Reid, Golledge, Kingwell.
Statistical analysis: Ahimastos, Reid, Kingwell.
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Administrative, technical, or material support: Walker, Askew, Leicht, Pappas.
Study supervision: Ahimastos, Walker, Askew, Blombery, Golledge, Kingwell.
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Online-Only Material: eTables 1 through 5 and Author Audio Interview are available at http://www.jama.com.

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