Randomized clinical trial

Randomized clinical trial of angiotensin-converting enzyme inhibitor, ramipril, in patients with intermittent claudication

Y. Shahin[1], J. R. Cockcroft[2] and I. C. Chetter[1]

[1]Academic Vascular Surgical Unit, Hull York Medical School and University of Hull, Hull, and [2]Welsh Heart Research Institute, Cardiff University, Cardiff, UK

Correspondence to: Dr Y. Shahin, Academic Vascular Surgical Unit, Vascular Laboratory, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK (e-mail: yousef.shahin@yahoo.co.uk)

Background: **The aim was to investigate the effect of ramipril on clinical parameters in patients with peripheral arterial disease.**

Methods: **Patients with intermittent claudication were randomized to receive ramipril or placebo for 24 weeks in a double-blind study. Outcome measures were walking distance, arterial stiffness measurement and quality of life (QoL).**

Results: **A total of 33 patients were included (25 men; mean(s.d.) age 64·6(7.8) years); 14 received ramipril and 19 placebo. After 24 weeks, ramipril improved maximum treadmill walking distance by an adjusted mean (95 per cent confidence interval, c.i.) of 131 (62 to 199) m ($P = 0·001$), improved treadmill intermittent claudication distance by 122 (56 to 188) m ($P = 0·001$) and improved patient-reported walking distance by 159 (66 to 313) m ($P = 0·043$) compared with placebo. Ramipril reduced carotid femoral pulse wave velocity by −1·47 (95 per cent c.i. −2·40 to −0·57) m/s compared with placebo ($P = 0·002$). Resting ankle : brachial pressure index (ABPI) improved slightly in both ramipril and placebo groups (0·02 (95 per cent c.i. −0·08 to 0·11) *versus* 0·03 (−0·05 to 0·10); $P = 0·830$). Ramipril had a slight, non-significant effect on QoL physical domains compared with placebo.**

Conclusion: **Ramipril improved walking distance in patients with claudication; however, this improvement was not related to improved ABPI but might have been due to ramipril reducing arterial stiffness. Registration number: NCT01037530 (http://www.clinicaltrials.gov).**

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Introduction

Lower-limb peripheral arterial disease (PAD) is common, and affects 3–7 per cent of the general population and 20 per cent of people aged over 75 years[1]. It is associated with a mortality rate three to five times that of an age-matched population, mainly owing to cardiovascular and cerebrovascular complications. Symptomatic PAD causes intermittent claudication (IC), which is defined as pain in the leg, thigh or buttock muscles precipitated by walking and relieved by rest. The prevalence of IC ranges from 3 per cent in people aged 40 years to 6 per cent among those aged 60 years[2]. The overall prognosis for patients with PAD is poor, with a cumulative annual mortality rate of about 5 per cent. However, the prognosis for the leg is more benign; some 75 per cent of patients have stable claudication and only a minority progress to critical ischaemia. Owing to the increase in cardiovascular morbidity and mortality, it has been recommended that patients with PAD should have aggressive secondary prevention and management of risk factors[3–7].

The role of the angiotensin-converting enzyme (ACE) inhibitor, ramipril, in reducing cardiovascular morbidity and mortality in patients with PAD (who have no evidence of left ventricular dysfunction or heart failure) is supported by level I evidence[8–12]. However, the evidence regarding the effect of ramipril on walking distance in patients with IC is limited; only one controlled trial exists which was limited to non-diabetic patients with infrainguinal PAD[13]. There are no data concerning the effect of ramipril on quality of life (QoL) in patients with IC.

Therefore, the aim of this clinical trial was to evaluate the effects of the ACE inhibitor, ramipril, compared with placebo, on clinical parameters of PAD (walking distance;

ankle : brachial pressure index, ABPI), arterial stiffness, biomarkers of inflammation, cardiovascular prognosis and ischaemia–reperfusion, and QoL in patients with IC.

Methods

The ACE inhibitor in intermittent claudicants (ACEIIC) trial was designed as a prospective, randomized, double-blind, placebo-controlled, single-centre trial. Patients with stable unilateral or bilateral IC (Fontaine stage II or higher) on stable medication for at least 6 months, with an ABPI below 0·9, were recruited into the study. To assess the effect of ramipril on walking distance independent of its effect on blood pressure (BP), patients were included if they had a brachial (peripheral) systolic BP of 160 mmHg or less and brachial diastolic BP of no more than 90 mmHg at the time of inclusion. Exclusion criteria were: critical leg ischaemia with rest pain, leg ulcer or gangrene; recent (within 3 months) angioplasty or lower limb bypass surgery; concomitant disease limiting exercise capacity (such as severe angina, chronic obstructive pulmonary disease or osteoarthritis); being on ACE inhibitors or angiotensin receptor blockers (ARBs) already; contraindications to ACE inhibitors (such as documented bilateral renal artery stenosis or history of angioneurotic oedema); existing indications for treatment with ACE inhibitors (for example documented heart failure (New York Heart Association class III or IV), uncontrolled hypertension at screening, recent myocardial infarction (less than 3 months previously), or stroke or chronic renal impairment (creatinine level exceeding 250 μmol/l)); hyperkalaemia (potassium over 5·9 mmol/l); or an increase in creatinine level by more than 30 per cent since the baseline visit[14].

The study was approved by the local research ethics committee and the Medicines and Healthcare products Regulatory Agency in the UK. The study was conducted in accordance with the Helsinki Declaration (current version) and the International Conference for Harmonization and Good Clinical Practice Guidelines, and all patients gave written informed consent. The study was registered as a randomized clinical trial with ClinicalTrials.gov (registration number: NCT01037530; http://clinicaltrials.gov).

Patient randomization, blinding and study visits

After a run-in phase of 2 weeks (2·5 mg ramipril (or placebo) once daily for 1 week increased to 5 mg once daily for another week) followed by a washout interval of 2 weeks, patients were randomized, using computer-generated blocks of ten, to ramipril 5 mg once daily for 2 weeks increased to 10 mg once daily for 22 weeks, or to placebo, in a parallel-group design. Ramipril and placebo tablets were identical. Patients received placebo or ramipril for a total of 24 weeks following randomization. Tests for renal function (serum urea; creatinine; estimated glomerular filtration rate, eGFR) were carried out at the end of each week during the run-in phase and during each visit after randomization. Patients were followed at 2, 6 and 24 weeks following randomization. Clinical parameters of PAD, arterial stiffness, biomarkers of cardiovascular prognosis, ischaemia–reperfusion and inflammation, and QoL were also assessed at similar intervals after randomization. Both investigators and patients were blinded to the drug assignment and the randomization list was kept off-site for the duration of the trial. No patient assigned to ramipril crossed over to placebo, or vice versa.

Walking distance

Patients underwent a treadmill exercise test according to a constant standard fixed-load laboratory protocol at a constant treadmill speed of 2·5 km/h and a constant incline of 10 per cent[15] for a maximum of 10 min. Intermittent claudication distance (ICD), maximum walking distance (MWD, up to a maximum of 426 m) and patient-reported walking distance (PRWD, up to a maximum of 1000 m) were recorded. ICD was defined as the distance a patient could walk until the onset of leg pain. MWD was defined as the distance beyond which treadmill exercise could not be tolerated owing to claudication pain.

Ankle : brachial pressure index

ABPI was assessed at rest (r-ABPI) and after the treadmill exercise test (t-ABPI). ABPI of the more symptomatic leg was entered into the analysis.

Arterial stiffness

Arterial stiffness indices were measured after resting supine for 10–15 min. Pulse wave velocity between the carotid and the femoral artery (PWVcf), which is considered the standard for arterial stiffness assessment[16], was measured using a SphygmoCor® device (model SCOR-Pvx, software version 8; AtCor Medical, Sydney, New South Wales, Australia). The carotid and femoral pulse waveforms were recorded sequentially using the transducer, and at the same time an electrocardiogram was recorded as a reference to calculate transit time (tt) using the foot-to-foot method. The distance the pulse waveform travelled between the two recording sites (carotid and femoral) was measured using a tape measure over the body area. PWVcf was calculated

as distance (m)/tt (s)[17]. PWVcf measurements acquired in the trial had an operator index range of 85–100 per cent and a coefficient of variation of 5 per cent.

Pulse wave analysis indices were assessed using the same device. These included: aortic (central) systolic BP, aortic diastolic BP, aortic pulse pressure, mean arterial pressure, heart rate (HR), augmentation pressure, augmentation index (AIx), augmentation index adjusted to a HR of 75 beats/min (AIx@HR75), ejection duration index and subendocardial viability ratio. A hand-held high-fidelity tonometer (Millar Instruments, Houston, Texas, USA) was used for applanation tonometry of the right radial artery. The SphygmoCor® device generated an average radial pulse wave contour after a 10-s recording interval. This was then converted to an aortic pulse wave using a general transfer function available within the SphygmoCor® device[18,19].

Laboratory measurements

Blood samples were obtained for a serum lipid profile including total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol, and *N*-terminal pro B-type natriuretic peptide (NTproBNP) measurement. Urine albumin creatinine ratio, a biomarker of ischaemia–reperfusion, was measured at rest (r-UACR) and after exercise (t-UACR). Biomarkers of inflammation measured included C-reactive protein (CRP) and fibrinogen.

Quality of life

QoL was evaluated using generic instruments, Short Form 36 (SF-36®; Medical Outcomes Trust, Waltham, Massachusetts, USA) and EQ-5D™ (EuroQol Group, Rotterdam, The Netherlands), and a disease-specific instrument: King's College Hospital's Vascular QoL questionnaire (VascuQol). SF-36® utilizes 36 items to derive eight domains, each scored from 0 (worst possible) to 100 (best possible). The EQ-5D™ utilizes responses to five domain questions which are transformed using a time trade-off tariff to a global index, scored on a scale from −0·513 (worst) to 1 (best). The VascuQol questionnaire consists of 25 questions that cover five domains (activities, symptoms, pain, and emotional and social items), with each domain scored on a scale from 0 (worst) to 7 (best). All instruments have been validated and used as a measure of effectiveness in patients with PAD[20–23].

Statistical analysis

Based on a previous trial[13], the study was designed to achieve 96 per cent power in detecting a change in MWD of 150 m with ramipril using a pooled standard deviation of 125 m. The planned sample size was 12 patients per group. With an estimated dropout of 30 per cent, the aim was to randomize a total of 32 patients.

Unless indicated otherwise, continuous variables are expressed as mean(s.d.) if normally distributed, with comparison between groups by means of the unpaired *t* test; values with a non-normal distribution are presented as median (interquartile range, i.q.r.) and were compared using the Mann–Whitney *U* test. Categorical variables were analysed using Fisher's exact probability test. Intragroup analysis of mean changes from baseline was done using one-way repeated-measures ANOVA. Intergroup differences were tested by means of one-way ANCOVA using baseline variables as co-variables in the model[24]. Therefore, adjusted mean changes with standard error (s.e.m.) or 95 per cent confidence interval (c.i.) are shown. Non-normally distributed baseline variables were log-transformed before being entered as co-variables in the ANCOVA model. *Post hoc* comparisons were done using the Bonferroni correction. Multivariable regression analysis was performed using the enter method to determine whether the effect of ramipril on walking distance was related to its effect on BP. All statistical tests were two-sided and $P < 0{\cdot}050$ was considered significant. SPSS® version 18 for Windows® (IBM, Armonk, New York, USA) was used for statistical analysis.

Results

The flow of patients through the trial is shown in *Fig. 1*. Overall, 166 patients were assessed for eligibility over 10 months from January 2011; 38 patients were recruited and started on the run-in phase, following which five withdrew and 33 were randomized to receive ramipril (14) or placebo (19); of these, 29 patients (ramipril 12, placebo 17) completed all trial follow-up. The most frequent reason for failing to be included in the trial was current treatment with an ACE inhibitor or ARB (59 patients). Baseline patient characteristics are summarized in *Table 1*. There was no significant difference between the two groups in terms of demographics, cardiovascular risk factors, site of arterial disease or concomitant medications.

Walking distance

There was no significant difference between the ramipril and placebo groups at baseline in MWD (median (i.q.r.) 137 (110–213) *versus* 143 (72–213) m; $P = 0{\cdot}760$) and ICD (81 (48–114) *versus* 94 (32–163) m; $P = 0{\cdot}986$). However, the groups had significantly different baseline PRWD (100

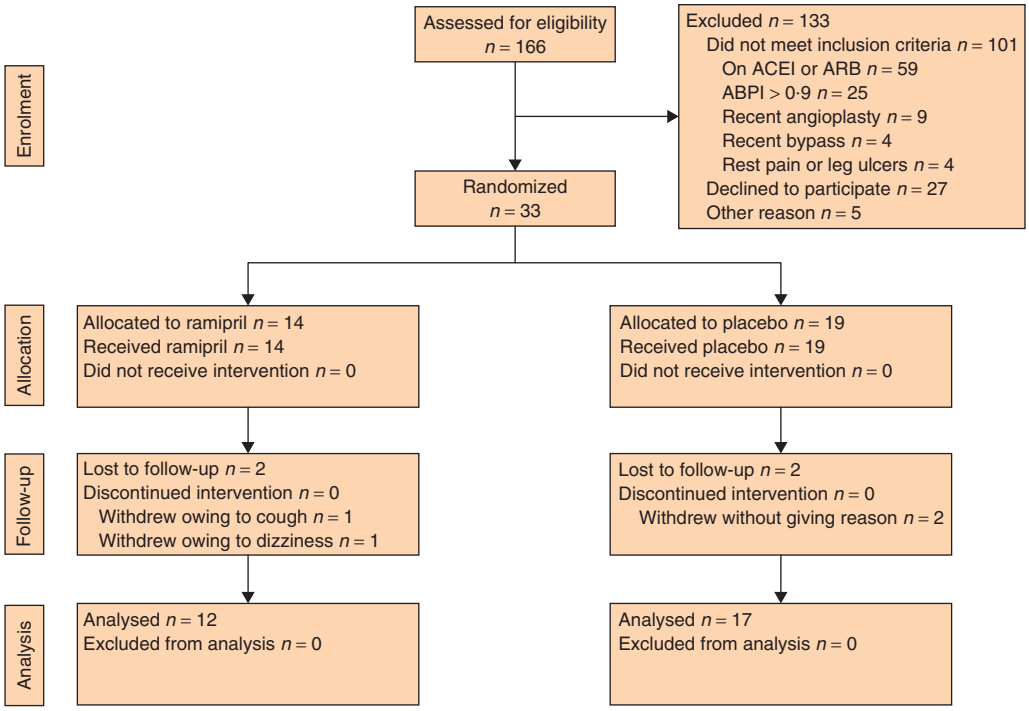

Fig. 1 CONSORT diagram for the trial. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ABPI, ankle : brachial pressure index

(87–263) and 229 (200–457) m respectively; $P = 0{\cdot}011$). Intragroup analysis showed that the mean change in MWD in the ramipril group increased significantly after 24 weeks compared with 2 weeks ($P = 0{\cdot}006$) and 6 weeks ($P = 0{\cdot}010$) ($P = 0{\cdot}226$ for comparison between mean changes at 2 and 6 weeks). In the placebo group, however, there was no significant increase in mean change in MWD at 24 weeks compared with 2 weeks ($P = 1{\cdot}000$) and 6 weeks ($P = 0{\cdot}937$) ($P = 0{\cdot}134$ for comparison of mean changes at 2 and 6 weeks). Intergroup analysis showed that the adjusted mean change from baseline in MWD after 24 weeks of treatment with ramipril was 131 (95 per cent c.i. 62 to 199) m longer than with placebo ($P = 0{\cdot}001$) (*Fig. 2a*).

In the ramipril group, ICD increased significantly at 24 weeks compared with 2 weeks ($P = 0{\cdot}020$) and 6 weeks ($P = 0{\cdot}042$) ($P = 0{\cdot}076$ for comparison between mean changes at 2 and 6 weeks). In the placebo group, there was no significant change at 24 weeks compared with 2 weeks ($P = 0{\cdot}693$) and 6 weeks ($P = 1{\cdot}000$) ($P = 0{\cdot}377$ for comparison between changes at 2 and 6 weeks). The adjusted mean change in ICD with ramipril was 122 (95 per cent c.i. 56 to 188) m longer than with placebo after 24 weeks ($P = 0{\cdot}001$) (*Fig. 2b*).

In the ramipril group, PRWD was non-significantly longer at 24 weeks compared with 2 weeks ($P = 0{\cdot}312$) and 6 weeks ($P = 1{\cdot}000$) ($P = 0{\cdot}585$ for comparison between changes at 2 and 6 weeks). In the placebo group, there was no significant change in PRWD at 24 weeks compared with 2 weeks ($P = 1{\cdot}000$) and 6 weeks ($P = 0{\cdot}816$) ($P = 1{\cdot}000$ for comparison between mean changes at 2 and 6 weeks). Nonetheless, PRWD significantly improved after 24 weeks of treatment with ramipril, by 159 (95 per cent c.i. 6 to 313) m compared with placebo ($P = 0{\cdot}043$) (*Fig. 2c*).

Ankle : brachial pressure index

Baseline r-ABPI and t-ABPI were comparable between the ramipril and placebo groups (r-ABPI: 0·59(0·19) and 0·66(0·16) respectively, $P = 0{\cdot}250$; t-ABPI: 0·32(0·29) and 0·44(0·21), $P = 0{\cdot}188$). Ramipril significantly increased r-ABPI by 0·03(0·08) at 24 weeks compared with 2 weeks (–0·04(0·09); $P = 0{\cdot}007$) and non-significantly compared with 6 weeks (–0·02(0·15); $P = 0{\cdot}590$) ($P = 0{\cdot}560$ for comparison between 2 and 6 weeks). In the placebo group, there was no significant change in r-ABPI at 24 weeks (0·02(0·18)) compared with 2 weeks (0·002(0·11); $P = 1{\cdot}000$) and 6 weeks (0·004(0·12); $P = 1{\cdot}000$) ($P = 1{\cdot}000$ for comparison between 2 and 6 weeks). There was no significant difference in adjusted mean changes of r-ABPI between the two groups at 2, 6 and 24 weeks (24 weeks:

Table 1 Baseline characteristics of patients according to treatment group

	Ramipril ($n = 14$)	Placebo ($n = 19$)	P†
Age (years)*	64·4(8·2)	64·7(7·7)	0·892‡
Sex ratio (M : F)	11 : 3	14 : 5	1·000
Body mass index (kg/m^2)*	28·1(3·8)	28·3(4·2)	0·885‡
Cardiovascular risk factors			
Smoking			
Current smoker	7	9	1·000
Ex-smoker	7	6	0·472
Never smoked	0	4	0·119
Diabetes mellitus	4	7	0·738
Dyslipidaemia	12	18	0·561
Hypertension	7	13	0·472
Coronary artery disease	2	2	1·000
Previous PAD treatment			
Angioplasty	4	7	0·719
Peripheral bypass surgery	1	0	0·424
Concomitant medications			
Antiplatelet agents	14	17	0·496
Lipid-modifying agents	12	16	1·000
Beta-blockers	2	1	0·561
Calcium channel blockers	6	9	1·000
Diuretics	2	3	1·000
Arterial stenosis site			
Infrainguinal	12	15	1·000
Suprainguinal	0	2	0·496
Mixed	2	2	1·000

*Values are mean(s.d.). PAD, peripheral arterial disease. †Fisher's exact test, except ‡unpaired t test.

0·02 (95 per cent c.i. −0·08 to 0·11) *versus* 0·03 (−0·05 to 0·10); $P = 0·830$) (*Fig. 2d*).

With regard to t-ABPI, there was a non-significant increase in the ramipril group at 24 weeks (0·05(0·12)) compared with 2 weeks (0·03(0·07); $P = 1·000$) and 6 weeks (0·05(0·15); $P = 1·000$) ($P = 1·000$ for comparison between 2 and 6 weeks). There was no significant change in t-ABPI in the placebo group at 24 weeks (0·02(0·14) compared with 2 weeks (0·00(0·10); $P = 1·000$) and 6 weeks (0·04(0·10); $P = 0·960$) ($P = 0·110$ for comparisons between 2 and 6 weeks). There was no significant difference in adjusted mean (95 per cent c.i.) changes in t-ABPI between the ramipril and placebo groups at 2 weeks (0·03 (−0·03 to 0·09) *versus* 0·005 (−0·04 to 0·05) respectively; $P = 0·490$), 6 weeks (0·05 (−0·03 to 0·13) *versus* 0·05 (−0·02 to 0·11); $P = 0·950$) and 24 weeks (ramipril 0·04 (−0·04 to 0·12) *versus* 0·02 (−0·04 to 0·09); $P = 0·720$).

Arterial stiffness and haemodynamic measurements

There was no significant difference in baseline PWVcf and indices of pulse wave analysis between the two groups. However, there was a significant difference in baseline brachial diastolic BP between the groups ($P = 0·021$). Results of arterial stiffness and haemodynamic measurements throughout the trial are shown in *Table 2*. Ramipril decreased AIx after 24 weeks of treatment compared with 2 weeks ($P = 0·016$); however, AIx non-significantly increased in the placebo group at 24 weeks compared with 2 and 6 weeks ($P = 0·012$, $P = 0·002$ and $P < 0·001$ for comparison between groups at 2, 6 and 24 weeks). Ramipril decreased augmentation pressure at 24 weeks compared with 2 weeks ($P < 0·001$) and 6 weeks ($P < 0·001$). Similarly, augmentation pressure decreased in the placebo group at 24 weeks compared with 2 weeks ($P < 0·001$) and 6 weeks ($P < 0·001$) ($P = 0·026$ at 6 weeks and $P = 0·080$ at 24 weeks for comparison between the groups).

By 24 weeks, compared with placebo, ramipril significantly reduced PWVcf (adjusted mean change −1·47 (95 per cent c.i. −2·40 to −0·57) m/s; $P = 0·002$), aortic systolic blood pressure ($P < 0·001$) ($P = 0·008$ for comparison between the groups at 6 weeks), aortic diastolic BP ($P = 0·020$) ($P = 0·005$ for comparison between the groups at 2 weeks), aortic pulse pressure ($P = 0·001$), mean arterial pressure ($P < 0·001$) ($P = 0·021$ for comparison between the groups at 6 weeks) and AIx@HR75 ($P < 0·001$) ($P = 0·004$ and $P = 0·001$ for comparison between the groups at 2 and 6 weeks respectively). There was a non-significant change in systolic BP ($P = 0·092$), diastolic BP ($P = 0·183$) ($P = 0·022$ and $P = 0·005$ at 2 and 6 weeks respectively) and brachial pulse pressure ($P = 0·342$). Ramipril increased the subendocardial viability ratio significantly at 6 weeks ($P = 0·011$) and non-significantly at 2 weeks ($P = 0·281$) and 24 weeks ($P = 0·473$) compared with placebo. No significant change in ejection duration index was found between the groups at 2, 6 or 24 weeks.

Laboratory measurements

All laboratory measurements were comparable between the groups at baseline. Changes in laboratory measurements at 2, 6 and 24 weeks between the groups are shown in *Table S1* (supporting information). Intragroup analysis showed no significant change in the ramipril or placebo group in terms of lipid profile, eGFR, urea, creatinine, CRP, fibrinogen, NTproBNP, r-UACR and t-UACR, except for a significant change in total cholesterol in the ramipril group between 2 and 6 weeks ($P = 0·020$), and in LDL-C between the two groups at week 6 ($P = 0·041$). Nonetheless, after 24 weeks of treatment, there was a non-significant decrease in eGFR ($P = 0·232$) and NTproBNP ($P = 0·452$) in the ramipril group compared with placebo. Conversely, ramipril non-significantly increased creatinine ($P = 0·070$) and urea ($P = 0·330$) levels compared with placebo.

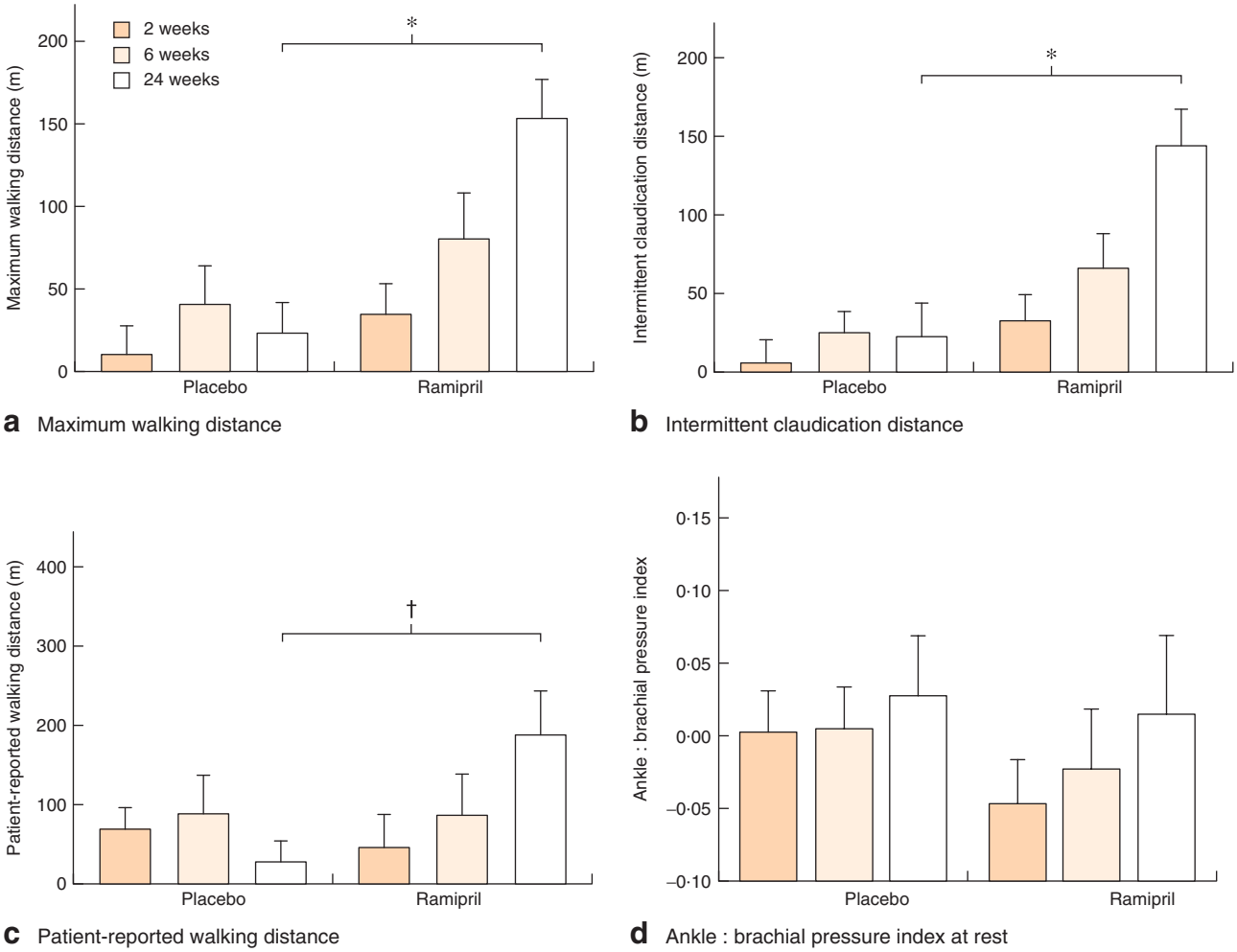

Fig. 2 Adjusted mean(s.e.m) changes in **a** maximum walking distance, **b** intermittent claudication distance, **c** patient-reported walking distance and **d** ankle : brachial pressure index at rest in ramipril and placebo groups at 2, 6 and 24 weeks. *$P = 0{\cdot}001$, †$P = 0{\cdot}043$ (1-way ANCOVA)

Quality of life

Results from the three questionnaires (EQ-5D™, SF-36® and VascuQol) are summarized in *Table S2* (supporting information). Overall, patients had low scores in most domains at baseline, with the lowest scores in the domains physical function, role physical and bodily pain of the SF-36®, and pain and activities of VascuQol. There was no significant difference between the groups at baseline. In addition, there was no significant difference between the groups in any of the SF-36® and VascuQol domains after 24 weeks of treatment. VascuQol and EQ-5D™ total scores did not differ significantly between the groups after 24 weeks either. Patients in the ramipril group scored significantly lower in the mental health domain than patients who received placebo after 2 weeks ($P = 0{\cdot}040$), but there was no significant difference at 6 and 24 weeks. Patients in the ramipril group had significantly lower scores in the social domain of VascuQol after 24 weeks compared with week 2 ($P = 0{\cdot}040$) and week 6 ($P = 0{\cdot}040$). However, there was no such change in the placebo group. Notably, ramipril had a slight positive, but non-significant, effect on the domains physical function and bodily pain in the SF-36®, and pain and activities in the VascuQol; this was comparable to changes seen in the placebo group.

Multivariable regression analysis

Multivariable regression analysis showed that the ramipril-induced change in MWD was not associated with its

Table 2 Arterial stiffness and haemodynamic measurements indices before and 2, 6 and 24 weeks after treatment

	Baseline		Change at 2 weeks		Change at 6 weeks		Change at 24 weeks	
	Placebo	Ramipril	Placebo	Ramipril	Placebo	Ramipril	Placebo	Ramipril
Brachial systolic blood pressure (mmHg)	146(4)	139(5)	−3(3)	−7(4)	−4(4)	−17(4)*	−2(3)	−13(4)
Brachial diastolic blood pressure (mmHg)	82(1)	76(3)§	0·5(2·0)	−6(2)*	−1(1)	−7(2)*	−0·2(1·0)	−3(2)
Brachial pulse pressure (mmHg)	64(4)	63(5)	−2(3)	−3(3)	−3(3)	−10(4)	−2(3)	−6(3)
Aortic systolic blood pressure (mmHg)	139(6)	130(4)	−3(3)	−10(4)	−1(4)	−14(4)*	4(3)	−16(3)*
Aortic diastolic blood pressure (mmHg)	83(2)	78(3)	2(2)	−5(2)*	−3(3)	−9(3)	−0·03(2·00)	−6(2)*
Aortic pulse pressure (mmHg)	55(6)	52(4)	−4(3)	−7(3)	3(5)	−11(5)	5(2)†	−10(3)*
Mean arterial pressure (mmHg)	105(3)	99(3)	−0·5(2·0)	−7(2)	−3(2)	−10(3)*	2(2)	−9(2)*
Heart rate (beats/min)	70(2)	68(3)	−0·2(1·0)	0·4(2·0)	−0·3(1·0)	−0·2(1·0)	−2(2)	5(2)* ‡
Augmentation pressure (mmHg)	19(2)	18(2)	−1(1)	−4(1)	2(2)	−5(3)*	−33(2)†‡	−40(3)†‡
Subendocardial viability ratio (%)	154(8)	144(7)	0·2(4·0)	8(5)	−4(4)	15(5)*	−1(4)	3(5)
Ejection duration index (%)	35(1)	36(1)	−0·03(1·00)	−0·4(1·0)	−0·1(1·0)	−1(1)	0·3(1·0)	0·04(1·00)
Augmentation index (%)	33(2)	34(3)	0·2(1·0)	−4(1)*	2(1)	−5(1)*	3(1)	−8(1)* †
Augmentation index adjusted to 75 beats/min (%)	31(1)	31(2)	0·6(1·0)	−4(1)*	2(1)	−5(1)*	2(1)	−6(1)*
Carotid femoral pulse wave velocity (m/s)	10·7(0·6)	11·2(0·7)	−0·2(0·3)	−0·3(0·3)	−0·9(0·3)	−0·9(0·4)	0·6(0·3)‡	−0·9(0·3)*

Values are mean(s.e.m.). *$P < 0·050$, adjusted mean changes at 2, 6 and 24 weeks between groups (1-way ANCOVA); $P < 0·050$, within-group *post* hoc comparison between †weeks 2 and 24 and ‡weeks 6 and 24 (1-way repeated-measures ANOVA); §$P < 0·050$, intergroup analysis at baseline (unpaired *t* test).

effect on systolic BP (standardized β coefficient −0·03, $P = 0·880$) or diastolic BP (standardized β coefficient −0·04, $P = 0·871$), but was independently associated with class of drug (ramipril or placebo; standardized β coefficient 0·60, $P = 0·001$) (adjusted R^2 for model = 0·30, $P = 0·008$).

Adverse events

Patients underwent clinical examination at each visit, including recording of vital signs, current medications and adverse events. Five of 38 patients enrolled in the run-in phase withdrew because of cough (4) and headache (1). Of 14 patients randomized to receive ramipril, four patients developed cough and one experienced dizziness. Consequently, two patients withdrew from the trial (1 owing to dizziness, one because of cough). Of 19 patients randomized to placebo, two withdrew without giving a reason. One patient in the ramipril group developed hyperkalaemia by 6 weeks of follow-up, which was resolved without complications and the patient was able to complete the trial. Renal function was monitored closely throughout the trial and no deterioration was observed in any of the trial subjects.

Discussion

This trial was designed to compare the effect of ramipril, an ACE inhibitor, with placebo in patients with IC. Ramipril significantly improved MWD, ICD and PRWD, and decreased indices of arterial stiffness (PWVcf and AIx) compared with placebo. Ramipril had no significant effect on ABPI, biomarkers of inflammation and ischaemia–reperfusion, or QoL scores compared with placebo. Although NTproBNP, a surrogate marker of cardiovascular prognosis, was reduced in ramipril-treated patients, this effect was not statistically significant.

Ramipril has been studied previously for PAD; in a double-blind placebo-controlled trial that was limited to non-diabetic patients with infrainguinal disease, Ahimastos and colleagues[13] showed that ramipril improved maximum walking time by 243 per cent, pain-free walking time by 164 per cent, r-ABPI by 0·07 and t-ABPI by 0·08 after 6 months. In contrast, such major improvements were not observed in the present trial, which showed an improvement in MWD by 106 per cent and in ICD by 152 per cent, with non-significant improvements in r-ABPI and t-ABPI. The present trial included patients with diabetes and different levels of arterial disease (suprainguinal, infrainguinal and

mixed), which makes this cohort more representative of the population with PAD.

The effect of other ACE inhibitors (cilazapril, captopril and perindopril) on walking distance or time has been studied in controlled trials[25–27]. These showed no significant improvement in walking distance, walking time or ABPI[28]. However, the duration of treatment with ACE inhibitors in these trials was relatively short (4–8 weeks) and two were crossover trials with only a small number of patients. The present trial suggests that a longer duration of treatment with an ACE inhibitor (6 months) improves efficacy.

From the clinical perspective, the most important finding of this trial was the improvement observed in ICD and MWD in the ramipril-treated group; however, this was not associated with improvements in QoL. In fact, ramipril had a slight non-significant effect on the domains physical function and pain. This trial may have been too small, as it was not powered to detect a difference in QoL between the two groups.

Several hypotheses have been suggested to explain the mechanism by which ramipril can improve walking distance in patients with PAD. One hypothesis suggests that ACE inhibitors increase blood flow to the legs by maintaining collateral circulation through their inhibitory effect on angiotensin II, a potent vasoconstrictor, and by reduction in the breakdown of bradykinin, causing vasodilatation, or perhaps through angiogenesis[13,25,29,30]. The improvement in walking distance in the ramipril cohort was not accompanied by significant improvements in ABPI; r-ABPI was almost unchanged after 24 weeks of treatment with ramipril and there was only a slight (non-significant) increase in postexercise ABPI after 24 weeks.

A second hypothesis is that endothelial dysfunction is an early step in atherosclerosis that precedes morphological change to the arterial wall[31–34]. In a meta-analysis, ACE inhibitors improved endothelial function[35], measured by brachial flow-mediated vasodilatation, by 1·26 per cent ($P = 0·002$) compared with placebo or no treatment, and by 0·89 per cent ($P = 0·009$) compared with other antihypertensive agents in patients with several pathological conditions. The ability of ACE inhibitors to improve endothelial function in patients with PAD could have been the reason behind the significant improvement in walking distance.

Arterial stiffness is associated with several pathological conditions[36,37], and patients with PAD are known to have increased arterial stiffness[38]. Overall, there is a lack of evidence of the effect of ACE inhibitors on arterial stiffness in patients with PAD, with only one trial in the literature evaluating this effect[38]. In the present study, ramipril significantly decreased arterial stiffness (measured by PWVcf) and wave reflections (measured by AIx) compared with placebo, in agreement with the previous trial[38]. The mean percentage change in PWVcf after 24 weeks was −9(10) per cent in the ramipril group, compared with an increase of 5(10) per cent in the placebo group ($P = 0·001$). Ramipril decreased arterial stiffness in patients with a number of pathological conditions by 1·69 m/s ($P < 0·001$) compared with placebo in a different cohort of 469 patients[39]. In the present study, the mean change in MWD after 24 weeks of treatment inversely correlated with changes in PWVcf ($r = −0·43$, $P = 0·020$). Therefore, the improvement in walking distance with ramipril might have resulted from reduced arterial stiffness, the most likely explanation in the present study population.

Of importance, the positive effect of ramipril on walking distance was independent of its effect on BP. All patients included in the trial had a systolic BP of 160 mmHg or less and diastolic BP of no more than 90 mmHg. Multivariable regression analysis showed no relationship between changes in walking distance and changes in BP. The regression coefficient for the groups (ramipril/placebo) remained significant ($P = 0·001$) in the model, indicating that ramipril-induced changes in MWD were independent of its effect on BP.

Limitations of this trial should be acknowledged. The study was small, and a number of patients withdrew because of cough. Patients included in the trial were offered smoking cessation advice, but were not enrolled in a supervised exercise programme. Furthermore, although treadmill testing is an objective measure, it can depend on patient motivation, which might have introduced bias into the trial. Nevertheless, improvements were observed in MWD, ICD and PRWD in the ramipril-treated group, compared with no significant improvement in the placebo group.

This trial has provided level I evidence for the benefit of ramipril in the treatment of claudication. Ramipril improved walking distance and decreased arterial stiffness in patients with PAD. The improvement in walking distance was more than that achieved with other drugs, such as pentoxifylline or cilostazol (80 per cent improvement)[40,41]; however, it was less than that of a supervised exercise programme (120 per cent improvement)[42].

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Laboratory measurements before, and 2, 6 and 24 weeks after treatment (Word document)

Table S2 Quality-of-life indices before, and 2, 6 and 24 weeks after treatment (Word document)