Primary research

No effects on myocardial ischaemia in patients with stable ischaemic heart disease after treatment with ramipril for 6 months

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Abstract

Objective: To assess the effects of a 6-month angiotensin-converting enzyme (ACE) inhibitor intervention on myocardial ischaemia.

Method: We randomized 389 patients with stable coronary artery disease to double-blind treatment with ramipril 5 mg/day ($n = 133$), ramipril 1.25 mg/day ($n = 133$), or placebo ($n = 123$). Forty-eight-hour ambulatory electrocardiography was performed at baseline, and after 1 and 6 months.

Results: Relevant baseline variables were similar in all groups. Changes over 6 months in duration of ≥1 mm ST-segment depression (STD), total ischaemic burden and maximum STD did not differ significantly between the treatment groups. There was no difference in the frequency of adverse events between the groups.

Conclusion: ACE inhibitor treatment has little impact on incidence and severity of myocardial ischaemia in patients with stable ischaemic heart disease.

Keywords: angiotensin-converting enzyme inhibitor, ischaemic heart disease, ambulatory electrocardiography, myocardial ischaemia

Introduction

ACE may play a key role in the pathophysiology of ischaemic heart disease, through its effects on levels of angiotensin II, bradykinin and nitric oxide (NO). Angiotensin II is a potent vasoconstrictor and induces growth of myocardial and vascular cells, as well as inducing increased deposition of collagen, causing vascular and myocardial remodelling [1]. Conversely, NO inhibits proliferation of vascular smooth muscle cells [2–4], and is necessary for relaxation of the vasculature [4]. ACE inhibitors may counteract the negative effects of angiotensin II, and potentiate the beneficial effects of bradykinin and NO [5], with consequent anti-ischaemic effects in the myocardium. Indeed, several studies [6–10] have shown beneficial effects of ACE inhibitors on ischaemia-related clinical events, as well as direct anti-ischaemic effects in patients with left ventricular systolic dysfunction. However, some studies failed to demonstrate anti-ischaemic effects of ACE inhibitor treatment [11,12], and reports of anti-ischaemic effects of ACE inhibition in patients with ischaemic heart disease and preserved left ventricular systolic function are somewhat scarce [13–16].

ACE = angiotensin-converting enzyme; NO = nitric oxide; STD = ST-segment depression.

The present study (the Low-dose Ramipril Against Myocardial Ischaemia [LORAMI] study) was performed in order to investigate the effects on myocardial ischaemia of a 6-month intervention with 1.25 mg/day and 5 mg/day of the ACE inhibitor ramipril in comparison with placebo, in patients with stable ischaemic heart disease and preserved left ventricular systolic function. The main efficacy variables were duration of STD, total ischaemic burden (total area of significant STD) and maximum STD on 48-h ambulatory electrocardiography. The use of a low dose of ramipril (1.25 mg/day) was based on prior findings in experimental [17] and clinical [18] studies of possible beneficial effects of low doses of ramipril that do not affect blood pressure.

Methods

Patients

Patients (aged 30–80 years) with stable symptomatic or asymptomatic ischaemic heart disease (on the basis of a history of myocardial infarction or typical angina pectoris, with positive exercise test and/or a pathological coronary angiogram) were examined by ambulatory electrocardiography. Those who showed at least 10 min STD of at least 0.1 mV during 48 h were eligible for inclusion, irrespective of the presence of symptoms. Patients who had symptomatic heart failure and/or left ventricular systolic dysfunction (which constitutes an indication for ACE inhibition), a contraindication to ACE inhibitor treatment, ACE inhibitor treatment within 3 months before study initiation, continuing digitalis treatment, non-sinus rhythm, an inconclusive ambulatory electrocardiogram or unstable angina were excluded. All patients gave written informed consent to participate the study, which was approved by the local ethics committee.

Intervention

After a 2-week, single-blind, placebo run-in period, patients were randomly assigned on a 1:1:1 basis to receive double-blind treatment with ramipril 5 mg once daily or 1.25 mg once daily, or placebo, in addition to the baseline medication. During the first week of randomized treatment, patients were titrated to target doses of the study medication. The randomized treatment was given for 24 weeks.

Ambulatory electrocardiography

Baseline ambulatory electrocardiography was performed before the run-in period. It was repeated after 1 month of double-blind treatment and at the study end, while the patients were still on randomized treatment. The analysis was performed using a Del Mar Avionics Strata Scan ECG analyser for STD (Del Mar Avionics, Irvine, CA, USA). Electrocardiography was done using tape recorders (Dynacord Model 423; Del Mar Avionics), with a 60-min cassette electrocardiography-tape and x, y and z orthogonal vector leads. Ischaemic STD was defined as at least 1 min of at least 0.1 mV depressions, as measured between a baseline measure point between P and Q on electrocardiography and another measure point 64 ms after the junction point. The ST-slope had to be horizontal or descending.

STD was quantified both as duration (min per 48 h) and as the area of STD, defined as the area between the electrocardiography baseline and the actual ST level during STD for the whole duration (ischaemic burden, mV/48 h).

During each of the six 24-h periods, the patient was asked to perform 6 min physical exercise at the maximal level that he/she could manage. All physical activities were registered by the patient in a specially designed diary with written instructions for physical activity. The patients were asked to repeat this physical activity during each of the 24-h electrocardiography monitoring periods, and to maintain a level of routine daily activity throughout the investigational periods.

Blood pressure measurement

Blood pressure was measured at baseline (ie at the time of randomization). It was repeated after the titration period (after 1 week of randomized treatment), after 12 weeks of randomized treatment and at study end. Blood pressure was measured in the supine position in the right arm after at least 10 min rest using a standard sphygmomanometer. The supine systolic blood pressure is accounted for in the following analysis.

Sample size calculation

We assumed a difference between each of the two ramipril groups and placebo of 0.2 in the relative reduction of total ischaemic burden, and a standard deviation of 0.5. Using an α level of 0.025 for each test, 120 evaluable patients per group were required in order to obtain 80% power to detect a difference between a specific active group and placebo. This resulted in a power of approximately 70% to detect a difference between both active treatment groups and placebo, and a power of approximately 90% to detect a difference between at least one of the active treatment groups and placebo.

Statistical analysis

Efficacy was defined as the relative decrease in the respective efficacy variables from baseline to study end. The efficacy analyses were performed as analyses of covariance, adjusting for history of myocardial infarction and anti-ischaemic medication. Differences in adverse events were tested with a χ^2 test. In general, comparisons were made between ramipril 5 mg/day and placebo, as well as between ramipril 1.25 mg/day and placebo. Changes in the primary efficacy variables were related to the systolic blood pressure changes during the study by analysis of covariance, without adjustment for history of myocardial infarction or anti-ischaemic medication. Two-tailed $P < 0.05$ was considered statistically significant.

Table 1

Baseline demographics

Variable	Ramipril 5 mg ($n = 133$)	Ramipril 1.25 mg ($n = 133$)	Placebo ($n = 123$)
Age (years [range])	66 (47–80)	65 (32–79)	66 (39–78)
Female sex (%)	32	37	37
Height (cm [range])	171 (150–192)	170 (150–190)	170 (150–186)
Weight (kg [range])	76 (46–108)	75 (49–107)	75 (47–108)
Smoking status (%)			
Never	31	28	29
Prior	52	50	53
Current	17	22	18

Results

A total of 389 patients were randomized: 133 in the ramipril 5 mg/day group; 133 in the ramipril 1.25 mg/day group; and 123 in the placebo group. All of these patients were included in the safety analyses. Forty-two patients discontinued prematurely, and thus 347 patients completed the trial: 118 in the ramipril 5 mg/day group; 116 in the ramipril 1.25 mg/day group; and 113 in the placebo placebo. These patients were included in the efficacy analyses.

There were no significant differences between the groups in terms of frequency of discontinuations. The reasons for discontinuation were mainly cough in the ramipril groups (47% of discontinuations) and unspecified patient request in the placebo group (50%). Baseline demographic data are shown in Table 1. Concomitant medication did not differ between groups. The most frequently used categories of drugs were acetylsalicylic acid (approximately 87%), statins (45%), β-blockers (38%), glycerylnitrate (36%), isosorbide-mononitrate (27%), and calcium-channel blockers (19%). Concomitant diseases were similar in the three groups. Around one-quarter of the patients had a history of hypertension, approximately one in 10 had diabetes, around half had undergone cardiac surgery, and around half of the patients had a history of myocardial infarction.

Baseline and study end data for the three main efficacy variables are shown in Table 2. There were no significant differences between the three groups in any of these variables.

It has been suggested that patients with coronary artery disease who respond to an ACE inhibitor with a systolic blood pressure reduction of 10 mmHg or more benefit the most from such treatment in terms of exercise tolerance [13]. Therefore, a prespecified aim of the study was to investigate whether any improvements in the primary efficacy variables were related to the systolic blood pressure changes during the study. We examined whether the changes from baseline to study end in duration of STD and total ischaemic burden were related to the blood pressure changes from baseline to the following time points: the end of the titration period (after 1 week of randomized treatment); 12 weeks of randomized treatment; and study end. Ramipril patients who had a systolic blood pressure reduction of 10 mmHg or more and ramipril patients who had a blood pressure reduction of below 10 mmHg (including those with no fall or a blood pressure increase) at the respective time points were compared with all placebo patients. We also compared the two ramipril patient categories with one another. The same comparisons were performed using a systolic blood pressure cutoff value of 20 mmHg. There were no significant differences in any of these comparisons.

There were no differences between the treatment groups in terms of adverse events or other safety data. At least one adverse event during the double-blind study period was reported by 58% of the patients in the ramipril 5 mg group, by 56% in the ramipril 1.25 mg group and by 50% in the placebo group (not significant). A total of 45 serious adverse events were reported, with no between-group differences in number or type of serious adverse events. None of the serious adverse events were judged to be related to the study drug. There were no deaths during the study period.

Discussion

There were no differences in the primary efficacy variables between the three treatment groups (ramipril 5 mg/day, ramipril 1.25 mg/day and placebo) in terms of changes over the 24 weeks from baseline to study end. Indeed, there were no trends in favour of ramipril in any dose compared with placebo in terms of myocardial ischaemia as assessed by ambulatory electrocardiography. Ramipril was well tolerated, and there were no significant differences in the frequency of adverse events between the ramipril groups and placebo.

Table 2

ST-segment analysis

		Ramipril 5 mg			Ramipril 1.25 mg			Placebo		
Variable	Visit	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
STD duration (min)	Baseline	133	361	443	133	393	468	123	426	467
	1 month	123	319	463	120	326	473	113	406	480
	Study end	117	332	480	116	367	493	113	318	418
Ischaemic burden	Baseline	133	1428	3248	133	1571	3213	123	1387	2299
	1 month	123	1309	2950	120	1302	2855	113	1366	2505
	Study end	117	1276	2612	116	1467	3394	113	1101	2527
Maximum STD (mV)	Baseline	133	0.23	0.09	133	0.24	0.10	123	0.26	0.11
	1 month	123	0.18	0.12	121	0.20	0.13	113	0.22	0.12
	Study end	118	0.22	0.15	116	0.22	0.13	113	0.23	0.14

There were no significant differences in the changes from baseline to study end between the ramipril groups and placebo. STD is defined as ST-segment depression of ≥0.1 mV. STD duration and ischaemic burden are given per 24 h. SD, standard deviation.

What is ST-segment depression on ambulatory electrocardiography?

STD on ambulatory electrocardiography is considered to reflect myocardial ischaemia, but the mechanisms responsible are not fully understood. STD probably reflects myocardial ischaemia precipitated both by increased cardiac work through static stenoses, and by increased vascular tone and/or coronary spasm in dynamic stenoses.

Possible short-term anti-ischaemic effects of angiotensin-converting enzyme inhibition

ACE inhibitor treatment may decrease myocardial ischaemia by improving coronary blood flow and microcirculation. On a short-term basis, this may be caused by improved endothelial function as a consequence of decreased levels of angiotensin II, and increased levels of bradykinin and NO [19]. In addition, the tendency toward vascular spasm may be counteract by ACE inhibitors; ACE expression and angiotensin II production are increased in atherosclerotic tissue [20], and local ACE inhibition may decrease oxidative stress and improve endothelial function at the sites of plaques. That ACE inhibitor treatment impacts on endothelial function is supported by the findings of prior studies. The Trial on Reversing Endothelial Dysfunction (TREND) [21,22] demonstrated an improvement in endothelial vasomotor dysfunction in patients with ischaemic heart disease treated with quinapril over 6 months, and it was indicated that ACE inhibition increased microvascular coronary blood flow. Moreover, in a study by Gasic *et al* [23], cilazapril improved regional myocardial blood flow to the ischaemic myocardium in patients with stable angina.

Angiotensin II facilitates the release of noradrenaline from sympathetic nerve terminals [24], and ACE inhibitors have been shown [25–27] to exert parasympathomimetic effects, to improve baroreflex sensitivity in patients after myocardial infarction [28] and to reduce sympathetic vasomotor tone in hypertensive patients [29]. Consequently, an ACE-inhibitor-induced reduction in sympathetic activity due to decreased levels of angiotensin II may, in the short term, contribute to a decrease in myocardial ischaemia. However, how ACE inhibition modulates sympathetic activity in humans is still controversial [30].

A haemodynamic effect due to decreased preload and afterload resulting from ACE inhibitor-induced vasodilatation may also contribute to an anti-ischaemic effect by reducing cardiac work and oxygen consumption.

Possible long-term anti-ischaemic effects of angiotensin-converting enzyme inhibition

An improved neurohormonal balance may, in the long term, induce regression of structural myocardial changes, such as myocardial fibrosis. Such an effect may be independent of any haemodynamic effects and attributed to inhibition of cardiac tissue ACE, as seen in experimental studies [31]. Even a modest regression of fibrosis may improve coronary vessel compliance, especially a reduction in perivascular fibrosis [32,33]. Such a change may improve coronary reserve, which in particular might attenuate postexercise ischaemia.

Several experimental [34–36] and clinical [37] studies have shown that ACE inhibitors are able to inhibit the atherosclerotic process. However, ACE inhibitors have shown little success in preventing restenosis after angioplasty in humans [38], and in the Quinapril Ischemic Event Trial (QUIET) [6] treatment with quinapril after angioplasty failed to reduce mortality and recurrence of angina pectoris in comparison with placebo. An antiatherogenic effect of ACE inhibition would most likely take quite some time to develop.

Why was the study result neutral?

Too low doses of ramipril

There may be several reasons for the neutral study result. The doses of ramipril might have been too low. The recommended dose in clinical practice is 5 mg twice a day or 10 mg once a daily (ie twice as much as the highest dose and eight times the lower dose in the present study). Why was such a low dose as 1.25 mg/day chosen? The reason is that we wanted to test the hypothesis that a dose that does not affect central haemodynamics would still decrease myocardial ischaemia. This hypothesis was based on findings in experimental [17] and clinical [18] studies that suggested an antiremodelling effect of low, nonantihypertensive doses of ramipril. This hypothesis was clearly not supported by the results of the present study.

Inadequate method for detecting myocardial ischaemia

The method used might not have been relevant to the study efficacy variables, although we have shown that ambulatory electrocardiography has the same diagnostic accuracy for myocardial ischaemia as does exercise electrocardiography examination [39]. However, ambulatory electrocardiography may overlook myocardial ischaemia in patients who predominantly develop ischaemia with STD at high exercise loads. Thus, if such patients benefit from a real anti-ischaemic effect of ramipril, then very little or none of that effect may be registered unless the patients perform high-intensity exercise.

Influence of concomitant treatment

An interaction between acetylsalicylic acid and ACE inhibitors may exist, although this is considered controversial [40]. Because 87% of the patients studied were treated with acetylsalicylic acid, it is possible that such an interaction might have blunted any beneficial effect of ramipril. Statins are known to improve endothelial function [41]. In the present study, almost half of the patients were being treated with a statin, and it may be that there is little to gain by adding an ACE inhibitor to the regimen of such patients.

There may be no anti-ischaemic effects of angiotensin-converting enzyme inhibitors

Perhaps there are no true anti-ischaemic effects of ACE inhibition. Indeed, it has been indicated [42] that ACE inhibitors may not inhibit angiotensin II production in the coronary circulation, and short-term ACE inhibition has failed to reduce myocardial ischaemia [11,12]. Despite clear haemodynamic effects, captopril had only marginal anti-ischaemic effects, in monotherapy as well as combined with isosorbide dinitrate [12]. However, true anti-ischaemic effects have been indicated in patients with left ventricular systolic dysfunction [9,10]. Therefore, an alternative explanation for the neutral finding of the present study is that ACE inhibitors may not have anti-ischaemic effects in patients with stable coronary artery disease and preserved left ventricular systolic function. Although anti-ischaemic effects of ACE inhibition have been indicated in such patients [13–16], perindopril was shown to have a significantly less pronounced anti-ischaemic effect in patients with normal left ventricular systolic function than in those with impaired ejection fraction [43].

Effects on clinical end-points are not equivalent to anti-ischaemic effects

The beneficial effects of ACE inhibition on clinical end-points related to myocardial ischaemia that have been demonstrated in previous studies [6–8,44,45] do not represent evidence for a direct anti-ischaemic effect, and might have an alternative explanation. The mechanisms that underlie ischaemic events include plaque destabilization, among others, whereas angina is caused by an imbalance between the oxygen supply and demand. An ACE inhibitor need not equally affect these parameters. Indeed, captopril treatment for 1 year after a myocardial infarction significantly reduced the incidence of ischaemia-related clinical events, but had no anti-ischaemic effects during exercise testing [46]. Consequently, the results of clinical end-point trials do not contradict the present findings.

Other reasons

The study duration may have been too short to demonstrate any beneficial effects of ACE inhibition. However, as mentioned above, some of the mechanisms by which ACE inhibition may counteract myocardial ischaemia might be expected to develop within the time frame of the present study. Indeed, the benefits in the TREND study were demonstrated within 6 months [21,22].

Although we made every effort to include patients with coronary artery disease, the patients selected for the present study might not all have had true myocardial ischaemia. It is well known that 'unspecific' STD may be the result of left ventricular hypertrophy. This is especially likely if STD occurs during most of the 24-h monitoring period. Some of the patients in this study might have been such patients, and anti-ischaemic effects of ramipril cannot be anticipated in these patients. On the other hand, it is likely that STD in such patients is due to endothelial dysfunction, which should be at least partly reversible by ACE inhibition [32].

Did the present study show any beneficial effects of ramipril?

A random subset of 98 of the patients in the present study was examined by echocardiography/Doppler at baseline and study end. There was a significant beneficial effect of ramipril on resting left ventricular function and on postexercise left ventricular filling, as compared with patients treated with placebo [47]. However, these effects may not necessarily have been caused by anti-ischaemic mechanisms of the ramipril intervention. Further analyses have

shown that only those ramipril-treated patients who showed a clear blood pressure reduction experienced improved left ventricular function at rest and after exercise, whereas those who did not respond to the ramipril intervention by a clear blood pressure reduction did not improve (Willenheimer R, *et al*, unpublished data). This relation was independent of the ramipril dose. The observation might be explained by a more pronounced reduction in afterload among patients with a clear blood pressure response, and need not affect myocardial ischaemia, as indicated previously [12].

Conclusion

Six months of treatment with ramipril in patients with stable ischaemic heart disease and preserved left ventricular systolic function did not exhibit any favourable effects on myocardial ischaemia, as assessed by ambulatory electrocardiography. There are a number of possible explanations for this neutral study result, including too low a dose of ramipril, patient selection, a suboptimal method for the detection of an anti-ischaemic effect, and insufficient study duration. However, it is also possible that ACE inhibitors have no direct anti-ischaemic effects, despite their well-documented ability to protect against ischaemia-related clinical events. Future studies will have to investigate further whether ACE inhibitors have true anti-ischaemic effects in patients with stable ischaemic heart disease and preserved left ventricular systolic function.

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