Fosinopril reduces left ventricular mass in untreated hypertensive patients: a controlled trial

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Aims Left ventricular hypertrophy is a powerful predictor of cardiovascular morbidity and mortality. We tested the hypothesis that fosinopril, an angiotensin-converting enzyme inhibitor, reduces left ventricular mass in hypertensive patients.

Methods Thirty-three patients with untreated mild essential hypertension were randomised to treatment with oral fosinopril (10 mg–20 mg daily) or placebo for 12 weeks. The primary outcome measure was the change in left ventricular mass index determined by echocardiography.

Results Diastolic blood pressure changed from 95.5 ± 2.1 mmHg at baseline to 96.6 ± 2.8 mmHg at the final visit in control patients and changed from 96.6 ± 2.3 mmHg to 91.5 ± 3.0 mmHg in patients treated with fosinopril ($P = 0.04$). Systolic blood pressure changed from 147.4 ± 3.2 mmHg at baseline to 152.7 ± 4.4 mmHg at the final visit in control patients and changed from 157.6 ± 5.1 mmHg to 149.1 ± 6.1 mmHg in patients treated with fosinopril ($P = 0.02$). Fosinopril reduced diastolic pressure by 6.3 (95%CI 0.3–12.4) mmHg and systolic pressure by 13.3 (95%CI 2.7–23.8) mmHg compared with placebo. The left ventricular mass index changed from 110.0 ± 8.3 g m^{-2} to 113.1 ± 8.7 g m^{-2} in the control patients and changed from 120.8 ± 5.8 g m^{-2} to 109.0 ± 7.5 g m^{-2} in patients treated with fosinopril ($P = 0.02$). Fosinopril reduced left ventricular mass index by 14.9 (95%CI 2.2–27.6) g m^{-2} compared with placebo. There was no significant change in the left ventricular systolic or diastolic function, nor were there any significant changes in plasma electrolytes and renal function.

Conclusions Treatment with fosinopril for 12 weeks reduced left ventricular mass significantly in hypertensive patients.

Keywords: hypertension, left ventricular hypertrophy, angiotensin-converting enzyme inhibitors, fosinopril

Introduction

Left ventricular hypertrophy (LVH) is one of the most powerful predictors, independent of blood pressure, of cardiovascular morbidity and mortality [1]. LVH reduces coronary reserve, increases myocardial oxygen requirements, and impairs left ventricular filling and contractility. Patients with LVH are more prone to heart failure, myocardial infarction and sudden death [2]. Data from the Framingham study showed that the risk of cardiovascular complications increases six to eight-fold in the presence of LVH [1]. As LVH is most likely to occur in hypertensive patients, these two risk factors act together to increase cardiovascular risk. LVH is not uncommon among hypertensive patients, but its prevalence will be underestimated if echocardiography is not performed because the electrocardiogram (ECG) is abnormal in only a proportion of patients with LVH. The Treatment of Mild Hypertension Study (TOMHS), using echocardiography, showed that LVH was present in 15% of asymptomatic patients with only mild hypertension [3].

Although evidence from prospective studies demonstrating that regression of LVH increases longevity are eagerly awaited, there are reasons to believe that this may be the case [4, 5]. Meta-analysis suggest that angiotensin converting enzyme inhibitors (ACEIs) may be the most effective class of drugs in reducing left ventricular mass [6]. One of the proposed mechanisms is that ACEIs may operate at the tissue level to inhibit ventricular hypertrophy directly in addition to lowering blood pressure and reducing afterload. A study by Oren and colleagues demonstrated that taking fosinopril for only 12 weeks

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significantly reduced left ventricular mass [7]. This study involved relatively few patients and there was no control group, but it raises the possibility that fosinopril may reduce left ventricular hypertrophy after only a short period of treatment.

Most trials on regression of LVH have not been randomised and controlled, did not have left ventricular mass as the primary endpoint, or recruited patients who had been treated previously [8, 9]. Even in controlled studies, the control treatment was not placebo in most studies. It may not be acceptable to randomise hypertensive patients with LVH (a manifestation of end-organ damage) to placebo treatment for extended periods, but a placebo-controlled trial is necessary to ascertain the true treatment effect of antihypertensive drugs, particularly since TOMHS showed that non-pharmacological intervention *per se* could lead to regression of LVH [10]. Similarly, a regular supervised exercise programme has been shown to reduce blood pressure and regress LVH in black hypertensive patients [11]. It is also important to study untreated patients since previous drug treatment is a major confounding factor in regression of LVH studies. Previous drug treatment may have caused regression of LVH already, whilst lack of response to previous treatment may indicate resistant hypertension or poor compliance.

Hence, we tested the hypothesis that treatment with an ACE inhibitor reduces blood pressure and, even in short-term treatment, reduces left ventricular mass in a randomised placebo-controlled parallel-group study in which mild hypertensive patients, who were otherwise untreated, were randomised to receive either fosinopril or placebo for 3 months. The primary parameter was the change in left ventricular mass index. Changes in other risk factors were also assessed.

Methods

The study was randomised double-blind placebo-controlled parallel-group in design, with double-blind assessment of endpoints. The setting was the hypertension outpatient clinic of a university teaching hospital. The study protocol was approved by the Faculty Ethics Committee. Written informed consent was obtained from every patient.

Patients who satisfied the inclusion criteria and gave written informed consent were recruited. The inclusion criteria were (1) age between 18 and 75 years inclusive; (2) diastolic blood pressure 90–110 mmHg inclusive or systolic blood pressure over 160 mmHg; (3) Essential hypertension newly diagnosed or previously diagnosed but untreated (defined as never been on regular antihypertensive medications for more than 3 months in the past and received no antihypertensive drugs in the previous 3 months). The exclusion criteria were: (1) serious symptomatic cardiac disease including previous myocardial infarction, angina and heart failure; (2) history of transient ischaemic attacks or stroke; (3) known or suspected renovascular disease; (4) plasma creatinine >200 mmol l^{-1}; (5) pregnancy or possibility of pregnancy (inadequate contraceptive measures); (6) allergy to ACE inhibitors; (7) any serious concomitant disease.

Study protocol

The study involved five scheduled visits to the hypertension research outpatient clinic.

At Visit 1 (week 2), a full medical history was obtained, physical examination (including height and weight measurements), urine analysis and ECG were performed. The patient's cardiovascular risk factors, including family history, smoking, obesity and inactivity, were assessed. If the patient's blood pressure fulfilled the inclusion criteria, then blood was taken for a full blood count (haemoglobin, haematocrit, white blood count, differential white count and platelet count), erythrocyte sedimentation rate (ESR), renal and liver function tests (sodium, potassium, urea, creatinine, glucose, total bilirubin, total protein, albumin, ALT and alkaline phosphatase). Full informed written consent was requested and the patient started a 2 week single-blind placebo run-in phase. A posteroanterior chest X-ray was performed.

At each subsequent visit, body weight, blood pressure and heart rate were measured and any adverse event recorded. If the patient's blood pressure fulfilled the inclusion criteria at visit 2 (week 0), an echocardiogram was performed. Blood was taken from the patient who had fasted overnight to measure fasting lipid profile.

Eligible patients were randomised at visit 2 (week 0) to 10 mg fosinopril daily or placebo in a double-blind manner by allocation to the next treatment number. Patients were instructed to take the trial medications once daily, between 07.00 to 09.00 h and delay taking the medications on the morning of each visit until after the visit.

All patients were advised, where applicable, to stop smoking, alter diet, lose weight and take up suitable exercise. At subsequent visits, any change in these lifestyle parameters was recorded and appropriate recommendations to changes in lifestyle given or re-emphasised.

At visit 3 (week 2), if the blood pressure was inadequately controlled, defined as mean seated diastolic blood pressure ≥ 90 mmHg or mean seated systolic blood pressure ≥ 160 mmHg, the dosage of the trial medication was doubled (i.e. 2 tablets daily, 2×10 mg fosinopril or $2 \times$ placebo). Blood was also taken at this visit for assessment of renal function.

At visit 4 (week 6), if the blood pressure was inadequately controlled, the dose of the trial medications

could be doubled to a maximum of two trial tablets daily. If the patient had been taking two tablets daily and the mean seated diastolic blood pressure at this visit was <85 mmHg, the dose of the trial medications was reduced to one tablet daily.

At the final visit, visit 5 (week 12), blood pressure and heart rate were measured, and adverse events recorded. Physical examination were performed and blood was taken at this visit for full blood count, urea and electrolytes, liver function and fasting lipid profile. An electrocardiogram and an echocardiogram were performed again to assess left ventricular mass, systolic and diastolic function. A 24 h urine collection were performed while the patient was on trial medication.

Blood pressure and heart rate

The blood pressure of each patient was measured using a mercury sphygmomanometer and a cuff of the appropriate size around the right arm after the patient had been sitting in a chair, at rest, for 15 min. Blood pressure was measured four times at 5 min intervals and the heart rate was determined three times, at 5 min intervals between the blood pressure measurements. The first blood pressure measurement was to familiarise the patient with the procedure and the sensation of the inflated cuff. The three subsequent systolic and diastolic blood pressure readings were recorded to the nearest 2 mmHg. The means of these three readings were used in decision-making and analysis of results. The radial pulse was counted for 30 s to assess the heart rate. The first reading was not recorded. The mean of the next two readings, i.e. between the 2nd and 3rd blood pressure reading, and between the 3rd and 4th blood pressure reading was used to determine the heart rate.

Electrocardiography

Electrocardiography was performed before the study, at visit 2 and visit 5. Electrocardiograms obtained at visit 2 and 5 were read by two blinded observers. Electrocardiographic left ventricular hypertrophy (ECG-LVH) was determined using (1) Sokolow and Lyon's voltage criteria for ECG-LVH $=$ depth of S wave in V_1 + height of R wave in either V_5 or V_6 whichever is taller >35 mm; and (2) Cornell criteria $=$ height of R wave in aVL + depth of S wave in $V_3 > 28$ mm in men or 20 mm in women. As neither the Sokolow and Lyon nor Cornell criteria has high sensitivity (22% and 42% respectively) but both have high specificity (100% and 96% respectively) [12], satisfaction of either criteria was taken to indicate ECG-LVH.

Echocardiography

Each patient underwent echocardiography at visit 2 and 5 for the assessment of left ventricular mass, systolic and diastolic function. Echocardiography was performed using an Accuson 128XP/10C computed sonograph with a 2.5 MHz transducer, with the patient lying in the left lateral decubitus position. Disposable ECG leads were attached for the purpose of timing the cardiac cycle.

The transducer was placed over the 3rd or 4th left intercostal space near the left sternal edge to obtain two-dimensional parasternal long-axis views of the left ventricle. M-mode measurements were made with the cursor placed perpendicular to the interventricular septum and the posterior wall of the left ventricle at the level of the junction between papillary muscle and mitral chordae. The gain control was adjusted to obtain the clearest image of the endocardial and epicardial surfaces. At least five cardiac cycles of good quality were recorded on VHS videotape with a Panasonic AG-7350 super-VHS videocassette recorder and also printed on paper with a Sony UP-860 CE videographic printer.

LV measurements were performed using the leading-edge-to-leading-edge technique at end-diastole (onset of QRS) according to American Society of Echocardiography recommendations, and also the Penn convention (exclusion of endocardial interfaces from septal and posterior wall thickness, and onset of diastole at peak of R wave) [13, 14]. The main parameters measured were interventricular septal thickness at end diastole (IVSTd), posterior wall thickness at end diastole (PWTd), left ventricular internal diameter at end diastole (LVIDd) and systole (LVIDs). Left ventricular mass (LVM) was calculated from Penn measurements according to the equation of Devereux and Reichek: $LVM = 1.04([IVSTd + PWTd + LVIDd]^3 - [LVIDd]^3) - 13.6g$. Left ventricular mass index (LVMI) was calculated by dividing LVM (g) by the body surface area (m^2). Echocardiographic LVH was defined as LVMI ≥ 125 g m^{-2} for men and ≥ 110 g m^{-2} for women.

Left ventricular ejection fraction (EF) was calculated as follows:

$$EF = [(LVIDd^3 - LVIDs^3)/LVIDd^3] \times 100\%$$

Apical 4-chamber views were also recorded. Transmitral flow was studied using pulsed Doppler with sample volume at leaflet tips during diastole. Early and late diastolic flow were traced using the leading edge (black-white interface) method to determine the peak E and A velocities on three cycles showing the highest velocity. Isovolumic relaxation time (IVRT) was measured using pulsed Doppler in the apical 5-chamber view which included the aortic valve.

Each patient had two echocardiographic examinations

by the same sonographer who was blind to the treatment, dosage and clinical information (including the patient's blood pressure). Measurements were done in triplicate. The mean of the on-line measurements was used for data analysis and the standard deviation used to estimate the intraobserver coefficient of variation (7% for LVMI). At the end of the study, a physician who was blind to treatment, blood pressure and adverse event data studied the videotaped sequences and photographic printouts to verify the on-line measurements made by the sonographer. The sonographer's and the physician's measurements agreed closely; the inter-observer coefficient of variation was 14% for LVMI.

Urinary analysis

Before visits 2 and 5, a 24 h urine collection was performed for the determination of 24 h sodium and albumin excretion and creatinine clearance. Urine analysis with test strips was performed at visit 1, 3 and 5 for the detection of glucose, blood and protein.

Angiotensin-converting enzyme genotype

Genomic DNA was extracted from peripheral leucocytes in the buffy coat and amplified by polymerase chain reaction (PCR) using standard primers and conditions [15].

Compliance

Patients were requested to return all the containers containing trial medications for assessment of compliance. Returned tablets were counted after each visit to assess compliance. Subjects who took at least 90% of the prescribed tablets were considered compliant. Patients found to be non-compliant at visit 2 would not be randomised and would be withdrawn.

Adverse events

All adverse events, whether thought to be related to study drugs or not, were recorded in the Case Record Booklets. Both spontaneously reported adverse events and adverse events reported after direct questioning were documented. Patients would be withdrawn if a serious adverse event occurred, or if the mean seated diastolic blood pressure at any study visit exceeded 115 mmHg.

Statistical analysis

Baseline characteristics were compared using Mann-Whitney U test or χ^2-tests. $P<0.05$ was regarded to suggest a significant difference in the baseline characteristic. This served to identify significant differences in baseline characteristics which needed to be corrected for as covariates in subsequent analysis.

The primary parameter of the study was the change in LVMI. The changes in LVMI in the two treatment groups were compared using Mann-Whitney U test. $P<0.05$ was considered significant. When this was significant, repeated measures analysis of variance with treatment as the factor and protected *t*-test were performed since parametric statistics allow the calculation of standard errors. The secondary parameter (seated diastolic blood pressure at trough) and other parameters were compared using repeated measures analysis of variance, with drug as the factor and drug-time interaction as the parameter of interest. Categorical variables were compared using χ^2-tests. As multiple comparisons were made in such *post-hoc* analysis, any significant results ($P<0.05$) were regarded as hypothesis-generating rather than conclusive. Finally, a multiple linear regression model was set up to identify the factors influencing left ventricular mass index and blood pressure in this study.

There are no standard methods for calculating the power of non-parametric tests and analysis of variance. However, the power of an unpaired *t*-test to compare changes in LVMI due to two different treatment regimes can be calculated as follows:

$$\gamma = (\mu_1 - \mu_2)/\sigma$$

where γ is the effect size, $\mu_1 - \mu_2$ is the expected difference in change in LVMI, and σ is the standard deviation of the change in LVMI.

If we assume, using data from a similar previous study [7], that $\mu_1 - \mu_2$ is 11%, and the standard deviation, σ, is also 11%, then:

$$\gamma = 1$$

$$\delta = \gamma\sqrt{N} = 1\sqrt{12} = 3.46$$

If the Type I error (α) is set at 0.05, the study had 0.93 power to detect a 1 s.d. difference in treatment effect.

Results

Forty patients started the study. Thirty-three patients were randomised as seven patients were not eligible for randomisation after the single-blind placebo phase. Of these seven patients, six patients had mean blood pressures which fell below the inclusion criteria after taking placebo for 2 weeks and one patient was non-echogenic. Thirty-two patients completed the study. One patient who had been randomised to placebo saw another doctor after visit 3 and was prescribed atenolol. This patient was withdrawn at visit 4 because of protocol violation, but was included in the analysis. Inclusion or exclusion of this patient did not materially affect the main endpoints.

Baseline characteristics of patients are shown in Tables 1–3. There were no significant differences in baseline characteristics between the fosinopril-treated and the control patients. Eighteen patients (nine in placebo and nine in fosinopril group) had never taken any antihypertensive medications in their lives. The remaining patients never had sustained treatment of hypertension (longer than 3 months) and none had taken any antihypertensive medications in the previous 3 months.

Blood pressure and heart rate

Systolic blood pressure changed from 147.4 ± 3.2 mmHg at baseline to 152.7 ± 4.4 mmHg at the final visit in control patients and changed from 157.6 ± 5.1 mmHg to 149.1 ± 6.1 mmHg in patients treated with fosinopril ($P=0.02$) (Table 2). Diastolic blood pressure changed from 95.5 ± 2.1 mmHg at baseline to 96.6 ± 2.8 mmHg at the final visit in control patients and changed from 96.6 ± 2.3 mmHg to 91.5 ± 3.0 mmHg in patients treated with fosinopril ($P=0.04$) (Figure 1). Fosinopril reduced diastolic pressure by 6.3 (95%CI 0.3–12.4) mmHg and systolic pressure by 13.3 (95%CI 2.7–23.8) mmHg compared with placebo.

The mean dose of fosinopril at the final visit was 16 mg (seven patients on 10 mg and 10 patients on 20 mg). The response rate was 53% and 31% for fosinopril and placebo respectively if the target is defined as diastolic blood pressure <90 mmHg or a fall of at least 5 mmHg at the final visit compared with baseline. Only 35% and 25% of fosinopril and control patients respectively attained at the final visit a mean diastolic blood pressure of less than 90 mmHg.

There were no significant changes in the heart rate with either treatment.

Table 1 Baseline characteristics.

	Placebo n = 16	*Fosinopril* n = 17
Sex (M/F)	9/7	11/6
Age (years)	44.3 ± 12.3	54.7 ± 14.5
Height (cm)	162 ± 11	164 ± 9
Weight (kg)	67.5 ± 12.0	65.6 ± 9.9
Body mass index	25.5 ± 3.7	24.4 ± 2.0
ACE genotype (DD : ID : II)	2 : 4 : 5	3 : 4 : 7
History of hypertension (months; median, range)	18 (4–120)	12 (1–192)
Hypertension in close blood relatives	8/16	6/17
Regular smoking	1/16	2/17
Regular alcohol consumption	7/16	4/17

Left ventricular mass and function

At baseline, 11 of 17 patients in the fosinopril group and 7 of 16 patients in the control group had echocardiographic LVH. During the study, the left ventricular mass index (LVMI) changed from 110.0 ± 8.3 g m^{-2} to 113.1 ± 8.7 g m^{-2} in the controls and changed from 120.8 ± 5.8 g m^{-2} to 109.0 ± 7.5 g m^{-2} in patients treated with fosinopril ($P=0.027$, Mann-Whitney U test; $P=0.023$, analysis of variance). Fosinopril reduced left ventricular mass index by 14.9 (95%CI 2.2–27.6) g m^{-2} compared with placebo (Figure 2). There were no significant changes in body weight during the study in controls (0.99 ± 0.67 kg) nor in patients

Table 2 Haemodynamic and biochemical parameters.

	Placebo n = 16		Fosinopril n = 17	
	Baseline	*Final visit*	*Baseline*	*Final visit*
Diastolic blood pressure (mmHg)	95.5 ± 2.1	96.6 ± 2.8	96.6 ± 2.3	91.5 ± 3.0**
Systolic blood pressure (mmHg)	147.4 ± 3.2	152.7 ± 4.4	157.6 ± 5.1	149.1 ± 6.1***
Heart rate (beats min^{-1})	81.6 ± 2.7	81.4 ± 2.9	78.7 ± 2.2	75.6 ± 2.1
Plasma sodium (mmol l^{-1})	140 ± 1	140 ± 1	140 ± 1	140 ± 1
Plasma potassium (mmmol l^{-1})	4.03 ± 0.10	4.00 ± 0.08	3.95 ± 0.10	4.15 ± 0.09
Plasma creatinine (μmol l^{-1})	81.4 ± 3.6	84.8 ± 4.1	90.1 ± 4.0	90.7 ± 3.1
Fasting blood glucose (mmol l^{-1})	6.04 ± 0.40	5.31 ± 0.20	5.44 ± 0.13	5.04 ± 0.11
Plasma cholesterol (mmol l^{-1})	5.21 ± 0.28	5.24 ± 0.25	5.18 ± 0.26	4.91 ± 0.17
Plasma LDL-C (mmol l^{-1})	3.29 ± 0.25	3.25 ± 0.20	3.35 ± 0.23	3.03 ± 0.16
Plasma HDL-C (mmol l^{-1})	1.07 ± 0.07	1.00 ± 0.09	1.18 ± 0.12	1.14 ± 0.10
Plasma triglycerides (mmol l^{-1})	1.83 ± 0.27	2.75 ± 0.46	1.54 ± 0.18	1.63 ± 0.25
Urinary sodium excretion (mmol day^{-1})	201 ± 29	117 ± 20	155 ± 21	161 ± 20***
Urinary albumin excretion (g day^{-1})	0.16 ± 0.06	0.17 ± 0.05	0.17 ± 0.05	0.13 ± 0.01
Creatinine clearance (ml min^{-1})	92.0 ± 10.1	88.9 ± 9.4	90.5 ± 4.1	83.9 ± 7.1

**$P<0.05$, secondary endpoint; ***$P<0.05$, *post hoc* analysis.

Table 3 Echocardiographic parameters.

	Placebo n = 16		Fosinorpril n = 17	
	Baseline	*Final visit*	*Baseline*	*Final visit*
LVM (g)	188.3 ± 15.1	192.6 ± 15.2	206.9 ± 11.4	186.6 ± 14.1***
LVMI ($g\,m^{-2}$)	110.0 ± 8.3	113.1 ± 8.7	120.8 ± 5.8	109.0 ± 7.5*
Septal wall thickness (cm)	1.06 ± 0.06	0.97 ± 0.07	1.13 ± 0.06	0.92 ± 0.04
LV posterior wall thickness (cm)	0.86 ± 0.05	0.85 ± 0.05	0.94 ± 0.05	0.83 ± 0.04
LV diameter in diastole (cm)	4.68 ± 0.12	4.84 ± 0.15	4.60 ± 0.15	4.82 ± 0.11
LV diameter in systole (cm)	3.14 ± 0.13	3.25 ± 0.17	3.04 ± 0.15	3.15 ± 0.13
Ejection fraction	60.6 ± 2.6	60.8 ± 2.0	63.2 ± 2.2	60.1 ± 2.8
E/A ratio	0.95 ± 0.09	0.89 ± 0.06	1.04 ± 0.09	0.91 ± 0.09
Isovolumic relaxation time (ms)	102 ± 15	96 ± 8	108 ± 14	91 ± 6

*$P<0.05$, primary endpoint; ***$P<0.05$, *post-hoc* analysis.

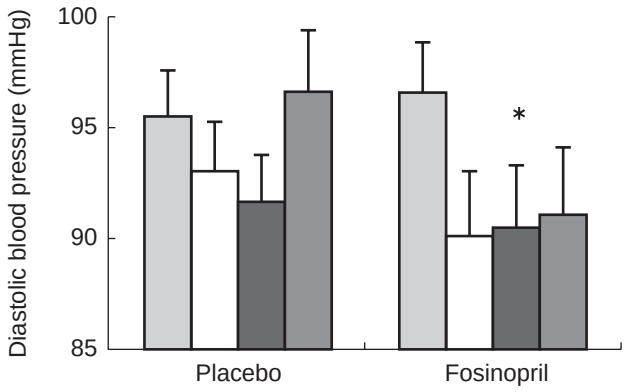

Figure 1 Diastolic blood pressure on placebo and fosinopril on visit 2 (▨), visit 3 (□), visit 4 (▧) and visit 5 (▩). $P=0.04$ *vs* placebo.

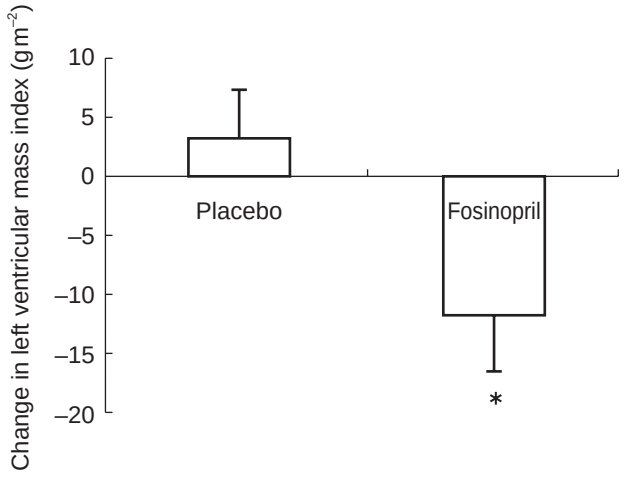

Figure 2 Change in left ventricular mass index after placebo and fosinopril. *$P=0.02$.

(−0.49 ± 0.37 kg). Although the left ventricular mass (LVM) was not a primary endpoint, it changed significantly ($P=0.02$) from 206.9 ± 11.4 g to 186.6 ± 14.1 g in the fosinopril-treated group compared with controls, from 188.3 ± 15.1 g to 192.6 ± 15.2 g. The interventricular septum thickness and the posterior wall thickness were also reduced in the fosinopril-treated group, although these did not reach statistical significance (Table 3). Multiple regression analysis showed that drug treatment accounted for a significant proportion of the variance in change in LVMI ($r^2=0.14$, $P=0.03$), which was not explained by the change in blood pressure nor by the baseline LVMI. Moreover, the partial correlation between drug treatment and change in LVMI remained significant after controlling for change in blood pressure ($r=0.34$, $P=0.046$), or baseline LVMI ($r=0.38$, $P=0.026$).

There were no significant changes in ejection fraction or left ventricular end-diastolic diameter. The E/A ratio was <1 at baseline in 16 of the 33 patients (8 in placebo group and 8 in fosinopril group). There were no significant changes in the diastolic filling (E/A ratio and isovolumic relaxation time) in either the control group or the fosinopril-treated group.

Electrocardiogram

Three patients in the placebo and seven in the fosinopril group had electrocardiograms characteristic of ECG-LVH at the beginning of the study. At the final visit, two patients in the control group and three patients in the fosinopril-treated group had ECG-LVH. The difference was not statistically significant.

Cornell voltage increased by 0.88 ± 2.2 mm (0.088 ± 0.22 mV) in the control group and decreased by 3.54 ± 1.6 mm (0.35 ± 0.16 mV) in the fosinopril group. The difference between the two groups was 4.42 mm (95%CI: −1.2–10.0 mm).

Laboratory tests

There were no significant changes in plasma sodium, urea or creatinine. Plasma potassium was not significantly

higher in the fosinopril-treated patients and none of the patients had a level which was outside the normal limit. There was no significant change in fasting blood glucose with either treatment. Neither plasma cholesterol, nor the subfractions of cholesterol, were altered significantly.

Urinary sodium increased significantly in patients treated with fosinopril. Baseline 24 h urinary albumin excretion showed that 89% of patients had microalbuminuria ($0.03–0.3\ g\ day^{-1}$) and 7% had $>0.3\ g\ day^{-1}$. There were no significant changes in 24 h urinary albumin excretion or creatinine clearance during the treatment period. There was a trend towards decrease in 24 h albumin excretion in the fosinopril-treated group, but this did not reach statistical significance.

Adverse events

Six patients in the placebo group reported adverse events. These included single episodes of headache, palpitations, sore throat and sore eyes. Flu-like symptoms, dizziness and finger numbness were reported by two patients. Eleven patients in the fosinopril group reported adverse events during the treatment period. The incidence of adverse events was not significantly different in the two treatment groups ($P>0.1$). Adverse events experienced by fosinopril-treated patients included headaches, palpitations, chest pain, abdominal pain, diarrhoea, bitter taste and rash. Three patients reported dizziness and four patients had a dry cough.

Lifestyle changes

There were no significant changes in body weight during study with either treatment. Six of the 33 patients (18%; two in the placebo group and four in the fosinopril group) reported an increase in exercise activity. Eleven patients (33%; six in the placebo group and five in the fosinopril group) reported a change in diet.

Discussion

The present study is one of few placebo-controlled trials assessing the reduction in indexed left ventricular mass as the primary endpoint in untreated hypertensive patients. No concurrent antihypertensive medications were allowed, so that we were studying purely the efficacy of the study drug. Previous regression of LVH trials were either uncontrolled, relying on before-after comparison, or used an active control, or allowed additional medications in both placebo and treatment groups (which confound the results) [8, 9].

Regression to the mean is a statistical phenomenon which occurs when there is selection of extreme values and variability (intrinsic variation and observer error). Therefore, it is a common problem in trials of antihypertensive drugs and trials of LVH regression. In our study, we tried to minimise this by avoiding selection of patients based on LV mass, careful echocardiographic measurements and using the mean of triplicate measurements, and including a parallel placebo control.

ACE inhibitors have several theoretical advantages in the treatment of LVH. These drugs are not negatively inotropic and improve morbidity and mortality in patients with heart failure and after myocardial infarction [16, 17]. They appear to be the most effective class of drugs in reducing left ventricular hypertrophy (LVH) [6]. Fosinopril was chosen for investigation in this study because fosinopril treatment for 12 weeks decreased left ventricular mass in a previous study [7]. As the study was primarily a haemodynamic study with invasive monitoring, only eight subjects completed and there was no placebo control. However, it suggested, in *post-hoc* analysis, that fosinopril might reduce left ventricular mass significantly in 3 months, which is the duration of non-pharmacological treatment in our clinic for new patients with mild essential hypertension. Although our control group did not receive any drug treatment, they had a full assessment of lifestyle and risk factors, and were strongly encouraged to alter these to reduce cardiovascular risk. The present study therefore confirmed the results of Oren & colleagues [7] using change in left ventricular mass as the primary endpoint.

There was only one patient withdrawn during the study because of protocol violation and there were no serious adverse events which required patient withdrawal, consistent with a high degree of tolerability of fosinopril [18]. Some of the fosinopril-treated patients developed a dry cough, which could have been due to or aggravated by fosinopril. Because of protocol and blinding, it was not possible to ascertain the diagnosis of ACEI-induced cough by withdrawal and re-challenge. Nevertheless, none of the patients's cough was severe enough to require withdrawal. It has been claimed that fosinopril has lesser tendency to cause dry cough [19]. The present study was not designed to investigate this issue, but the rate of cough in these patients with mild hypertension treated short-term with fosinopril was considerable. Dizziness, altered taste sensation and rash were reported by patients in the fosinopril group. These are known side effects of ACEIs and may be attributable to fosinopril [18].

Twelve weeks of treatment with fosinopril resulted in a significant fall in systolic and diastolic blood pressure. The fall in diastolic blood pressure (DBP) with drug treatment was modest in our study. This might be due to the use of monotherapy throughout and the reduction in dose if the DBP response was good. Nevertheless, the response rate was acceptable and suggested that fosinopril can be used as monotherapy in a subset of patients with

mild to moderate hypertension. Nevertheless, diuretics and β-adrenoceptor-blockers should be considered first-line treatment in mild-to-moderate essential hypertension because of the data on long-term outcome and mortality [20]. Similar evidence for ACEIs are lacking at the moment. The uncertainty and controversy surrounding short-acting calcium channel blockers emphasised the importance of such long-term data. However, ACEIs reduce mortality in patients with heart failure and acute myocardial infarction [16, 17]. In diabetic hypertensive patients, the recently-published FACET study showed that those treated with fosinopril suffered fewer cardiovascular events than those treated with amlodipine [21].

Our results agree with the observations in TOHMS and HYCAR that the degree of regression of LVMI was not related to the change in diastolic blood pressure nor systolic blood pressure [10, 22]. Moreover, the change in LVMI was related to drug treatment but not the baseline LVMI.

There were no significant differences in changes in ECG-LVH between the treatment groups. In this study, only a proportion of patients had ECG-LVH at baseline, so the power to investigate this parameter was limited. Nevertheless, the Cornell voltage tended to decrease in fosinopril-treated patients compared to control, consistent with the reduction in LV mass observed.

How ACEIs achieve regression of LVH independent of blood pressure reduction is uncertain, but it may involve the inhibition of the renin-angiotensin-aldosterone system [23]. Angiotensin II has been shown to be a growth factor stimulating myocardial cellular hypertrophy and extracellular matrix formation [24]. On the other hand, kinins may also contribute to the cardiovascular effects of ACEI [25]. As angiotensin-converting enzyme is involved in the breakdown of kinins, so ACEIs tend to augment the levels of bradykinin. Plasma kinins are difficult to measure and kinin concentration in human tissues is not accessible to measurement. However, the cardiovascular effects of kinins may not be insignificant and this issue assumes importance when angiotensin II antagonists are used instead of ACEI. Indeed, there is no reason to assume that antihypertensive drugs with the same efficacy in lowering blood pressure will have the same efficacy in regression of LVH. ACEIs have been found to be the most effective class of drugs in a meta-analysis, although this was not confirmed in the TOMHS study [6, 10].

There was no significant change in systolic function or diastolic function as a result of short-term treatment with fosinopril. These observations are consistent with previous studies [7], although improvement in diastolic function after fosinopril has been reported [26]. The possibility that longer term treatment may alter systolic or diastolic function cannot be excluded.

The use of ACEIs is often tempered by concern over renal function. This is especially important in patients with pre-existing renal impairment or renal artery stenosis. In our group of hypertensive patients treated with fosinopril, there was no significant impairment of renal function, either in terms of plasma creatinine or the more sensitive 24 h creatinine clearance. Moreover, plasma potassium was not significantly affected, and none of the patients had a plasma potassium which was outside normal limits. Urinary sodium tended to be high in fosinopril-treated patients, which is consistent with the known renal action of ACEIs. Interestingly, 24 h urinary sodium excretion decreased with placebo treatment, suggesting that our patients had carried out the dietary advice to eat less salt. Increased urinary albumin excretion, which may be an early abnormality in hypertensive renal disease [27], was found in most patients in this study. The plasma creatinine in these patients remain within the normal range because raised creatinine is a late manifestation of renal dysfunction [28]. The high frequency of raised albumin excretion in our patients who were untreated for hypertension was unexpected. Drug treatment, particularly with an ACEI, may reduce urinary albumin excretion [29]. Our study was of short duration and so could not investigate if long-term treatment with this ACEI may prevent progression of albuminuria. However, there was a trend towards lower albumin excretion in fosinopril-treated patients which need to be confirmed in a study of longer duration.

In conclusion, this randomised controlled study showed that treatment with fosinopril for 12 weeks reduced left ventricular mass significantly in hypertensive patients. This suggests that fosinopril, by controlling blood pressure and reducing LV mass, can modify two potent risk factors for cardiovascular events.

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