Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy

Björn Dahlof\textsuperscript{a}, Alberto Zanchetti\textsuperscript{b}, Javier Diez\textsuperscript{c}, M. Gary Nicholls\textsuperscript{e}, Cheuk-Man Yu\textsuperscript{f}, Vivencio Barrios\textsuperscript{d}, Peter Aurup\textsuperscript{g}, Ronald D. Smith\textsuperscript{g}, Magnus Johansson\textsuperscript{a}, for the REGAAL Study Investigators

\textbf{Objective} To compare the effects of the angiotensin II antagonist, losartan, with those of atenolol on left ventricular hypertrophy (LVH), blood pressure and neurohormone concentrations in hypertensive patients with LVH.

\textbf{Design} A multinational, randomized, double-blind trial.

\textbf{Setting} Hospital.

\textbf{Patients} Hypertensive patients with an echocardiographically documented left ventricular mass index (LVMI) \textgreater{} 120 g/m\textsuperscript{2} (men) or \textgreater{} 105 g/m\textsuperscript{2} (women).

\textbf{Interventions} Patients allocated randomly to groups received either losartan or atenolol 50 mg/day for 36 weeks, with possible titration to 100 mg/day, and addition of hydrochlorothiazide 12.5 or 25 mg/day.

\textbf{Main outcome measures} Changes in LVMI and sitting systolic (SBP) and diastolic (DBP) blood pressures after 36 weeks of treatment (study powered for non-inferiority hypothesis). All echocardiographic data were read in a central laboratory by staff blinded to the treatments and sequence of echocardiographic tapes.

\textbf{Results} The estimated treatment difference between the losartan and atenolol regimens (mean change from baseline at week 36) in LVMI was \(-2.5\) g/m\textsuperscript{2} [95\% confidence interval (CI) \(-7.36\) to \(2.37\) g/m\textsuperscript{2}] in favor of losartan, indicating that losartan was significantly non-inferior (\(P < 0.001\), non-inferiority limit \(8\) g/m\textsuperscript{2}) and numerically superior to atenolol in reducing LVMI. The losartan-based regimen significantly reduced LVMI after 36 weeks compared with baseline (\(-6.56\) g/m\textsuperscript{2}, 95\% CI \(-10.24\) to \(-2.88\) g/m\textsuperscript{2}, \(P < 0.001\)), whereas the atenolol-based regimen had no significant effect (\(-3.71\) g/m\textsuperscript{2}, 95\% CI \(-7.75\) to \(0.32\) g/m\textsuperscript{2}, \(P = \) NS). In a subset of 82 patients, significant changes in serum concentrations of atrial natriuretic peptide, brain natriuretic peptide and immunoreactive amino-terminal pro-brain natriuretic peptide were recorded in losartan-treated (\(P < 0.01\)) but not atenolol-treated patients. Losartan and atenolol significantly decreased SBP and DBP from baseline after 6, 12, 24 and 36 weeks. The changes from baseline in DBP were greater in the atenolol group at weeks 6 and 36 [difference \(-2.6\) mmHg (\(P = 0.016\)) at week 36]. However, both treatment regimens achieved similar SBP/DBP values at week 36 (141.1 \pm 12.8/86.8 \pm 8.2 mmHg for losartan and 141.4 \pm 17.2/85.0 \pm 10.1 mmHg for atenolol, respectively). Overall, losartan treatment was associated with significantly fewer drug-related clinical adverse events, compared with atenolol (10 and 22\%, respectively, \(P = 0.028\)).

\textbf{Conclusions} Both losartan- and atenolol-based regimens effectively decreased blood pressure. Losartan was non-inferior and numerically superior to atenolol in regression of LVH. The reduction in hypertrophy with losartan treatment was accompanied by reductions in circulating concentrations of cardiac natriuretic peptides. Losartan, by specifically blocking angiotensin II, may therefore have effects on the heart beyond those expected from the decrease in blood pressure alone. Losartan was better tolerated than atenolol. \textit{J Hypertens} 20:1855–1864 © 2002 Lippincott Williams & Wilkins.

\textbf{Keywords:} losartan, atenolol, hypertension, left ventricular hypertrophy, echocardiography, neurohormones, atrial natriuretic peptides

\*University of Göteborg-Ostra University Hospital, Göteborg, Sweden, \*Centro di Fisiologia Clinica e Ipertensione, University of Milan, Ospedale Maggiore and Istituto Auxologico Italiano, Milan, Italy, \*University of Navarra, Pamplona, Spain, \*Hospital Ramon y Cajal, Madrid, Spain, \*Christchurch Hospital, Christchurch, New Zealand, \*University of Hong Kong, Queen Mary Hospital, Hong Kong, China and \*Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

\textbf{Sponsorship:} This study was funded by Merck & Co., Inc.

\textbf{Conflicts of interest:} None.

\textbf{Correspondence and requests for reprints to Dr Björn Dahlof, University of Göteborg, Department of Medicine, Ostra University Hospital, CK Plan 2, S-41685, Sweden. Tel: +46 31 343 5305; fax: +46 31 842 217; e-mail: bdahlof@scandinaviancri.se}

\textbf{Received 14 March 2002 Revised 27 May 2002 Accepted 3 June 2002}
Introduction

Left ventricular hypertrophy (LVH) in hypertension is a powerful predictor of stroke, sudden death, coronary heart disease and heart failure, in addition to other manifestations of cardiovascular disease [1,2]. The prevention or reversal of LVH has therefore become an important objective of antihypertensive treatment. However, the relationship between blood pressure reduction and attenuation of LVH is not well established. Even when ambulatory blood pressure, rather than clinic blood pressure, is assessed, there is a rather weak association between blood pressure reduction and reduction in LVH [3], suggesting the involvement of additional factors.

According to meta-analyses of available studies, angiotensin-converting enzyme inhibitors appear to be the most effective antihypertensive agents in reducing left ventricular mass index (LVMI) [4,5], suggesting that angiotensin II (Ang II) or bradykinin may have roles independent of blood pressure per se. Unfortunately, there is a paucity of comparative studies large enough and with sufficient power to provide definitive information. In addition, even randomized double-blind studies were rarely designed to avoid readers’ bias of echocardiographic parameters and the risk of regression to the mean.

The discoveries of losartan and the new class of specific inhibitors of the Ang II type 1 (AT1) receptors have provided the means to assess the importance of stimulation of these receptors in the development or maintenance of cardiac hypertrophy in hypertensive patients [6]. Ang II has been shown to have several direct and indirect actions on cardiac cells that might influence cardiac hypertrophy. These include actions on cardiomyocytes [7,8], fibroblasts [9], sympathetic nerves [10], coronary vascular smooth muscle [11] and coronary endothelial cells [12,13]. All these effects are blocked by losartan and are, by convention, designated AT1-mediated [10–12].

A number of relatively small studies in hypertensive patients [14–20] have shown that specific blockade of the AT1 receptor decreases blood pressure and left ventricular mass (LVM). However, no large study comparing an AT1 receptor antagonist with another antihypertensive agent on LVM regression has been reported to date, and no clinical investigation has simultaneously explored the effects of different antihypertensive agents on LVM and neurohormonal factors such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), adrenomedullin and catecholamines, which are considered sensitive indices of activation of hypertrophy-related processes [21–23].

The present study was planned to compare the effects of a losartan-based antihypertensive treatment with those of antihypertensive treatment based on the widely used β1-selective β-blocker, atenolol, both on echocardiographic parameters of ventricular geometry and on cardiac neurohormones. Furthermore, the study was carefully designed to use echocardiographic measurements made by certified examiners and with the tapes read in a central laboratory by individuals blinded not only to the antihypertensive agent, but also to the sequence of data acquisition.

Methods

The Losartan LVH Regression Study (REGAAL) is a 36-week, randomized, multi-centre, double-blind, parallel-group study comparing the effects of losartan with those of atenolol on LVMI in patients with mild-to-moderate essential hypertension. The procedure was approved by the appropriate institutional review boards or ethics review committees of each study centre, and the study was conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki. Every patient gave written informed consent to their inclusion in the study.

Patients

The study included men and women, aged 21–80 years, with mild-to-moderate essential hypertension and echocardiographically documented LVH assessed up to 30 days before enrolment. Eligible patients had trough sitting diastolic blood pressure (DBP) of 95–115 mmHg or sitting systolic blood pressure (SBP) of 160–200 mmHg, or both, while receiving placebo for 2–4 weeks, and a left ventricular mass index (LVMI) > 120 g/m2 for men and > 105 g/m2 for women. Patients with a left ventricular end-diastolic dimension > 60 mm, irrespective of the LVMI, systolic dysfunction or significant valvular disease, were excluded. The patient population included in this study consisted of individuals different from those included in the LIFE echocardiographic sub-study [24], although the treatment regimens compared were the same.

Study procedure

All patients qualified for entry to the study on the basis of a screening echocardiogram, read at a central laboratory. If LVMI fell within the predefined limits, and the other entry criteria were met, the patients entered a 4-week placebo run-in period (2-week placebo period for previously untreated patients), at the end of which patients who satisfied all entry criteria entered into the active treatment period, during which visits were scheduled at weeks 6, 12, 24 and 36. Patients were randomly assigned, in a double-blind manner, to receive losartan or atenolol (50 mg once daily) for 36 weeks (Fig. 1). Patients not achieving the goal blood pressure (< 140/90 mmHg) after 6 weeks of treatment
also received hydrochlorothiazide (HCTZ) 12.5 mg daily. Patients who still failed to attain the DBP goal after 12 weeks then received a double dose of study drug and, if necessary, HCTZ 25 mg daily. Patients were instructed to take study medications at the same time each day, preferably between 0800 and 1000 h.

**Trough blood pressure measurements**
Clinic diastolic and systolic blood pressures were measured at trough (22–26 h after the previous study medication) with a standard mercury sphygmomanometer, with the patient in the sitting position after 5 min of rest, at every clinic visit (baseline and treatment). The means of three consecutive measurements at 2–3 min intervals were used.

**Echocardiographic measurements**
Two-dimensionally guided M-mode echocardiographic recordings were performed on three occasions: 1) before entry to the study (qualifying echo); 2) on completion of the 4-week placebo run-in (baseline echo); 3) at week 36 (end-of-study echo). Procedures identical to those used in the PRESERVE study [25] and LIFE echocardiographic sub-study [24] were used. In brief, echocardiograms were made using commercially available phased-array echocardiographs with M-mode, two-dimensional, pulsed- and continuous-wave Doppler. Correct orientation of planes for imaging recordings was verified. Recordings were made by a commercially available ultrasound system using 3.0–3.5 MHz and 2.0–2.5 Hz transducers, super or standard VHS recorders. Quality control of echocardiographic data was ensured not only by centralized control of baseline and end-of-study echocardiograms shortly after acquisition, but also by centralized quantitative reading of all recordings at completion of the study by readers blinded to the sequence of their acquisition. The central echocardiographic laboratory was located at Ostra University Hospital.

The primary endpoint of the study was the change in LVMI from baseline after 36 weeks of treatment, evaluated by echocardiography. Secondary endpoints included left ventricular morphology assessed at 36 weeks (i.e. changes in posterior wall thickness, left ventricular internal diameter at end systole, left ventricular internal diameter at end diastole, interventricular septal thickness, relative wall thickness, left ventricular mass), cardiac function and transmitral flow assessed at 36 weeks [i.e. changes in ejection fraction, fractional shortening, stroke volume, left ventricular ejection time index, peak velocity of rapid filling (peak E velocity), late transmitral peak flow velocity (peak A velocity), peak E/A ratio], and blood pressure assessed at weeks 6, 12, 24 and 36.

**Neurohormone measurements**
Neurohormone measurements were obtained in 82 of the 225 patients allocated randomly to groups. Venous blood samples (10 ml) were taken via an indwelling catheter between 0800 and 1130 h, after the patient had spent 30 min in the supine position, for measurement of several neurohormones, including ANP [26], BNP [27], immunoreactive amino-terminal pro-brain natriuretic peptide (NT-BNP) [23,28], adrenomedul-lin(1–52) [29] adrenaline and noradrenaline [30], aldosterone [31] and endothelin-1 [32]. Samples were drawn at the completion of the 4-week placebo run-in period and at weeks 6, 12 and 36. Plasma was stored at −80°C until assayed at one central site (Endolab, Christchurch Hospital, Christchurch, New Zealand) by staff blinded to study treatment and sample sequence. All samples from an individual patient were measured in a single assay, to avoid interassay variability. Intra-
The primary efficacy analysis was based on the week 36 change from baseline in LVMI and analysed using analysis of variance (ANOVA), adjusted for centre and treatment. The primary hypothesis of non-inferiority was tested by constructing a 95% two-sided confidence interval (95% CI) around the treatment differences in least square means from this model. Losartan was compared and was used to corroborate the conclusions drawn from the intention-to-treat analysis.

The secondary efficacy echocardiographic variables of left ventricular morphology and cardiac function, in addition to SBP and DBP measurements, were analysed using an ANOVA model on the change from baseline (adjusted for centre and treatment). Between-treatment group differences were tested using type III Sums of Squares in the PROC SAS GLM procedure [33,34]. Within-group changes from baseline were analysed using t-tests. Biochemical markers and neurohormones were an exploratory objective and were analysed similarly after a logarithmic transformation in a subset of 82 patients.

The relationship between the various efficacy parameters (e.g. left ventricular morphology, blood pressure control and biochemical markers) was studied by correlation analysis. The relationship between subgroups based on demographic characteristics (age, sex and race) and treatment effect on the primary endpoint was assessed using an ANOVA model containing centre, treatment, subgroup and treatment-by-subgroup interactions. Comparison of the incidence of an adverse experience, and the number of patients who were not titrated between the active treatment groups, was made using Fisher’s Exact test.

Results
Patient accounting
A total of 431 patients with essential hypertension were screened; 225 of them were enrolled at 29 centres in nine countries. Two hundred and ten patients completed 36 weeks of double-blind treatment with either losartan (n = 111) or atenolol (n = 99). Fifteen patients withdrew from the trial (four in the losartan group and 11 in the atenolol group) because of: 1) adverse clinical experiences (one losartan, seven atenolol), 2) lack of antihypertensive efficacy (one losartan, one atenolol), 3) procedure violations (one atenolol) or other reasons (two losartan, two atenolol).

Of the 225 patients who had taken at least one dose of treatment, six lacked either the baseline measurement or one measurement during the active treatment period (one losartan, five atenolol) and were excluded from the intention-to-treat analysis of the LVMI. At week 36, 183 patients (96 losartan, 87 atenolol) were included in the per-procedure analysis. The main reasons for exclusion were: baseline LVMI < 120 g/m² for men or < 105 g/m² for women (19 patients); no LVMI measurement in the week 36 per-procedure time window (15 patients); other causes (two patients). For those patients in whom the treatment echocardiograms and blood pressure measures were obtained before the week 36 window, the values were attributed to week 36 (last observation carried forward analysis).

Baseline characteristics
The losartan and atenolol groups were similar with respect to age, sex, race, weight, baseline LVMI, and DBP and SBP (Table 1). No clinically meaningful difference between the two groups was apparent with respect to the presence of co-morbid conditions or pharmacological treatment (including antihypertensive treatments) before random allocation to groups or during the 36-week active treatment phase. During the 30 days before visit 1 (screening), 78% of the patients subsequently assigned to receive losartan and 75% of the patients subsequently assigned to receive atenolol had received one or more antihypertensive agents. The most frequently used agents were similar in the atenolol group and included amlodipine (15%), atenolol (12%), doxazosin (5%), indapamide (5%), nifedipine (14%) and verapamil (5%).
Blood pressure at trough

Losartan and atenolol produced significant reductions in SBP and DBP after 6, 12, 24 and 36 weeks of double-blind treatment (Fig. 2). No statistically significant difference between losartan and atenolol was apparent for SBP at any time point; at week 36, the atenolol group had a greater reduction in DBP compared with the losartan group (2.6 mmHg, \( P = 0.016 \)). However, both treatment regimens achieved similar SBP/DBP values at week 36 (141.1 \( \pm \) 12.8/86.8 \( \pm \) 8.8 mmHg for losartan and 141.4 \( \pm \) 17.2/85.0 \( \pm \) 10.1 mmHg for atenolol). The blood pressure profiles were substantially superimposable (Fig. 2). The majority of patients in both the losartan (78.2%) and atenolol (78.9%) groups attained blood pressure goals (SBP/DBP < 140/90 mmHg) with a dosage regimen titrated up to 100 mg plus addition of 12.5 mg HCTZ. In the losartan and atenolol groups, respectively, 13.0% and 21.1% of the patients continued to take the starting dose (50 mg) of blinded treatment (\( P = 0.05 \)), 86.1% and 78.0% took at least one dose of 12.5 mg HCTZ, 49.6% and 47.7% took at least one double dose of blinded medication, and 20.9% and 21.1% took at least one double dose of HCTZ. Compliance with study medica-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Losartan (n = 115)</th>
<th>Atenolol (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ( \pm ) 11</td>
<td>57 ( \pm ) 11</td>
</tr>
<tr>
<td>Sex M/F (%)</td>
<td>67/33</td>
<td>60/40</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>Asian</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ( \pm ) 14</td>
<td>76 ( \pm ) 12</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>149 ( \pm ) 30</td>
<td>148 ( \pm ) 31</td>
</tr>
<tr>
<td>Sitting diastolic blood pressure (mmHg)</td>
<td>98 ( \pm ) 9</td>
<td>99 ( \pm ) 8</td>
</tr>
<tr>
<td>Sitting systolic blood pressure (mmHg)</td>
<td>165 ( \pm ) 15</td>
<td>169 ( \pm ) 15</td>
</tr>
<tr>
<td>Median heart rate (beats/min)</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>Prior antihypertensive treatment (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taken within 30 days before visit 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more</td>
<td>78.3</td>
<td>74.5</td>
</tr>
<tr>
<td>None</td>
<td>21.7</td>
<td>25.5</td>
</tr>
<tr>
<td>Taken during placebo run-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more</td>
<td>5.2</td>
<td>5.5</td>
</tr>
<tr>
<td>None</td>
<td>94.8</td>
<td>94.5</td>
</tr>
</tbody>
</table>

Values are mean \( \pm \) SD where relevant. LVMI, left ventricular mass index.
Echocardiographic measurements

The mean changes from baseline were \(-6.56\) \text{g/m}^2 (95% CI \(-10.24\) to \(-2.88\) \text{g/m}^2, \(P < 0.001\)) for losartan-treated patients and \(-3.71\) \text{g/m}^2 (95% CI \(-7.75\) to \(0.32\) \text{g/m}^2, \(P = \text{NS}\)) for atenolol-treated patients (Table 2). The estimated treatment difference with respect to the mean change in LVMI from baseline at week 36 with the intention-to-treat analysis was \(-2.5\) \text{g/m}^2 (95% CI \(-7.36\) to \(2.37\) \text{g/m}^2) in favor of losartan. Losartan was significantly non-inferior (\(P < 0.001\)) and numerically superior to atenolol in reducing LVMI. This was substantiated by the results of the per-protocol analysis (Table 2). During the 36-week treatment period, mean LVMI decreased significantly in the losartan group, but not in the atenolol group.

Table 2 also shows that significant decreases from baseline values occurred in LVM and left ventricular posterior wall thickness at 36 weeks in the losartan group, but not in the atenolol group. There was a small increase in mean left ventricular ejection fraction in both treatment groups and small non-significant decreases in left ventricular internal diameter and interventricular septal thickness at end of diastole at 36 weeks in both the losartan and atenolol groups. No significant change from baseline occurred with respect to mean mitral inflow A- and E-wave maximal velocity in either treatment group. The peak E/A ratio change from baseline was \(-0.03 \pm 0.29\) for losartan and \(0.06 \pm 0.27\) for atenolol (\(P < 0.05\)).

Table 3 shows that, in the losartan treatment group, the decreases in LVMI at week 36 were significantly correlated with the reduction from baseline in trough DBP only. In the atenolol treatment group, the decrease in LVMI at week 36 correlated with the change from baseline in DBP, SBP and mean arterial pressure. However, in all cases, the correlation coefficients were rather low.

### Table 2: Effects on mean echocardiographic measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>Change at week 36</th>
<th>Baseline</th>
<th>Change at week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI ((\text{g/m}^2)) ITT(^b) analysis (n = 114/105)</td>
<td>150 ± 30</td>
<td>(-6.6 \pm 0.3)(^{**})</td>
<td>148 ± 30</td>
<td>(-3.7 \pm 0.2)</td>
</tr>
<tr>
<td>LVMI ((\text{g/m}^2)) PP(^c) analysis (n = 96/87)</td>
<td>154 ± 29</td>
<td>(-7.4 \pm 0.3)(^{**})</td>
<td>149 ± 26</td>
<td>(-4.5 \pm 0.2)</td>
</tr>
<tr>
<td>LV (g)</td>
<td>276 ± 68</td>
<td>(-12 \pm 0.3)(^{***})</td>
<td>272 ± 62</td>
<td>(-9 \pm 0.2)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.65 ± 0.8</td>
<td>0.2 ± 0.8</td>
<td>0.65 ± 0.9</td>
<td>0.3 ± 0.8(^{**})</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>50 ± 5</td>
<td>(-0.2 \pm 0.3)</td>
<td>50 ± 6</td>
<td>(-0.2 \pm 0.4)</td>
</tr>
<tr>
<td>LVIDs (mm)</td>
<td>32 ± 5</td>
<td>(-0.9 \pm 0.3)</td>
<td>32 ± 6</td>
<td>1.3 ± 0.6(^{**})</td>
</tr>
<tr>
<td>LVPWd ((\text{mm}))</td>
<td>14 ± 2</td>
<td>(-0.3 \pm 0.3)</td>
<td>14 ± 2</td>
<td>(-0.1 \pm 0.3)</td>
</tr>
<tr>
<td>Mitral inflow A wave maximal velocity ((\text{m/s}))</td>
<td>0.7 ± 0.2</td>
<td>(-0.0 \pm 0.3)</td>
<td>0.7 ± 0.2</td>
<td>(-0.0 \pm 0.3)</td>
</tr>
<tr>
<td>Mitral inflow E wave maximal velocity ((\text{m/s}))</td>
<td>0.7 ± 0.2</td>
<td>(-0.0 \pm 0.3)</td>
<td>0.7 ± 0.2</td>
<td>(-0.0 \pm 0.3)</td>
</tr>
<tr>
<td>Peak E/A ratio</td>
<td>1.0 ± 0.3</td>
<td>(-0.0 \pm 0.3)</td>
<td>1.0 ± 0.3</td>
<td>(-0.0 \pm 0.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD. LVMI, left ventricular mass index; LVMI, left ventricular mass; LVEF, left ventricular ejection fraction; LVIDd, LVIDs, left ventricular internal diameter at end systole and end diastole; LVPWd, left ventricular posterior wall thickness at end diastole; Peak E/A ratio, ratio of mitral inflow E/A maximal velocities. \(^b\)Change from baseline at week 36; negative value indicates larger decrease in losartan group; \(^c\)ITT, intention-to-treat analysis (for all parameters unless otherwise indicated, n = 114/105); \(^p\)PP, per procedure analysis. \(^* P < 0.05, \quad \text{**} P < 0.01, \text{***} P < 0.001\) compared with baseline.

### Table 3: Correlation between change from baseline in left ventricular mass index and change in blood pressure (BP) parameters

<table>
<thead>
<tr>
<th>Blood pressure parameter</th>
<th>Losartan ((n = 111))</th>
<th>Atenolol ((n = 99))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.15 (-0.03 to 0.33)</td>
<td>0.29 (0.09 to 0.46)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>(-0.11) (-0.29 to 0.07)</td>
<td>0.02 (-0.18 to 0.22)</td>
</tr>
<tr>
<td>Sitting systolic BP</td>
<td>0.03 (-0.16 to 0.21)</td>
<td>0.24(^*) (0.04 to 0.42)</td>
</tr>
<tr>
<td>Sitting diastolic BP</td>
<td>0.22(^*) (0.04 to 0.30)</td>
<td>0.34(^{***}) (0.15 to 0.50)</td>
</tr>
</tbody>
</table>

\(r\), correlation coefficient; CI, confidence interval. \(^* P < 0.05, \text{**} P < 0.01, \text{***} P < 0.001\).
similar to those in the total study population (data not shown). In this subset from which neurohormones were obtained, losartan significantly decreased baseline plasma ANP ($P < 0.001$), BNP ($P < 0.001$), and NT-BNP ($P < 0.001$), but did not significantly affect endothelin-1, adrenomedullin, aldosterone, noradrenaline or adrenaline (Table 3). In contrast, the only significant effect of atenolol ($n = 40$) was to increase the concentration of adrenomedullin ($P < 0.001$). A significantly larger decrease in the losartan group, compared with the atenolol group, was observed for ANP ($P < 0.01$), BNP ($P < 0.01$) and NT-BNP ($P < 0.01$), whereas for adrenomedullin there was a significant difference ($P < 0.001$) between the small decrease seen with losartan and the increase in the atenolol-treated patients (Table 4).

**Safety**

Of the 225 patients who received at least one dose of study drug, 56% in the losartan group and 48% in the atenolol group experienced at least one clinical adverse event ($P > 0.05$; Table 5). A significantly lower proportion of patients receiving losartan than of those receiving atenolol reported drug-related adverse clinical adverse events (10% compared with 22%, $P = 0.028$). The most frequently reported drug-related clinical adverse events were asthenia/fatigue, epigastric discomfort, dizziness, bradycardia, headache and nausea. With the exception of one patient who experienced renal insufficiency while receiving atenolol, all serious clinical adverse experiences were considered definitely or probably unrelated to the study drug. Significantly more patients discontinued the study in the atenolol group than in the losartan group because of drug-related clinical adverse experiences (6% compared with 1%, respectively, $P = 0.013$; Table 5). Reasons for discontinuation of atenolol treatment included epigastric discomfort (one), dyspnoea (one), asthenia/fatigue (one), renal insufficiency (one), bradycardia (one) and muscular cramp (one). One patient treated with losartan was withdrawn from treatment because of cerebral infarction, viewed by the physician as probably not drug related. No significant difference was apparent between the two study groups with respect to adverse results from laboratory tests. However, atenolol was associated with a significantly greater mean increase from baseline in serum uric acid concentrations at 36 weeks than was losartan (52.8 μmol/l compared with 10.8 μmol/l; $P < 0.001$).

**Discussion**

Our findings confirm those of previous smaller studies showing the ability of losartan [14–16,18,19] and other Ang II antagonists, including valsartan [17] and irbesartan [20], to produce significant improvements in one or more indices of LVH, including LVM, LVMI and left ventricular geometry, in hypertensive patients.

The between-treatment comparison led to the conclusion that losartan was significantly non-inferior to and numerically superior to atenolol in reducing LVMI. The losartan-based regimen significantly reduced LVMI compared with baseline after 36 weeks (primarily because of a decrease in left ventricular wall thickness), whereas the atenolol-based regimen had no

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Effects of losartan and atenolol on serum neurohormone concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration (pmol/l)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neurohormone</strong></td>
<td><strong>Losartan group</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Change at week 36 (%)$^a$</strong></td>
</tr>
<tr>
<td>ANP</td>
<td>$12.5 \pm 6.8$ ($n = 39$)</td>
</tr>
<tr>
<td>BNP</td>
<td>$6.9 \pm 5.8$ ($n = 41$)</td>
</tr>
<tr>
<td>NT-BNP</td>
<td>$23.9 \pm 39.3$ ($n = 41$)</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>$1.5 \pm 0.4$ ($n = 39$)</td>
</tr>
<tr>
<td>Aldrenomedullin</td>
<td>$6.9 \pm 3.7$ ($n = 43$)</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>$175.7 \pm 98.8$ ($n = 43$)</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>$2.2 \pm 1.3$ ($n = 43$)</td>
</tr>
<tr>
<td></td>
<td>$144.3 \pm 140.3$ ($n = 42$)</td>
</tr>
</tbody>
</table>

$^a$Losartan compared with atenolol; NS, not significant. $^b$Determined by the investigator as probably, possibly or definitely drug-related. $^c$Withdrawn because of the adverse event.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Summary of clinical and laboratory adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
<td><strong>Losartan</strong></td>
</tr>
<tr>
<td><strong>Clinical and other</strong></td>
<td>$(n = 115)$</td>
</tr>
<tr>
<td>Any</td>
<td>$64 (56)$</td>
</tr>
<tr>
<td>Drug-related$^a$</td>
<td>$12 (10)$</td>
</tr>
<tr>
<td>Serious</td>
<td>$7 (6)$</td>
</tr>
<tr>
<td>Withdrawn$^a$</td>
<td>$1 (1)$</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>$(n = 115)$</td>
</tr>
<tr>
<td>Any</td>
<td>$17 (15)$</td>
</tr>
<tr>
<td>Drug-related$^a$</td>
<td>$5 (4)$</td>
</tr>
<tr>
<td>Serious</td>
<td>$0 (0)$</td>
</tr>
<tr>
<td>Withdrawn$^a$</td>
<td>$0 (0)$</td>
</tr>
</tbody>
</table>

$^a$Losartan compared with atenolol; NS, not significant. $^b$Determined by the investigator as probably, possibly or definitely drug-related. $^c$Withdrawn because of the adverse event.

Values are mean ± SD, $n$, number of patients; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; NT-BNP, immunoreactive amino-terminal pro-brain natriuretic peptide $^a$Percent change from baseline at week 36; $^b$Losartan compared with atenolol. $^c$Withdrawn because of the adverse event.
significant effect, despite generally comparable reductions in sitting DBP and SBP. The relatively short duration of the study (36 weeks) may have prevented the findings of a greater reduction in LVMI in both treatment groups. Indeed, in a recent study comparing irbesartan and atenolol, reductions in LVMI at week 24 were approximately 50% those seen at week 48 [20]. The numerically greater reduction in LVH in the losartan regimen is consistent with the findings of previous clinical trials comparing atenolol with blockers of the renin–angiotensin system, including valsartan, irbesartan and ramipril, in hypertensive patients [17, 20,36].

The changes with both agents were smaller compared with several previous results. However, from a methodological perspective, the influence of experimental bias cannot be excluded from some of the previous studies, for two reasons. First, in several studies, analysis of echocardiograms was carried out by investigators who were aware of visit date and, hence, the sequence of recordings. Therefore, expectation of therapeutic-related regression may have generated some reading bias and exaggerated the extent of the regression. Second, in most of the previous studies the baseline echocardiogram was used as a reference point against which to calculate change in LVMI, as well as for screening purposes, and thus the data could be potentially affected by regression to the mean. Our study was designed to minimize both those sources of potential error. Determination of LVMI was performed using standardized procedures similar to those described in the PRESERVE study [25] and LIFE substudy [24], and with equipment externally calibrated at all study sites. To optimize the accuracy and reproducibility of LVMI measurements, the initial analysis of echocardiographic data performed by the examining physician was followed by subsequent analysis of the recordings at a central reading laboratory by specially trained investigators who were unaware of patients’ assignments to study groups or of the sequence of the tapes analysed. Furthermore, to reduce the phenomenon of ‘regression to the mean’ patients qualified for entry to the study on the basis of a screening echocardiogram, but all evaluations were made by comparing changes between the baseline value (after a 4-week placebo run-in) and the end-of-study value. It is interesting to note that other investigators using the same type of technical precautions as those described here have also reported smaller treatment-associated changes in LVMI [37]. This type of analytical approach, which avoids the types of factors that potentially overestimate LVH reduction but provides continuing quality control of echocardiographic data, will probably become standard procedure in future studies assessing the effect of pharmacological interventions on LVH.

Despite the careful technical precautions taken, it must be recognized that our study also has some limitations: 1) regression to the mean was minimized, but cannot be entirely excluded; 2) the number of patients allocated to the study groups was larger than in most previous studies, but smaller than that we aimed to include when sample size was calculated; 3) blood pressure was measured, as usual, at the brachial artery in the clinic, more precise 24-h monitoring of ambulatory blood pressure could not be included in the procedure, and central blood pressure was not measured.

The findings on neurohormones support the concept that the effects of the two agents on LVH may be substantially different. In the subpopulation of patients in whom neurohormones were measured losartan, but not atenolol, significantly decreased the concentrations of ANP, BNP and NT-BNP. Treatment-related differences in the effects on all these neurohormones were statistically significant. ANP and BNP are believed to be tissue markers for LVH and cardiac impairment [21,23,38,39], and their reduction may afford more sensitive indices of LVH regression than LVMI. In-vitro data showing that Ang II may play a part in mediating upregulation of ANP and BNP genes [40,41] suggest a direct role of Ang II receptor blockade in the cardiac effects of losartan. Changes in neurohormones in losartan-treated patients, but not in atenolol-treated patients, may also hint at a different effect of the two treatments on myocardial fibrosis – a hypothesis that has also been investigated in the REGAAL study by analysing biochemical [42] and ultrasonic [43] markers of cardiac fibrosis. The results of these analyses will be reported separately.

Overall, both the losartan and atenolol regimens were well tolerated, although the incidence of drug-related clinical adverse events in patients receiving losartan was significantly lower than that in patients receiving atenolol. The low incidence of clinical adverse experiences with losartan was generally comparable to those in other published studies in patients with hypertension [44]. Patients receiving losartan had a significantly lower mean increase from baseline in serum uric acid concentrations at 36 weeks compared with those assigned to receive atenolol (diuretic use comparable in each treatment group). A uricosuric effect of losartan is consistent with previous findings [45]. As hyperuricemia represents a potentially powerful marker for cardiovascular disease, [46,47] the ability of losartan to decrease serum uric acid concentrations (an effect not shared with other Ang II antagonists) may contribute to a lower overall cardiovascular risk in hypertensive patients.

Acknowledgement

The authors acknowledge the efforts of the study coordinator Steven J. Justice (Merck & Co., Inc.), the
statistician Thomas Dumortier, and the data coordi- 
tor Sophie-Anne Prevot (Clinical Biostatistics and 
Research Data Systems, Merck Sharp & Dohme [Europe] 
Inc).

References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic 
implications of echocardiographically determined left ventricular mass in 

2. Koren MJ, Devereux RB, Casale PN, Savage DD, Lassig JH. Relation of 
left ventricular mass and geometry to morbidity and mortality in uncomplic-

Fogari R, et al. Ambulatory blood pressure is superior to clinic blood 
pressure in predicting treatment-induced regression of left ventricular 

4. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular 
remodelling by angiotensin II receptor blockers: a randomized 

5. Schmieder RE, Martus P, Klingbeil A. Decrease of left ventricular 
remodelling by angiotensin II receptor blockers: a randomized 

6. Timmermans PBMWM, Duncia JV, Carini DJ, Chiu AT, Wong PC, Wexler 
iM. The use of a new antihypertensive agent, valsartan, in the treatment of 
patients with essential hypertension and left ventricular hypertrophy. 

7. Paradis P, Dali-Youcef N, Paradis FW, Thibault G, Nemer M. Over-
expression of angiotensin II type I receptor in cardiomyocytes induces 

Effects of losartan on left ventricular mass in essential hypertension. 

cardiac angiotensin II levels induce right and left ventricular hypertrophy 


11. Yandle TG, Richards AM, Espiner EA, Yandle TG, Frampton C. 
Renal, endocrine, and hemodynamic interactions of atrial and brain natriuretic 

Fogari R, et al. Ambulatory blood pressure is superior to clinic blood 
pressure in predicting treatment-induced regression of left ventricular 

vascular permeability factor gene-expression by human vascular smooth-

14. Acarturk E, Demir M, Demircan S. Regression of left ventricular 
hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg 

15. Kario K, Nishikimi T, Yoshitake K, Takaishi S, Yamaoka R, Matsuo T, 
et al. Plasma levels of natriuretic peptides and adrenomedullin in elderly 
 hypertensive patients: relationships to 24 h blood pressure. J Hypertens 1998; 
16:1253–1256.

16. Kario K, Morita H, Yokokawa K, Murakawa K, Yasunari K, Akioka K, 
et al. Brain natriuretic peptide as a cardiac hormone in essential hypertension. 

Regression of left ventricular hypertrophy in hypertensive patients treated 
with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. 

18. Kario K, Nishikimi T, Yoshitake K, Takaishi S, Yamaoka R, Matsuo T, 
et al. Plasma levels of natriuretic peptides and adrenomedullin in elderly 
 hypertensive patients: relationships to 24 h blood pressure. J Hypertens 1998; 
16:1253–1256.

19. Kario K, Morita H, Yokokawa K, Murakawa K, Yasunari K, Akioka K, 
et al. Brain natriuretic peptide as a cardiac hormone in essential hypertension. 

20. Wiese S, Breyer T, Dragu A, Wakili R, Burkard T, Schmidt-Schweda S, 
et al. Gene expression of brain natriuretic peptide in isolated atrial and 
ventricular human myocardium: influence of angiotensin II and diastolic 

21. Savadori J, Izu M. Molecular characterization of angiotensin 
II-induced hypertrophy of cardiac myocytes and hyperplasia of cardiac 
fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 1993; 
72:413–423.

Usefulness of serum carboxy-terminal propeptide of procollagen type I in 
Losartan vs atenolol in reducing LHV Dahlof et al. 1863


**Appendix**

The REGAAL Study Investigators included the following individuals and centres (by country):

**Canada**
E. Burgess, Foothills Hospital, Calgary, Alberta; Jacques Lenis, Private Practice, Longueuil, Québec; Michelle Robitaille, Hôpital Laval, Ste-Foy, Québec; Denis C. Planeuf, CHUM Hotel-Dieu de Montréal, Montréal, Québec; Kelly B. Zarnke, University Campus London Health Sciences Centre, London, Ontario.

**China**
Li Sheng Liu, Fu Wai Hospital, Beijing, China; Jing Xuan Guo, The 3rd Affiliated Hospital of Beijing Medical University, Beijing; Wen Hang Qi, Rui Jin Hospital Shanghai Second Medical University, Shanghai; Yu Hua Liao, Union Hospital, Wuhan.

**Croatia**
Borut Kolslek, Klinicni Center Ljubljana, Klinika za Hipertenzijo, Ljubljana; Mirko Bombeck, Spionska Boinica Maribor, Interne Klinike, Maribor.

**Italy**
Bruno Trimarco, Clinica Medica I Università degli Studi di Napoli, Napoli; Gastone Leonetti, Università di Milano, Istituto Auxologico Italiano, Ospedale San Luca, Milano; Enrico Agabiti-Rosei, Università di Brescia, Brescia; Antonio Salvetti, Clinica Medica I, Università di Pisa, Pisa.

**Lithuania**
Petras Zabiela, Kaunas Medical Academy, Kaunas; Algimantas Kirkutis, Seamen Hospital, Klaipeda.

**New Zealand**
Denis Friedlander, Lipid Clinic, Hamilton; Leigh Nairn, Private Practice, Tauranga; Andrew Hamer, Nelson Hospital, Nelson; Gary Nicholls, Christchurch Hospital, Christchurch.

**Spain**
Javier Balaguer-Recena, Hospital General Universitario, Guadalajara; Celia Fernandez-Torres, Hospital Virgen de Las Nieves, Granada; Ignacio Ferreira-Monero, Hospital Clinico Universitario, Zaragoza; Miguel Angel Rodriguez-Garcia, Complejo Hospitalario de Leon, Leon; Txomin Sagastagorita, Hospital de Basurto, Montevideo.

**Sweden**
Kurt Boman, Medicinkliniken, Skellefteå; Ronnie Willenheimer, University Hospital, Malmö; Christer Högland, Stockholm Heart Centre, Stockholm.

**United Kingdom**
John Stephens, Oldchurch Hospital, Romford, Essex.