Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol

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Summary

Background Blood pressure reduction achieved with β-blockers and diuretics is the best recorded intervention to date for prevention of cardiovascular morbidity and death in patients with hypertension. Left ventricular hypertrophy (LVH) is a strong independent indicator of risk of cardiovascular morbidity and death. We aimed to establish whether selective blocking of angiotensin II improves LVH beyond reducing blood pressure and, consequently, reduces cardiovascular morbidity and death.

Methods We did a double-masked, randomised, parallel-group trial in 9193 participants aged 55–80 years with essential hypertension (sitting blood pressure 160–200/95–115 mm Hg) and LVH ascertained by electrocardiography (ECG). We assigned participants once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction, or stroke). We used Cox regression analysis to compare regimens.

Findings Blood pressure fell by 30-2/16-6 (SD 18-5/10-1) and 29-1/16-8 mm Hg (19-2/10-1) in the losartan and atenolol groups, respectively. The primary composite endpoint occurred in 508 losartan (23-8 per 1000 patient-years) and 583 atenolol patients (27-9 per 1000 patient-years; relative risk 0-87, 95% CI 0-77–0-98, p=0-021). 204 losartan and 588 atenolol patients (27-9 per 1000 patient-years; relative risk 0-87, 95% CI 0-77–0-98, p=0-021) died from cardiovascular disease independent of blood pressure,3 angiotensin II is associated with development of LVH,4 and blocking angiotensin II could be especially effective in reversing LVH.5,6 Experimental5 and clinical6 evidence suggests that blocking the actions of angiotensin II might confer protective benefits beyond lowering blood pressure. To date, no drug for the treatment of essential hypertension has prevented cardiovascular morbidity and death beyond the reductions in blood pressure achieved with β-blockers and diuretics.1,3,5

Losartan was the first available selective angiotensin-II type 1-receptor antagonist7 and atenolol was chosen as a suitable drug for comparison with losartan because it was recognised worldwide as a first-line treatment for hypertension with similar antihypertensive efficacy to losartan8 and benefits for hypertension treatment and secondary cardiovascular protection.9,10–13 Hydrochlorothiazide can be added to both drugs in case of insufficient reduction in blood pressure. The primary hypothesis of the LIFE study was that selective angiotensin-II type 1-receptor antagonism with losartan would be more effective than β-blockade with atenolol in reducing cardiovascular morbidity and death in patients with essential hypertension and signs of LVH. LIFE is an investigator-initiated, double-masked, double-dummy, randomised comparison of the long-term effects of losartan with atenolol in patients with hypertension and LVH. The primary endpoint was cardiovascular morbidity and death, a composite endpoint of cardiovascular death, myocardial infarction, and stroke. Other outcome measures were total...
mortality, angina pectoris or heart failure requiring admission to hospital, coronary or peripheral revascularisation procedures, resuscitated cardiac arrest, and new-onset diabetes mellitus.

Methods

Participants

The complete study protocol with design, organisation, clinical measures, endpoint definitions, basis for choice of comparative agent, statistical power calculations, recruitment details, baseline characteristics, and 1-year follow-up results for the LIFE population have been published.2,14,15

We included patients aged 55–80 years, with previously treated or untreated hypertension and ECG signs of LVH. We excluded patients with secondary hypertension; myocardial infarction or stroke within the previous 6 months; angina pectoris requiring treatment with β-blockers or calcium-antagonists; heart failure or left ventricular ejection fraction of 40% or less; or a disorder that, in the treating physician’s opinion, required treatment with losartan or another angiotensin–II type 1-receptor antagonist, atenolol or another β-blocker, hydrochlorothiazide, or angiotensin-converting-enzyme inhibitors. We randomly assigned participants losartan-based or atenolol-based regimens after 1–2 weeks of based or atenolol-based regimens after 1–2 weeks of placebo if trough sitting blood pressures were 160–200 mm Hg systolic, 95–115 mm Hg diastolic, or both. The trial protocol was approved by all local ethics committees and done in accordance with the Declaration of Helsinki. The study was overseen by an independent data and safety monitoring board.2 All participants gave written informed consent.

Procedures

We followed up patients for at least 4 years with regular visits and increases in drug doses to reach a target blood pressure of less than 140/90 mm Hg (figure 1). All screening, baseline, serial, yearly, and endpoint electrocardiograms were centrally assessed for signs of LVH and Minnesota coded at one reading centre. Because combined ECG assessment of QRS voltage and duration enhances sensitivity for detection of LVH at acceptable levels of specificity,16,17 we used the product of QRS duration and Cornell voltage (with adjustment of 8 mm in women16 and a partition value of >2440 mm·ms) to recognise LVH. For patients recruited after April 30, 1996 (n=7708) we reduced adjustment of Cornell voltage to 6 mm in women and accepted a Sokolow-Lyon voltage of greater than 38 mm as an alternative LVH criterion.2,19,20

In a pilot study for LIFE, almost 25% of treated patients with hypertension aged 55–80 years showed signs of LVH by our ECG criteria.1 These composite ECG criteria have about 95% specificity in healthy people and 50% sensitivity in patients with LVH ascertained at necropsy or by echocardiography LVH. From these data we estimated (and later confirmed)17 that at least 70% of patients who met our ECG criteria from one screening electrocardiogram had anatomical LVH.

An endpoint classification committee of two masked clinicians reviewed clinical records of all cardiovascular events reported by clinical centres to determine whether they met endpoint criteria. The committee used results from Minnesota coding of electrocardiograms by the core laboratory for the presence and serial evolution of signs of myocardial infarction or other disorders. Disagreements about classification of endpoints were resolved by joint in-person reviews. Deaths were reported separately and directly to the independent data and safety monitoring board for validation.

We also measured serum and plasma concentrations, in two central laboratories, of haemoglobin, creatinine, alanine aminotransferase, glucose, uric acid, sodium, potassium, total and HDL cholesterol, and urine concentrations of albumin and creatinine. The ECG core centre also assessed silent or unrecognised myocardial

![Figure 1: Titration schedule and electrocardiography criteria](HCTZ=hydrochlorothiazide)
Sitting blood pressure was measured at trough (ie, 24 h after drug dose, range 22–26 h). Adverse experiences, classed as drug-related or non-drug related and serious or non-serious, were monitored throughout the study.

Follow-up of endpoints was stopped when sufficient primary endpoints for study power were predicted to have occurred (Sept 16, 2001, at 2400 h local time). After the end date, patients had a follow-up clinic visit or at least a vital status check within 6 weeks. All clinical data were verified from source documents before addition to a laptop-based remote data-entry system by field monitors and electronic transfer to a central database.

**Statistical methods**

For detection of a relative difference between treatment groups of at least 15% with 80% power with a two-sided 5% level of significance, we planned to continue the study until at least 1040 patients experienced a primary endpoint (but until at least 4 years after the last patient was enrolled). The planned sample size of 8300 patients was based on projection of a 15% 5-year event rate in the atenolol group (12·75% in the losartan group) and designed to include 1040 primary endpoints within 4 years from enrolment of the last patient.

Allocation numbers were associated with treatment groups by use of a computer-generated allocation schedule; we classed patients as assigned to a group when they had received an allocation number. All patients received masked losartan and masked atenolol, one active and one placebo tablet.

Analysis of all cardiovascular endpoints was by intention to treat; all randomised patients were included in their treatment groups, and all available follow-up data were included from randomisation to the end of the study. Analysis of the primary composite endpoint was confirmed with an on-treatment approach that censored endpoints from patients 14 days after the study drug was permanently stopped. We excluded endpoints not confirmed by the endpoint committee. Patients who underwent more than one endpoint event were counted as having had an event in all relevant endpoint analyses; however, only the first event in a specific category was counted in individual analyses. Safety analyses included all

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Losartan (n=4605)</th>
<th>Atenolol (n=4588)</th>
<th>All (n=9193)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>66·9 (7·0)</td>
<td>66·9 (7·0)</td>
<td>66·9 (7·0)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>2487 (54%)</td>
<td>2476 (54%)</td>
<td>4963 (54%)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4258 (92%)</td>
<td>4245 (93%)</td>
<td>8503 (92%)</td>
</tr>
<tr>
<td>Black</td>
<td>270 (6%)</td>
<td>263 (6%)</td>
<td>533 (6%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>47 (1%)</td>
<td>53 (1%)</td>
<td>100 (1%)</td>
</tr>
<tr>
<td>Asian</td>
<td>25 (0·5%)</td>
<td>18 (0·4%)</td>
<td>43 (0·5%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (0·1%)</td>
<td>9 (0·2%)</td>
<td>14 (0·2%)</td>
</tr>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>174·3 (14·2)</td>
<td>174·5 (14·4)</td>
<td>174·4 (14·3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>97·9 (8·8)</td>
<td>97·7 (9·0)</td>
<td>97·8 (8·9)</td>
</tr>
<tr>
<td>Heart rate (bpm)*</td>
<td>73·9 (11·0)</td>
<td>73·7 (11·2)</td>
<td>73·8 (11·1)</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>28·0 (4·8)</td>
<td>28·0 (4·8)</td>
<td>28·0 (4·8)</td>
</tr>
<tr>
<td>Framingham voltage-duration product (mm×ms)*</td>
<td>2824·1 (1033·3)</td>
<td>2828·1 (1049·5)</td>
<td></td>
</tr>
<tr>
<td>Framingham risk score*</td>
<td>0·225 (0·096)</td>
<td>0·225 (0·096)</td>
<td>0·224 (0·096)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular disease</td>
<td>1203 (26%)</td>
<td>1104 (24%)</td>
<td>2307 (25%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>771 (17%)</td>
<td>698 (15%)</td>
<td>1469 (16%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>369 (8%)</td>
<td>359 (8%)</td>
<td>728 (8%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>276 (6%)</td>
<td>244 (5%)</td>
<td>520 (6%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>150 (3%)</td>
<td>174 (4%)</td>
<td>324 (4%)</td>
</tr>
<tr>
<td>Isolated systolic hypertension†</td>
<td>660 (14%)</td>
<td>666 (15%)</td>
<td>1326 (14%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>586 (13%)</td>
<td>609 (13%)</td>
<td>1195 (13%)</td>
</tr>
</tbody>
</table>

Bpm=beats per minute. BMI=body mass index. Data are number (%) unless otherwise indicated. *Data are mean (SD). †Definition >160/<90 mm Hg.
patients from the time of randomisation to the end of the study, or to the point at which the study drug was permanently stopped, whichever came first.

The difference between treatment groups with respect to clinical events was assessed by a Cox regression model with degree of LVH (measured as a continuous variable) and the Framingham risk score defined by baseline characteristics as covariates. We chose this adjusted analysis before the start of the study to account for baseline differences in risk predictors. We did a secondary unadjusted analysis to validate the adjusted results. Treatment effects were measured by hazard ratios (relative risks) and 95% CIs by Cox regression models. The risk reduction for losartan against atenolol was calculated as Kaplan-Meier curves. Adjustment for blood pressure and the Framingham risk score defined by baseline characteristics as covariates. We chose this adjusted analysis to validate the adjusted results.

Role of the funding source
Study data are in a Merck database. Merck provided the paper and the outcome was validated independently by the steering committee statistician. Differences between groups in changes in ECG measures of LVH were analysed with the Wilcoxon rank-sum test, and the frequency of adverse experiences with Fisher’s exact test.

The independent data and safety board monitored the interim results of the trial. To adjust for two interim efficacy analyses (after one of three and two of three primary events), the final analysis of the primary endpoint variable was tested at a two-sided 4.6% significance level. All other tests were done at two-sided 5% significance levels.

Table 2: Number of participants on study drug at endpoint or end of follow-up

<table>
<thead>
<tr>
<th>Drug doses</th>
<th>Losartan (n=4605)</th>
<th>Atenolol (n=4588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg only</td>
<td>508 (11%)</td>
<td>588 (13%)</td>
</tr>
<tr>
<td>50 mg plus additional drugs*</td>
<td>204 (9%)</td>
<td>234 (5%)</td>
</tr>
<tr>
<td>100 mg with or without additional drugs*</td>
<td>37 (2%)</td>
<td>97 (2%)</td>
</tr>
</tbody>
</table>

*Including hydrochlorothiazide (HCTZ).

Table 3: Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Losartan (n=4605)</th>
<th>Atenolol (n=4588)</th>
<th>Adjusted hazard ratio (95% CI)†</th>
<th>p</th>
<th>Unadjusted hazard ratio (95% CI)†</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>508 (11%)</td>
<td>588 (13%)</td>
<td>0.87 (0.77–0.98)†</td>
<td>0.021</td>
<td>0.85 (0.76–0.96)†</td>
<td>0.009</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>204 (9%)</td>
<td>234 (5%)</td>
<td>0.89 (0.73–1.07)</td>
<td>0.206</td>
<td>0.87 (0.72–1.05)†</td>
<td>0.136</td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (2%)</td>
<td>97 (2%)</td>
<td>0.75 (0.63–0.89)</td>
<td>0.001</td>
<td>0.74 (0.63–0.88)†</td>
<td>0.006</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>37 (2%)</td>
<td>97 (2%)</td>
<td>1.07 (0.88–1.31)</td>
<td>0.491</td>
<td>1.05 (0.86–1.28)†</td>
<td>0.628</td>
</tr>
<tr>
<td>Other prespecified endpoints</td>
<td>37 (2%)</td>
<td>97 (2%)</td>
<td>0.90 (0.78–1.03)</td>
<td>0.128</td>
<td>0.88 (0.77–1.01)†</td>
<td>0.077</td>
</tr>
</tbody>
</table>

*Per 1000 patient-years of follow-up. †For degree of left ventricular hypertrophy and Framingham risk score at randomisation. ‡Cardiovascular mortality, stroke, and myocardial infarction (numbers of patients with a first primary event). §In patients without diabetes at randomisation (losartan, n=4019; atenolol, n=3979).

Table 3: Endpoints

Figure 3: Blood pressure during follow-up

9222 participants were assigned to treatment groups. 9193 were available for final analyses (figure 2)—this figure is given as 9194 in reference 15, however, one patient had wrongly been identified as randomised despite not receiving study drugs. We enrolled patients from June, 1995, to May 2, 1997, from 945 centres in Denmark (1391), Finland (1485), Iceland (133), Norway (1415), Sweden (2245), UK (817), and the USA (1707). Primary endpoints occurred in 1096 patients in 44 119 patient-years of follow-up. Table 1 shows that groups were closely matched with respect to demographic characteristics, severity of hypertension, prevalence of coexisting cardiovascular conditions, Framingham risk score, and ECG-LVH criteria.

Mean follow-up (from randomisation to death, loss to follow-up, or end of study) was 4.8 years (SD 0.9). Patients remained on study drugs for 84% and 80% of the losartan and atenolol groups, respectively. Table 2 shows the distribution of study drugs at the end of follow-up or at occurrence of the first primary endpoint, if earlier. The distribution of additional drugs on top of masked study drug and hydrochlorothiazide did not differ between groups. Mean doses of losartan and atenolol in patients who stayed on study drugs until the end of study were 82 (24) and 79 mg (26), respectively. Figure 3 shows that blood pressures were reduced substantially in both groups. Sitting systolic blood pressure at end of follow-up or at last visit before a primary endpoint occurred, if one did, fell by 30–60 mm Hg (19–22) in losartan and atenolol groups, respectively (treatment difference p=0.017). Sitting diastolic blood pressure was reduced by 16·6 (10·1) and 16·8 mm Hg (10·1), respectively.
among other prespecified endpoints (table 3), there was a 25% lower incidence of new-onset diabetes in the losartan than the atenolol group. There was also a trend for lower total mortality with losartan (table 3). The trend for non-cardiovascular mortality was also lower in the losartan group. No particular cause of death was predominantly affected.
Table 4: Adverse events

Table 4 shows prespecified adverse events and adverse events with a frequency of more than 5% in at least one treatment group and a difference of at least 1% between groups. Discontinuation as a result of all adverse events, drug-related adverse events, and serious and serious drug-related adverse events were significantly less common in losartan than atenolol patients (figure 6).

Table 5 shows changes in biochemical variables at end of study.

At end of study, mean Cornell voltage-duration product was reduced by 290 (733) and 124 mm×ms (807), respectively, in losartan and atenolol groups; and Sokolow-Lyon voltage was reduced by 4.6 (6.7) and 2.7 mm (6.9), respectively. Figure 7 shows the percentage reductions of each ECG-criterion at end of study.

Discussion

Our results show that losartan, an angiotensin II type 1-receptor antagonist, was better than atenolol in reducing the frequency of the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction. The reduction of the primary composite end-point of cardiovascular morbidity and mortality was significant both before (14.6%, p=0.009) and after (13.0%, p=0.021) adjustment for Framingham risk score and ECG-LVH degree at baseline. There was substantial blood-pressure reduction with both drugs, with small differences between groups in systolic and diastolic pressures but not in mean arterial pressure. Further adjustment of the main outcome for changes in systolic, diastolic, or mean arterial pressure yielded no appreciable change in reduction of the main end-point. Additionally, our results contrast with those from other studies comparing angiotensin-converting enzyme inhibitors, calcium-antagonists, and ?-blockers with ?-blockers, diuretic drugs, or both, in which primary outcome did not differ between treatment groups.1,4 Our results show that losartan reduces cardiovascular morbidity and mortality more than an established antihypertensive drug (atenolol).

Losartan substantially reduced the rate of fatal and non-fatal stroke more than other drugs.1 A 25% further reduction in stroke with losartan is important since stroke is a major cause of death and disability and was more frequent than myocardial infarction in our study and others during the past decade.14 That losartan could have a significant effect on stroke over and above blood pressure extends the results of the placebo controlled HOPE trial,7 which suggested that angiotensin-converting-enzyme inhibitors protect against stroke beyond reducing blood pressure. Furthermore, LVH (both on ECG and echocardiography) is a blood-pressure-independent predictor for cerebrovascular events.25

The lower rate of new-onset diabetes (difference of 25%) with losartan confirms studies with angiotensin-converting-enzyme inhibitors,7,26 and may be due to a differential effect on insulin resistance. Incidence of myocardial infarction did not differ between losartan and atenolol groups. This result is encouraging since reduction of heart rate, and hence myocardial oxygen demand, is generally thought to contribute to the cardioprotective properties of ?-blockers11,13 and might have outweighed beneficial coronary vascular effects of losartan.27

A frequent limitation in antihypertensive treatment is that up-titration of drugs to obtain better blood-pressure control increases side-effects, thereby reducing patients’
compliance. The lower rate of adverse events with losartan resulted in greater tolerability than atenolol. As a result, more patients in the losartan than in the atenolol group remained on masked drugs until the end of the study, which could have immediate implications for clinical practice.

One main reason for our choice of atenolol as the comparative agent was that β-blockade alone, or in combination with diuretics, had been shown to be better than placebo in trials of antihypertensive drugs and of secondary prevention in survivors of myocardial infarction.1,3–11 In the STOP-trial,16 in which β-blockers (including atenolol) and diuretics were compared with placebo, there was a 40% reduction of the primary composite endpoint of cardiovascular morbidity and mortality, with an event rate similar to that in our atenolol group. In other placebo-controlled studies of primary and secondary prevention, β-blockade or β-blocker-based regimens reduced rates of many cardiovascular events by 15–45%. Thus, the further 13%–0% reduction of the primary endpoint by losartan in our trial should be seen as an incremental benefit above the established effects of β-blockade.

Several mechanisms merit discussion. First, despite the central importance of blood pressure in the complications of hypertension, additional adjustment of the main our results are directly applicable in clinical practice and should affect future guidelines.

Contributors
The authors are the LIFE Steering Committee. All authors contributed to the writing of this paper.

LIFE committees
Endpoint committee—Daniel Levy (USA), Kristian Thynge (Denmark). Data safety and monitoring board—John Kjekshus (Norway), Lewis Kuller (USA), Pierre Larochelle (Canada), Giuseppe Mancia (Italy), Joel Minard (France), Stuart Pocock (UK), John Reid (UK), Michael Weber (USA). ECG core center (Clinical Experimental Research Laboratory, Department of Medicine, Safi/rjers Hospital/Ostra, Gothenburg, Sweden)—Sverker Jern, Eva Thydén, Agneta Frazer, Anna Johansson, Hannele Korhonen, Margareta Lejon, Christina Linner. Clinical data management
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Steve Snapinn (Merck research laboratories, West Point, PA, USA).

Figure 7: Change in Cornell voltage-duration product and Sokolow-Lyon from baseline

<table>
<thead>
<tr>
<th>Cornell product</th>
<th>Sokolow-Lyon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (%)</td>
<td><strong>p=0.0001</strong></td>
</tr>
</tbody>
</table>

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18 Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer electrocardiogram interpretation: necropsy validation. Circulation 1987; 75: 565–72.


27 Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986; 57: 43F–49F.


Conflict of interest statement
K Kristiansson is a Merck employee and was a non-voting member of the steering committee.

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References


4 Brunner HR. Experimental and clinical evidence that angiotensin II is an independent risk factor for cardiovascular disease. Am J Cardiol 2001; 87 (8A): 3C–9C.


10 Dahlöf B, Keller SE, Makris L, Goldberg AI, Sweet CS, Lim NY. Efficacy and tolerability of losartan potassium and atenolol in patients