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

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Summary

Background The most suitable antihypertensive drug to reduce the risk of cardiovascular disease in patients with hypertension and diabetes is unclear. In prespecified analyses, we compared the effects of losartan and atenolol on cardiovascular morbidity and mortality in diabetic patients.

Methods As part of the LIFE study, in a double-masked, randomised, parallel-group trial, we assigned a group of 1195 patients with diabetes, hypertension, and signs of left-ventricular hypertrophy (LVH) on electrocardiograms losartan-based or atenolol-based treatment. Mean age of patients was 67 years (SD 7) and mean blood pressure 177/96 mm Hg (14/10) after placebo run-in. We followed up patients for at least 4 years (mean 4.7 years [1.1]). We used Cox regression analysis with baseline Framingham risk score and electrocardiogram-LVH as covariates to compare the effects of the drugs on the primary composite endpoint of cardiovascular morbidity and mortality (cardiovascular death, stroke, or myocardial infarction).

Findings Mean blood pressure fell to 146/79 mm Hg (17/11) in losartan patients and 148/79 mm Hg (19/11) in atenolol patients. The primary endpoint occurred in 103 patients assigned losartan (n=586) and 139 assigned atenolol (n=609); relative risk 0.76 (95% CI 0.58–0.98), p=0.031. 38 and 61 patients in the losartan and atenolol groups, respectively, died from cardiovascular disease; 0.63 (0.42–0.95), p=0.028. Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; 0.61 (0.45–0.84), p=0.002.

Interpretation Losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes in patients with hypertension, diabetes, and LVH. Losartan seems to have benefits beyond blood pressure reduction.

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See Commentary page 990

Introduction

The Losartan Intervention For Endpoint reduction (LIFE) study was designed in the early 1990s when no drug class for the treatment of essential hypertension had been shown to be more effective in prevention of cardiovascular morbidity and mortality than β-blockers and diuretics. The main hypothesis of LIFE 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 mortality in patients with essential hypertension and signs of left ventricular hypertrophy (LVH) on electrocardiograms.

Diabetes mellitus doubles the risk of cardiovascular disease, even in patients with hypertension who are already at high risk because of their high blood pressure. Since many patients with hypertension develop diabetes, this combination of risk factors will account for a large proportion of cardiovascular morbidity and mortality. The frequency of diabetes mellitus is increasing rapidly worldwide. In the LIFE study, we compared the long-term effects of once-daily losartan-based with atenolol-based antihypertensive treatment in patients with hypertension and LVH on the frequency of cardiovascular morbidity and mortality (a composite of cardiovascular mortality, stroke and myocardial infarction). The most suitable drug to prevent premature cardiovascular disease in diabetic patients with high blood pressure is unclear. Therefore, we analysed the outcome in the prespecified subgroup of patients who had diabetes mellitus at the start of the LIFE study.

Methods

Patients and procedures

The LIFE study was a double-masked, randomised, parallel-group study with double dummy drugs. The main outcome and the complete study protocol with study design, organisation, clinical measures, endpoint definitions, exclusion criteria, reasons for choice of comparative agents, statistical power calculations, and baseline characteristics have been published. We included patients aged 55–80 years with hypertension (either treated or untreated) and signs of LVH on electrocardiograms. We gave patients placebo drugs for 1–2 weeks after which we assigned them to treatment groups if they had a sitting systolic blood pressure of 160–200 mm Hg, a diastolic pressure of 95–115 mm Hg, or both. In both groups, we added hydrochlorothiazide and...
other agents (but not \(\beta\)-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin-II antagonists) if blood pressure remained high during follow-up.\(^1\) 1195 (13%) of 9193 LIFE participants had a diagnosis of diabetes mellitus (most likely of type-2) at baseline. We randomly assigned 586 participants to losartan and 609 to atenolol. Figure 1 shows the trial profile and table 1 shows baseline characteristics. 767 (64%) participants came from the Nordic countries, 365 (31%) from the USA, and 63 (5%) from the UK. 86% were white. Before the start of the study, 958 patients had been treated with antihypertensive drugs, 472 (81%) in the losartan group and 486 (80%) in the atenolol group.

At baseline, antidiabetic drugs, insulin, or both, had been given to 669 (56%) patients: 323 in the losartan and 346 in the atenolol group. 526 (44%) had received oral drugs (sulphonylureas, biguanides, or both) and 186 (16%) insulin (table 2). We gave all patients who were not on these drugs non-pharmacological treatment during the study; additionally, 139 of the remaining 263 losartan patients and 136 of the remaining 263 atenolol patients started taking antidiabetic drugs during follow-up. 124 (21%) losartan patients and 127 (21%) atenolol patients were not treated with antidiabetic drugs or insulin during the trial. Groups were also well balanced for treatment with lipid-lowering drugs and aspirin during the study (table 2). Treatment for diabetes was at the discretion of patients' physicians.

We enrolled patients from June, 1995, to May, 1997, if a screening electrocardiogram fulfilled criteria for LVH.\(^1\) We followed up patients for at least 4 years with regular visits and upward-titration of study drugs to reduce blood pressure to below 140/90 mm Hg. We defined diabetes mellitus according to the 1985 WHO criteria.\(^8\) After the study end date in September, 2001, patients had a follow-up clinic visit or at least a vital status check within 6 weeks. Tests were done at two laboratories that assured comparability of measurements by crossvalidation, and all electrocardiograms were coded at the same electrocardiogram core centre.\(^1\) We recorded sitting blood pressure 24 h after study drug dose (range 22–26).

**Statistical analysis**

We assessed all endpoints by intention-to-treat analysis. We included all randomised patients and all available follow-up data from randomisation to the study end.
date. We included endpoints in analyses only if confirmed by the endpoint committee. We classified patients with more than one endpoint as having had an event in all relevant endpoint analyses; however, we counted only the first event in a specific category in individual analyses. We assessed the difference between treatment groups with respect to clinical events with a Cox regression model with degree of LVH (measured by voltage) and the Framingham risk score at baseline as covariates. We chose this adjusted analysis before the trial to account for any difference in key risk predictors at baseline. We also did a secondary unadjusted analysis. We measured treatment effects by hazard ratios (relative risks) and 95% CIs derived from Cox regression models. We calculated the risk reduction for losartan versus atenolol as 100 × (1–relative risk). We adjusted results for blood pressure according to Cox regression models with blood pressures throughout the trial as time-varying covariates. We analysed differences between groups in changes in electrocardiogram measures of LVH with the Wilcoxon rank-sum test, and the frequency of adverse experiences with Fisher’s exact test. The level of two-sided significance was 5%.

Role of the funding source
Study data are in a Merck database. Merck provided the study steering committee with free access to all data. The steering committee was free to interpret data and write the paper and the outcome was validated independently by the steering committee. Merck reviewed the paper.

Results
Groups were closely matched in demographic characteristics, severity of hypertension, prevalence of coexisting cardiovascular conditions, Framingham risk score, and electrocardiogram-based LVH criteria (table 1). Compared with the remaining LIFE participants without diabetes, patients with the disease had higher body-mass index, higher Framingham risk score, a higher prevalence of cardiovascular disease at baseline (table 1), higher systolic blood pressure (difference 3 mm Hg), lower diastolic pressure (2 mm Hg), higher pulse pressure (5 mm Hg), and higher serum glucose concentration (9·6 [SD 3·8] vs 5·5 [1·0] mmol/L). Fewer patients with diabetes smoked than other LIFE participants.1

Primary endpoints occurred in 242 (20%) patients during 5596 patient-years of follow-up (table 3): 103 in the losartan group (39·2 per 1000 patient-years) and 139 in the atenolol group (53·6), relative risk 0·76 (95% CI 0·58–0·98), p=0·031. 63 losartan patients (22·5 per 1000 patient-years) and 104 in the atenolol group (37·2) died from all causes (0·61, 0·45–0·84, p=0·002). 38 (13·6 per 1000 patient-years) and 61 patients (21·8) in the losartan and atenolol groups, respectively, died from cardiovascular disease (0·63, 0·42–0·95, p=0·028, table 3). Stroke occurred in 51 losartan and 65 atenolol patients (p=0·205), and myocardial infarction in 41 and 50 patients, respectively (p=0·373). 32 patients were admitted to hospital for heart failure (11·8 per 1000 patient-years) in the losartan group and 55 (20·7) in the atenolol group (0·59, 0·38–0·92, p=0·019). Figure 2 shows Kaplan-Meier curves for the primary composite endpoint, and figures 3 and 4 show Kaplan-Meier curves for individual endpoints and total mortality, respectively. Adjustment for baseline Framingham risk score and LVH had little effect on results (table 3). There was no evidence of interaction between treatment and sex for any of the endpoints.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Losartan (n=586)</th>
<th>Atenolol (n=609)</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>Losartan</td>
<td>Atenolol</td>
<td></td>
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<td></td>
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<tr>
<td>Primary composite endpoint</td>
<td>Rate† n</td>
<td>Rate† n</td>
<td>hazard ratio (95% CI) p</td>
<td></td>
<td>hazard ratio (95% CI) p</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>53·6 (193)</td>
<td>61 (100)</td>
<td>0·76 (0·58–0·98) 0·031</td>
<td>0·73 (0·57–0·95) 0·017</td>
<td></td>
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<tr>
<td>Stroke (all)</td>
<td>24·5 (11·9)</td>
<td>65 (11%)</td>
<td>0·79 (0·55–1·14) 0·204</td>
<td>0·78 (0·54–1·13) 0·190</td>
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<tr>
<td>Myocardial infarction (all)</td>
<td>18·7 (10%)</td>
<td>50 (8%)</td>
<td>0·83 (0·55–1·25) 0·373</td>
<td>0·81 (0·54–1·22) 0·318</td>
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<td></td>
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<tr>
<td>Other prespecified endpoints</td>
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<td></td>
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<tr>
<td>Total mortality</td>
<td>152 (47·7%)</td>
<td>16·2 (5·7%)</td>
<td>1·06 (0·64–1·76) 0·828</td>
<td>1·00 (0·60–1·66) 0·989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to hospital for</td>
<td></td>
<td></td>
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<tr>
<td>Angina pectoris</td>
<td>11·1 (30%)</td>
<td>11·1 (30%)</td>
<td>0·59 (0·38–0·92) 0·019</td>
<td>0·57 (0·37–0·89) 0·013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>11·8 (32%)</td>
<td>20 (59)</td>
<td>0·90 (0·64–1·26) 0·533</td>
<td>0·88 (0·63–1·24) 0·470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisation</td>
<td>23·5 (62%)</td>
<td>26·6 (70%)</td>
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</tbody>
</table>

*For degree of left-ventricular hypertrophy and Framingham risk score at randomisation.
We assigned patients with diabetes and untreated hypertension at baseline (n=237) to losartan (n=114) or atenolol (n=123). In this subgroup, the primary composite endpoint occurred in 17 (33·3 per 1000 patient-years) losartan and 34 atenolol patients (64·7), four (7·2) and 15 (26·6) died from cardiovascular disease, and five (9·1) and 24 (42·6) died from all causes, respectively.

Mean follow-up from randomisation to death, loss to follow-up, or end of the study was 4·7 years (1·1). The proportion of patients who were given additional drugs to the study drug and hydrochlorothiazide did not differ between groups. Table 4 shows that at the end of the trial, more patients in the atenolol group than in the losartan group had stopped taking the study drug (p=0·076).

Systolic, diastolic, and mean blood pressures fell substantially in both groups (figure 5). Mean blood pressure at the last visit before a primary endpoint, or at the end of follow-up, was 146/79 (17/11) and 148/79 mm Hg (19/11) in the losartan and atenolol groups, reductions of 31/17 (19/11) and 28/17 mm Hg (21/11), respectively. 499 (85%) losartan and 497 (82%) atenolol patients had diastolic blood pressure less than 90 mm Hg at the end of the study. 220 (38%) losartan and 205 (34%) atenolol patients had systolic blood pressure below 140 mm Hg; these results were not much different in LIFE patients without diabetes.

Mean arterial blood pressure at the end of the study was 101 (11) and 102 mm Hg (12) in losartan and atenolol groups, respectively. Adjustment for blood pressure during follow-up had little effect on the endpoint results (data not shown).

Fewer patients in the losartan group (2 [0·3%]) stopped taking the study drug because of serious drug-related adverse events than in the atenolol group (9 [2%], p=0·065). Tables 5 and 6 show results for selected adverse events and biochemical measurements, respectively. Albuminuria was reported less frequently (p=0·002) as an adverse event in the losartan than in the atenolol group (table 5). Serum glucose concentrations remained high throughout the study (figure 6, table 6),
and did not differ significantly between the groups (p=0.087). Table 7 shows serum creatinine concentrations and the number (%) of diabetic patients with clinical albuminuria.

Mean Cornell voltage-duration product fell more (p=0.0001) in the losartan group (8.4% reduction) than in the atenolol group (0.6%), and Sokolow-Lyon voltage decreased by 13.6% and 5.6%, respectively (p<0.0001, figure 7).

Discussion

Our results show that losartan was better than atenolol in reducing the risk of cardiovascular morbidity and mortality in patients with diabetes and hypertension. Results were especially marked in the small group (20%) of patients who had not been treated for hypertension before the study. We emphasise that we decided before the start of the study to adjust results for the Framingham risk score and degree of LVH to account for any difference in key risk predictors at baseline and thus accounted for the baseline differences between treatment groups. The LIFE study, although designed as a trial in patients with hypertension and LVH, was also a correctly randomised study with respect to the prespecified subgroup of patients with diabetes.

In terms of achieving reductions in cardiovascular morbidity and mortality, the benefits of treating hypertension in middle-aged and elderly patients with diabetes have been investigated mostly in subgroups of patients in prospective trials.10–13 Although the importance of effective blood pressure control in patients with hypertension and diabetes has been shown in controlled trials,10–13,15,16 the relative benefits of different antihypertensive drugs on the frequency of cardiovascular disease in this group of patients was not certain. Effective lowering of blood pressure may be even more important than glucose control in these patients.10–13 Angiotensin-II antagonists have beneficial renal effects in patients with diabetes and nephropathy.12,13 In our patients, albuminuria was reported significantly less often in the losartan than in the atenolol group.

Our results accord with those of CAPPP14 and to some extent HOPE,15 but differ from those of UKPDS,16 STOP Hypertension-2,17 NORDIL,18 and INSIGHT.19

Table 5: Adverse events

<table>
<thead>
<tr>
<th>Losartan (n=586)</th>
<th>Atenolol (n=609)</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Year 4</strong></td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>143.7 (12.9)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139.8 (2.7)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.16 (0.38)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>31.9 (22.6)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>9.0 (3.54)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.79 (1.11)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.32 (0.35)</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>324.8 (76.1)</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>90.5 (20.2)</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase. Data are mean (SD). *Among patients who also had a value at year 4.

Table 6: Biochemical variables

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that is magnified by hypertension. Furthermore, preliminary evidence suggests that LVH has predictive value for cardiovascular events in patients with diabetes.24,25 Thus, reversal of hypertensive LVH may be associated with improved cardiovascular outcome in these patients. More than half all diabetics have hypertension and LVH is very frequent in this group.26

Despite the fact that more of our patients in the losartan group remained on masked treatment until the end of the study, this difference did not contribute substantially to the effects of the drugs on the composite and individual endpoints (confirmed by an on-drug analysis, data not shown). Since patients were treated without restriction after study drug discontinuation, an open-labelled angiotensin-II antagonist or an angiotension-converting-enzyme inhibitor may have reduced the difference between groups. Therefore, our estimation of treatment differences is conservative.

Serum glucose was high at baseline and remained so in both groups (figure 6). Total cholesterol fell by 0.4 mmol/L in both groups (table 6). Other changes in biochemical measurements were as expected with the drugs involved. Fewer than 40% of all patients attained a systolic blood pressure below 140 mm Hg. The goal for systolic pressure in patients with diabetes was set to below 130 mm Hg in the 1999 WHO/International Society of Hypertension guidelines.23 Thus, the potential for more aggressive treatment to lower blood pressure remains for this group of patients as well as the need for better metabolic control (figure 6, table 7).

Systolic blood pressure during the trial was not associated with any change in risk of the primary composite endpoint and therefore adjustment for this factor had little effect on the results. Thus, the greater cardiovascular protective effect of losartan than atenolol could result from more pronounced blockade of the detrimental effects of angiotensin II. Losartan was more effective than atenolol in reversing LVH (figure 7), which is likely to result from more complete protection against angiotensin II with losartan, whether generated by the circulating renin-angiotensin system or other mechanisms, especially since angiotensin II is a myocardial growth factor and an independent risk factor for cardiovascular disease.27 Hence, the general message to the practising physician is that hypertensive diabetic patients with LVH benefit more from losartan than atenolol.

Contributors
L H Lindholm and H Ibsen were the subcommittee on diabetes. P Aurup, S Snapinn, and J Edelman are researchers at Merck. All other authors were members of the LIFE steering committee and have commented on the manuscript. A full list of the LIFE investigators and committees is given in reference 1.

Conflict of interest statement
K Kristansson is a Merck employee and was a non-voting member of the steering committee. P Aurup, S Snapinn, and J Edelman are employees of Merck.

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