

Articles

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 588 atenolol patients (27.9 per 1000 patient-years; relative risk 0.87, 95% CI 0.77–0.98, $p=0.021$). 204 losartan and 234 atenolol patients died from cardiovascular disease (0.89, 0.73–1.07, $p=0.206$); 232 and 309, respectively, had fatal or non-fatal stroke (0.75, 0.63–0.89, $p=0.001$); and myocardial infarction (non-fatal and fatal) occurred in 198 and 188, respectively (1.07, 0.88–1.31, $p=0.491$). New-onset diabetes was less frequent with losartan.

Interpretation Losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and is better tolerated. Losartan seems to confer benefits beyond reduction in blood pressure.

Lancet 2002; **359**: 995–1003

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Introduction

The benefits of drug intervention in hypertension to reduce blood pressure are well established, especially in high-risk individuals.¹ However, treated patients with hypertension still have significantly higher rates of hypertension-related cardiovascular complications than matched people without hypertension. This anomaly might result from failure to achieve normal blood pressure, residual target organ damage such as left ventricular hypertrophy (LVH), or both.

The Losartan Intervention For Endpoint reduction (LIFE)² study was designed in the early 1990s with consideration of several factors: β -blocker and diuretic antihypertensive drugs do not return rates of cardiovascular morbidity and death to normal in patients with hypertension, LVH is a cardinal manifestation of preclinical cardiovascular disease and an independent risk factor for all cardiovascular complications in hypertension, reversal of LVH has possible prognostic benefits that are 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} Experimental⁴ and clinical⁷ 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.^{1,8}

Losartan was the first available selective angiotensin-II type 1-receptor antagonist⁹ 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 losartan¹⁰ and benefits for hypertension treatment and secondary cardiovascular protection.^{8,11–13} 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

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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 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.

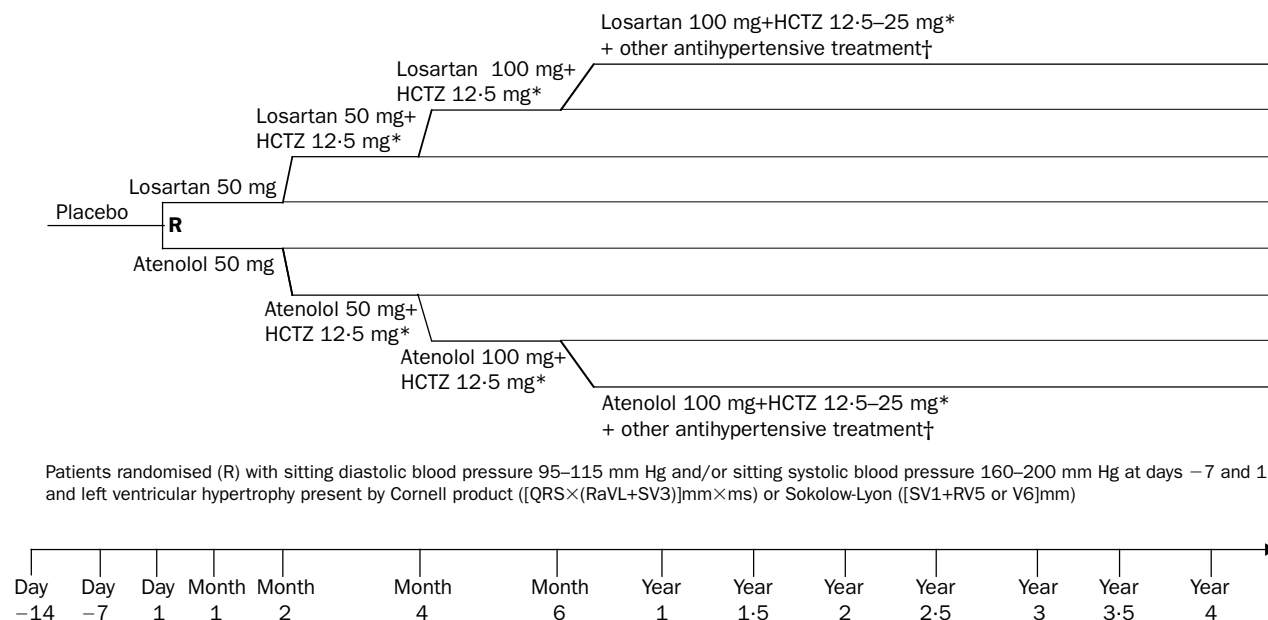
Procedures

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 women¹⁸ and a partition value of >2440 mm \times 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.² 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)²¹ 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



Patients randomised (R) with sitting diastolic blood pressure 95–115 mm Hg and/or sitting systolic blood pressure 160–200 mm Hg at days –7 and 1, and left ventricular hypertrophy present by Cornell product ($(QRS \times (RaVL + SV3))$ mm \times ms) or Sokolow-Lyon ($(SV1 + RV5$ or $V6)$ mm)

*Titration upward if sitting diastolic blood pressure ≥ 90 mm Hg or sitting systolic blood pressure ≥ 140 mm Hg.

†Titration encouraged if sitting diastolic blood pressure ≥ 90 mm Hg or sitting systolic blood pressure ≥ 140 mm Hg but mandatory if sitting blood pressure $\geq 160/95$ mm Hg. Addition of angiotensin-converting-enzyme inhibitors, angiotensin II type 1-receptor antagonists, or β -blockers prohibited.

Figure 1: Titration schedule and electrocardiography criteria

HCTZ=hydrochlorothiazide.

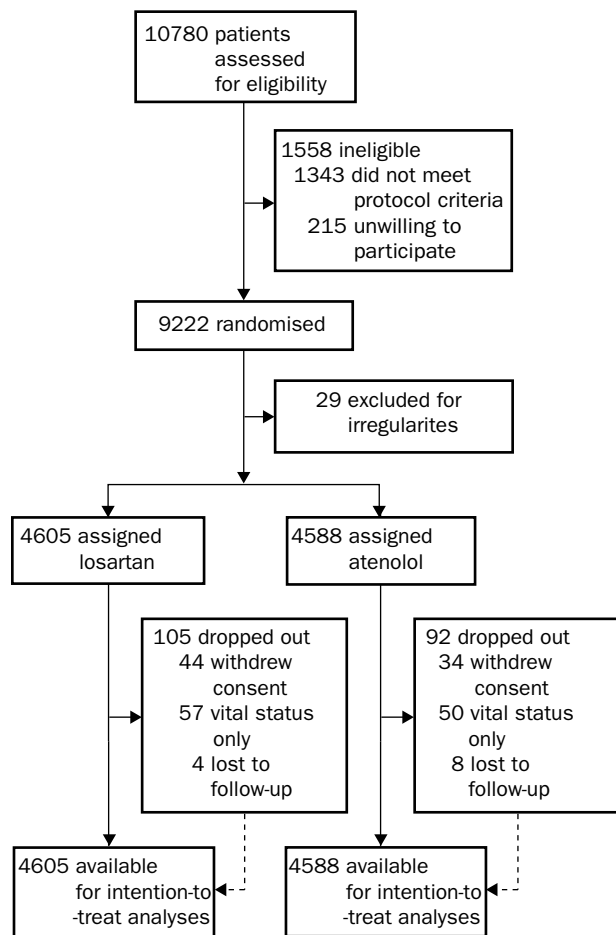


Figure 2: Trial profile

infarctions (data not shown) and regression of LVH. New-onset diabetes, defined according to 1985 WHO criteria,²² was assessed by a subcommittee of the steering committee. 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 group, 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

	Losartan (n=4605)	Atenolol (n=4588)	All (n=9193)
Demographic and clinical characteristics			
Age (years)*	66.9 (7.0)	66.9 (7.0)	66.9 (7.0)
Women	2487 (54%)	2476 (54%)	4963 (54%)
Ethnic origin			
White	4258 (92%)	4245 (93%)	8503 (92%)
Black	270 (6%)	263 (6%)	533 (6%)
Hispanic	47 (1%)	53 (1%)	100 (1%)
Asian	25 (0.5%)	18 (0.4%)	43 (0.5%)
Other	5 (0.1%)	9 (0.2%)	14 (0.2%)
Blood pressure (mm Hg)*			
Systolic	174.3 (14.2)	174.5 (14.4)	174.4 (14.3)
Diastolic	97.9 (8.8)	97.7 (9.0)	97.8 (8.9)
Heart rate (bpm)*	73.9 (11.0)	73.7 (11.2)	73.8 (11.1)
BMI (kg/m ²)*	28.0 (4.8)	28.0 (4.8)	28.0 (4.8)
Cornell voltage-duration product (mm×ms)*	2834.4 (1065.4)	2824.1 (1033.3)	2828.8 (1049.5)
Sokolow-Lyon (mm)*	30.0 (10.6)	30.1 (10.4)	30.0 (10.5)
Framingham risk score*	0.223 (0.095)	0.225 (0.096)	0.224 (0.096)
Current smokers	729 (16%)	770 (17%)	1499 (16%)
Medical history			
Any vascular disease	1203 (26%)	1104 (24%)	2307 (25%)
Coronary heart disease	771 (17%)	698 (15%)	1469 (16%)
Cerebrovascular disease	369 (8%)	359 (8%)	728 (8%)
Peripheral vascular disease	276 (6%)	244 (5%)	520 (6%)
Atrial fibrillation	150 (3%)	174 (4%)	324 (4%)
Isolated systolic hypertension†	660 (14%)	666 (15%)	1326 (14%)
Diabetes	586 (13%)	609 (13%)	1195 (13%)

Bpm=beats per minute. BMI=body mass index. Data are number (%) unless otherwise indicated. *Data are mean (SD). †Definition $\geq 160/ < 90$ mm Hg.

Table 1: Baseline characteristics

	Losartan	Atenolol
Drug doses		
50 mg only	434 (9%)	436 (10%)
50 mg plus additional drugs*	844 (18%)	930 (20%)
100 mg with or without additional drugs*	2284 (50%)	1979 (43%)
Alone	95 (2%)	78 (2%)
With HCTZ only	829 (18%)	713 (16%)
With other drugs only	162 (4%)	172 (4%)
With HCTZ and other drugs	1198 (26%)	1016 (22%)
Off study drugs	1043 (23%)	1243 (27%)

*Including hydrochlorothiazide (HCTZ).

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

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 score²³ 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 $100 \times (1 - \text{relative risk})$. Event rates over time are presented as Kaplan-Meier curves. Adjustment for blood pressure was derived from Cox regression models with blood pressures throughout the trial as time-varying covariates. Results of the primary endpoint analysis were independently validated 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.

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 statistician.

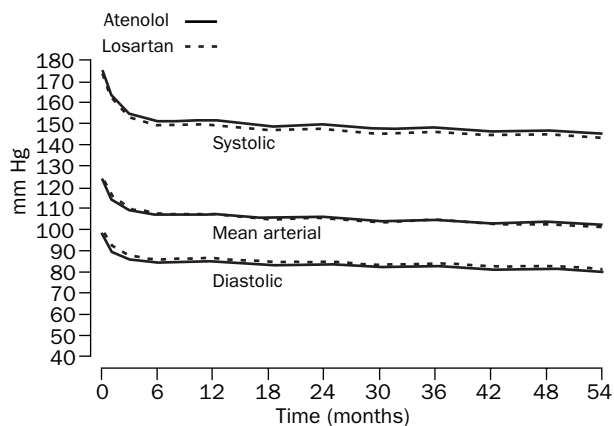


Figure 3: Blood pressure during follow-up

Results

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 follow-up in 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 30.2 (18.5) and 29.1 mm Hg (19.2) 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

Endpoint	Losartan (n=4605)		Atenolol (n=4588)		Adjusted hazard ratio (95% CI)†	p	Unadjusted hazard ratio (95% CI)	p
	n	Rate*	n	Rate				
Primary composite endpoint‡	508 (11%)	23.8	588 (13%)	27.9	0.87 (0.77–0.98)	0.021	0.85 (0.76–0.96)	0.009
Cardiovascular mortality	204 (4%)	9.2	234 (5%)	10.6	0.89 (0.73–1.07)	0.206	0.87 (0.72–1.05)	0.136
Stroke	232 (5%)	10.8	309 (7%)	14.5	0.75 (0.63–0.89)	0.001	0.74 (0.63–0.88)	0.0006
Myocardial infarction	198 (4%)	9.2	188 (4%)	8.7	1.07 (0.88–1.31)	0.491	1.05 (0.86–1.28)	0.628
Other prespecified endpoints								
Total mortality	383 (8%)	17.3	431 (9%)	19.6	0.90 (0.78–1.03)	0.128	0.88 (0.77–1.01)	0.077
Admitted to hospital for:								
Angina pectoris	160 (3%)	7.4	141 (3%)	6.6	1.16 (0.92–1.45)	0.212	1.13 (0.90–1.42)	0.284
Heart failure	153 (3%)	7.1	161 (4%)	7.5	0.97 (0.78–1.21)	0.765	0.95 (0.76–1.18)	0.622
Revascularisation	261 (6%)	12.2	284 (6%)	13.3	0.94 (0.79–1.11)	0.441	0.91 (0.77–1.08)	0.292
Resuscitated cardiac arrest	9 (0.2%)	0.4	5 (0.1%)	0.2	1.91 (0.64–5.72)	0.250	1.80 (0.60–5.36)	0.294
New-onset diabetes§	241 (6%)	13.0	319 (8%)	17.4	0.75 (0.63–0.88)	0.001	0.75 (0.63–0.88)	0.001

*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

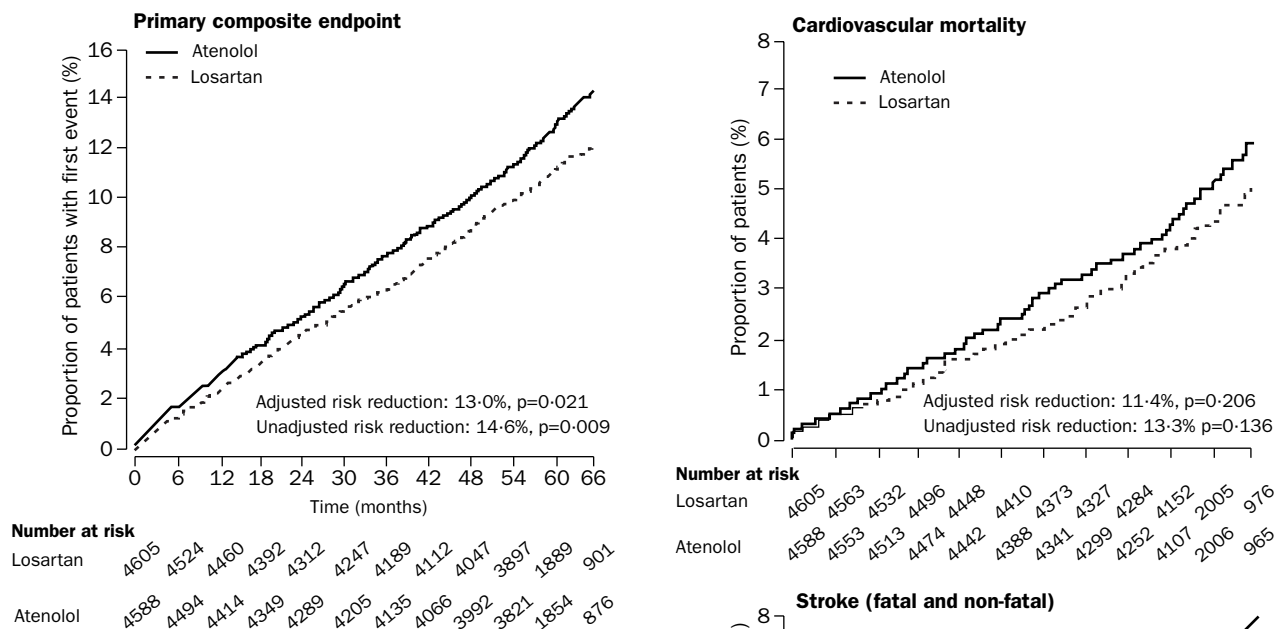


Figure 4: Kaplan Meier curves for primary composite endpoint

(p=0.37). Mean blood pressures at last visit were 144.1/81.3 (17.1/9.6) and 145.4/80.9 mm Hg (16.4/9.6) respectively, in losartan and atenolol groups. Mean arterial pressure was 102.2 and 102.4 mm Hg, respectively (not significant).

Blood pressure of less than or equal to 140/90 mm Hg was achieved in 2268 (49%) and 2099 (46%) losartan and atenolol patients, respectively, for systolic pressure; in 4017 (89%) and 4067 (89%) for diastolic pressure; and in 2196 (48%) and 2051 (45%), for both. Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 [12.8] and -1.8 [12.0] beats per minute, respectively, p<0.0001). Table 3 shows the rates of primary composite and individual endpoints and the relative risks (adjusted and unadjusted) for treatment.

Figure 4 shows Kaplan-Meier curves for the primary composite endpoint and figure 5 shows individual endpoints. For the primary endpoint, the overall 13.0% relative risk reduction on losartan is based on progressive separation of the survival curves over time. This primary result was slightly stronger, 14.6% (p=0.009), if not adjusted for Framingham risk score and ECG LVH at baseline. The curves for stroke also separated early, and the outcome was highly in favour of losartan, showing a 24.9% relative risk reduction compared with atenolol (p=0.001).

An on-treatment analysis as well as adjustment with blood pressure as a time-varying covariate did not change the outcome. An analysis with the ECG indices of LVH as time-varying covariates showed a partial (less than one third) relation with the effect of losartan-based treatment on the primary outcome. In the lower risk category of patients without vascular disease or diabetes, the primary endpoint rates were 232 (8%) of 3022 with losartan and 288 (9%) of 3089 with atenolol (relative risk 0.82, p=0.029).

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.

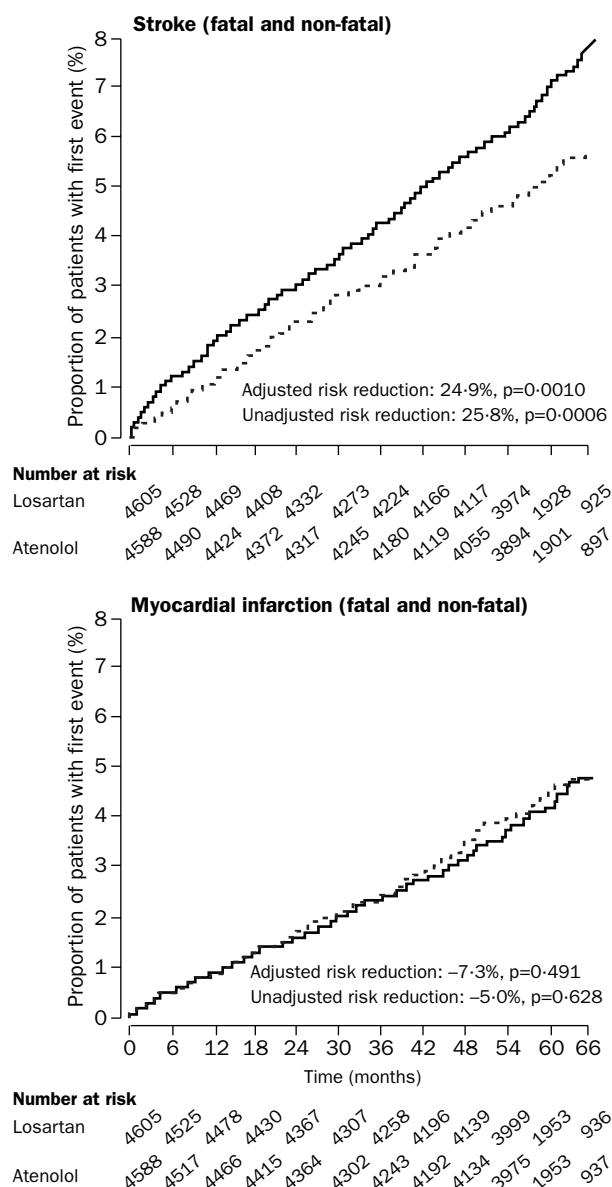


Figure 5: Kaplan-Meier curves for individual endpoints

	Losartan	Atenolol	p
Prespecified adverse events			
Angio-oedema	6 (0.1%)	11 (0.2%)	0.237
Bradycardia	66 (1%)	391 (9%)	<0.0001
Cancer	356 (8%)	315 (7%)	0.118
Cold extremities	178 (4%)	269 (6%)	<0.0001
Cough	133 (3%)	113 (2%)	0.220
Dizziness	771 (17%)	727 (16%)	0.247
Hypotension	121 (3%)	75 (2%)	0.001
Sexual dysfunction	164 (4%)	214 (5%)	0.009
Sleep disturbance	30 (0.7%)	38 (0.8%)	0.333
Additional common* adverse events			
Albuminuria	213 (5%)	293 (6%)	0.0002
Hyperglycaemia	239 (5%)	300 (7%)	0.007
Asthenia/fatigue	691 (15%)	802 (17%)	0.001
Back pain	568 (12%)	477 (10%)	0.004
Chest pain	519 (11%)	463 (10%)	0.068
Dyspnoea	457 (10%)	648 (14%)	<0.0001
Lower extremity oedema	539 (12%)	637 (14%)	0.002
Pneumonia	218 (5%)	269 (6%)	0.018

*An incidence >5% in one of the treatment groups and a difference between treatment groups >1%.

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 (753) 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-

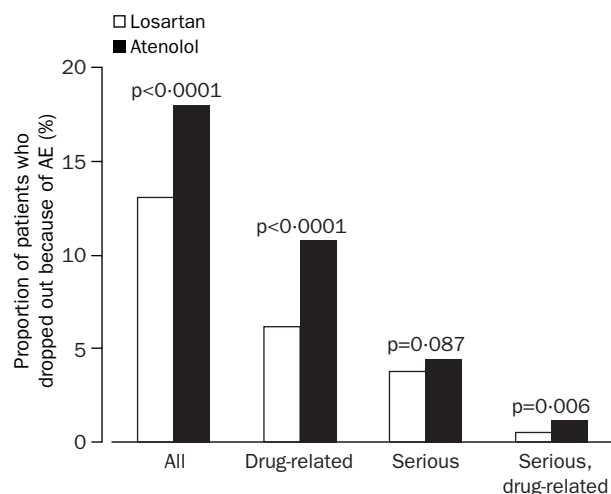


Figure 6: Adverse events (AE)

p is for between-group differences.

enzyme inhibitors, calcium-antagonists, and α -blockers with β -blockers, diuretic drugs, or both, in which primary outcome did not differ between treatment groups.¹⁸ 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.²⁴ 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 β -blockers^{12,13} 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'

	Losartan (n=4605)			Atenolol (n=4588)		
	Baseline	Year 4	Change	Baseline	Year 4	Change
Haemoglobin (g/L)	142.5 (11.8)	138.8 (13.8)	-3.7 (10.8)	142.8 (11.6)	141.5 (13.6)	-1.3 (10.8)
Sodium (mmol/L)	140.3 (2.5)	139.9 (3.1)	-0.5 (3.3)	140.3 (2.5)	140.0 (3.1)	-0.3 (3.4)
Potassium (mmol/L)	4.2 (0.4)	4.1 (0.4)	0.0 (0.4)	4.2 (0.4)	4.1 (0.4)	-0.1 (0.5)
Alanine aminotransferase (IU/L)	28.2 (25.7)	27.0 (18.7)	1.2 (25.5)	28.4 (19.0)	27.6 (17.8)	0.8 (18.7)
Glucose (mmol/L)	6.0 (2.0)	6.2 (2.3)	0.3 (2.2)	6.0 (2.1)	6.3 (2.2)	0.4 (2.2)
Total cholesterol (mmol/L)	6.0 (1.1)	5.7 (1.1)	-0.3 (1.0)	6.1 (1.1)	5.8 (1.1)	-0.3 (1.0)
HDL (mmol/L)	1.50 (0.43)	1.47 (0.38)	-0.03 (0.27)	1.50 (0.44)	1.41 (0.36)	-0.09 (0.27)
Uric acid (μ mol/L)	328.2 (76.9)	347.7 (90.0)	19.5 (72.2)	328.8 (77.1)	375.9 (93.1)	47.2 (76.8)
Creatinine (mmol/L)	85.9 (19.2)	97.0 (25.2)	11.2 (20.4)	85.2 (19.4)	96.2 (24.4)	11.0 (19.7)

Data are mean (SD).

Table 5: Biochemical variables

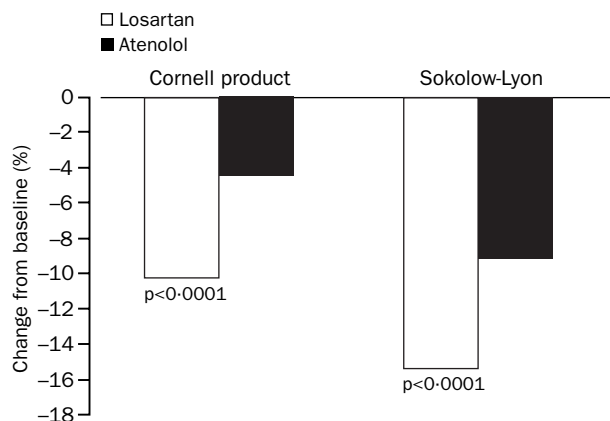


Figure 7: **Change in Cornell voltage-duration product and Sokolow-Lyon from baseline**
p is for between-group differences.

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.^{1,8,11-13} In the STOP-trial,²⁸ 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 outcome for small differences in systolic and diastolic pressure had little effect on the estimate of the benefit associated with losartan. Second, our results extend those of previous short-term studies by showing greater reduction of LVH, after more than 4 years of treatment, with losartan than with atenolol.^{6,29}

Finally, it is possible that the greater cardiovascular protective effect of losartan compared with atenolol is due to benefits beyond blood-pressure reduction and LVH regression. This benefit could result from increased protection against the detrimental effects of angiotensin II or from specific effects of losartan.

Some limitations to the study need to be mentioned. The study population was mainly white. Furthermore, participants were derived from a high-risk population of hypertensive patients and the outcome should be interpreted in this context.

Losartan has already been established as an effective once-daily blood-pressure-lowering drug with excellent tolerability, effective blocking of angiotensin II at the type 1-receptor, and protective properties in diabetic nephropathy.³⁰ The greater clinical benefit in high-risk

patients and enhanced tolerability with losartan than atenolol suggest that broader application will improve outcome for hypertensive patients. Our results are directly applicable in clinical practice and should affect future guidelines.

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Conflict of interest statement

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

Acknowledgments

We thank Sigrid Helle Berg, Peter Aupur, Jonathan Edelman, and Anita Holmner for work on this manuscript. The trial was supported by an unrestricted grant from Merck.

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