Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients With Isolated Systolic Hypertension and Left Ventricular Hypertrophy
A Losartan Intervention For Endpoint Reduction (LIFE) Substudy

Sverre E. Kjeldsen, MD

Björn Dahlöf, MD

Richard B. Devereux, MD

Stevo Julius, MD

Peter Aurup, MD

Jonathan Edelman, MD

Gareth Beevers, MD

Ulf de Faire, MD

Frej Fyhrquist, MD

Hans Ibsen, MD

Krister Kristianson, MD

Ole Lederballe-Pedersen, MD

Lars H. Lindholm, MD

Markku S. Nieminen, MD

Per Omvik, MD

Suzanne Oparil, MD

Steven Snapinn, PhD

Hans Wedel, PhD

for the LIFE Study Group

Context Drug intervention in placebo-controlled trials has been beneficial in isolated systolic hypertension.

Objective To test the hypothesis that losartan improves outcome better than atenolol in patients with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy (ECG-LVH).

Design Double-blind, randomized, parallel-group study conducted in 1995-2001.

Setting and Participants A total of 1326 men and women aged 55 through 80 years (mean, 70 years) with systolic blood pressure of 160 to 200 mm Hg and diastolic blood pressure of less than 90 mm Hg (mean, 174/83 mm Hg) and ECG-LVH, recruited from 945 outpatient settings in the Nordic countries, the United Kingdom, and the United States.

Interventions Patients were randomly assigned to receive once-daily losartan (n=660) or atenolol (n=666) with hydrochlorothiazide as the second agent in both arms, for a mean of 4.7 years.

Main Outcome Measure Composite end point of cardiovascular death, stroke, or myocardial infarction.

Results Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. The main outcome was reduced by 25% with losartan compared with atenolol, 25.1 vs 35.4 events per 1000 patient-years (relative risk [RR], 0.75; 95% confidence interval [CI], 0.56-1.01; $P=.06$, adjusted for risk and degree of ECG-LVH; unadjusted RR, 0.71; 95% CI, 0.53-0.95; $P=.02$). Patients receiving losartan had reductions in the following without a difference in the incidence of myocardial infarction: cardiovascular mortality (8.7 vs 16.9 events per 1000 patient-years; RR, 0.54; 95% CI, 0.34-0.87; $P=.01$), nonfatal and fatal stroke (10.6 vs 18.9 events per 1000 patient-years; RR, 0.60; 95% CI, 0.38-0.92; $P=.02$), new-onset diabetes (12.6 vs 20.1 events per 1000 patient-years; RR, 0.62; 95% CI, 0.40-0.97; $P=.04$), and total mortality (21.2 vs 30.2 events per 1000 patient-years; RR, 0.72; 95% CI, 0.53-1.00; $P=.046$). Losartan decreased ECG-LVH more than atenolol ($P<.001$) and was better tolerated.

Conclusion These data suggest that losartan is superior to atenolol for treatment of patients with isolated systolic hypertension and ECG-LVH.

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As described previously,[1] the Losartan Intervention For Endpoint reduction (LIFE) study was designed in the early 1990s when (1) reduction of cardiovascular (CV) morbidity and mortality with β-blocker- or diuretic-based antihypertensive therapy was suboptimal,[2-5] (2) left ventricular hypertrophy (LVH) was a cardinal manifestation of preclinical CV disease and was a strong and independent risk factor for CV complications in hypertension, (3) indications that reversal of LVH was thought to have had prognostic benefit independent of blood pressure,[6,7] (4) there was an association of angiotensin II with development of LVH, and (5) suggestive evidence that blocking angiotensin II was thought to be es-

pecially effective in reversing LVH and could confer protective benefits over and above blood pressure lowering.[8]

Losartan was the first available selective AT_1-receptor antagonist.[9] Atenolol was chosen as a comparative agent to losartan in the LIFE study[1] because it has similar antihypertensive effectiveness as losartan[10] and because β-blockers have been recognized as a first-line therapy for cardiovascular protection in hypertension.[11,12] Isolated systolic hypertension (ISH) carries higher risk than isolated diastolic blood pressure elevation.[13,14] The outcome of drug intervention in placebo-controlled trials has been highly beneficial in patients with ISH.[15-17] In a predefined substudy of LIFE,[18] we tested the hypothesis that losartan has preventive effects beyond blood pressure control in patients with ISH and LVH. This is the first comparative drug trial to report CV outcomes in ISH.

METHODS
Study Design and Organization
The LIFE study was an investigator-initiated, prospective, multinational, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel group study. The primary objective was to evaluate the long-term effects of once daily losartan-based vs atenolol-based antihypertensive therapy in patients with hypertension and electrocardiographically (ECG) documented LVH on the incidence of CV morbidity and mortality. The complete study protocol with study design, organization, clinical measures, end point definitions, basis for choice of comparative agent, and statistical considerations, as well as recruitment details, baseline characteristics, and outcome for the entire LIFE population have been published.[1,18-21] The trial protocol was approved by the ethics committees of all participating institutions and was conducted in accordance with the Declaration of Helsinki and was overseen by an independent data and safety monitoring board.[1]

Target Population and Treatment Schedule
This study included patients aged 55 through 80 years with previously treated or untreated hypertension and ECG evidence of LVH and who were not excluded.[1,18-21] Patients randomized to receive losartan- or atenolol-based regimens after 1 to 2 weeks of placebo were selected to be included in this analysis if trough sitting blood pressures were between 160 and 200 mm Hg systolic with diastolic pressure less than 90 mm Hg (FIGURE 1).[18] There was no stratification as part of the randomization process. From July 6, 1995, through May 2, 1997, a total of 1326 patients with ISH were randomly assigned: 164 in Denmark, 164 in Finland, 15 in Iceland, 194 in Norway, 323 in Sweden, 90 in the United Kingdom, and 376 in the United States. Patients were followed up for 4 or more years with regular visits and upward titration of medication to reach a goal systolic blood pressure of less than 140 mm Hg (Figure 1). Sitting blood pressure was recorded 24 hours after dose (range, 22-26 hours). Only 2 patients (0.2%) with ISH were lost to follow-up (FIGURE 2).
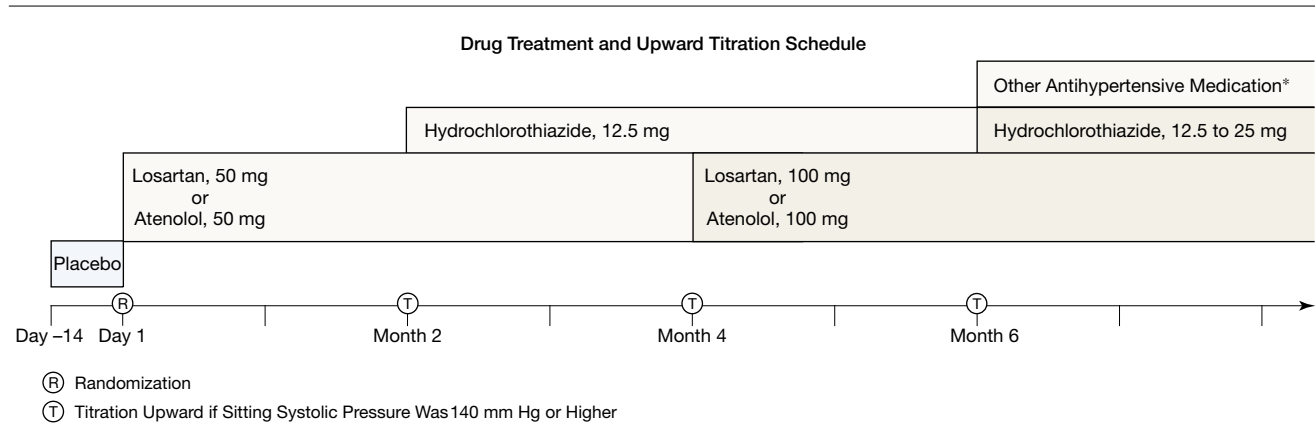
ECG Coding and LVH Criteria
All ECGs were evaluated at a central core reading center for LVH criteria and Minnesota code. The product of QRS duration times Cornell voltage (with adjustment of 6 mm in women and a partition value of >2440 mm × ms) and Sokolow-Lyon voltage greater than 38 mm were chosen to define LVH.[1,22-26]

Outcome Measures
The primary end point was a composite of CV death, stroke, and myocardial infarction. Other prespecified outcome measures were components of the primary end point (CV death, all stroke, and all myocardial infarction), total mortality, angina pectoris, or heart failure requiring hospitalization, coronary or peripheral revascularization procedures, resuscitated cardiac arrest, and new-

Figure 1. Titration Schedule and Electrocardiograph (ECG) Criteria

Drug Treatment and Upward Titration Schedule

Ⓡ Randomization
Ⓣ Titration Upward if Sitting Systolic Pressure Was 140 mm Hg or Higher

*Titration upward encouraged if sitting systolic pressure was 140 mm Hg or higher, but mandatory if it was 160 mm Hg or higher. Addition of angiotensin-converting enzyme inhibitors, other angiotensin II AT_1-antagonists, or other β-blockers prohibited.

onset diabetes mellitus.[1,18-21] Routine laboratory tests were performed in 2 central laboratories. New-onset diabetes, defined according to 1985 World Health Organization criteria,[27] was evaluated by a subcommittee of the steering committee. Adverse experiences were monitored throughout the study. The study ran its full course and end point follow-up was stopped on September 16, 2001, at midnight local time.[18]

Statistical Methods

The prespecified data analysis plan for the LIFE study highlighted ISH as being of particular interest and indicated that all end point analyses were to be performed in this subgroup. All CV end points and blood pressures were analyzed using the intention-to-treat approach. The findings in the analysis of the primary efficacy variable were confirmed with an on-treatment approach that censored end points from patients 14 days after permanent discontinuation of study drug. Patients with multiple end points were counted as having had an event in all relevant end point analyses; however, only the first event in a specific category counted in any individual analysis. Safety analyses included all randomized patients from the time of randomization through September 16, 2001, or permanent discontinuation of blinded study medication, whichever came first.

There were 6193 patient-years of follow-up. Treatment effects were measured by hazard ratios (relative risks [RRs]) and their 95% confidence intervals (CIs) based on Cox regression models, with degree of ECG-LVH and the Framingham risk score (sex, cholesterol, high-density lipoprotein cholesterol, smoking status, presence of diabetes and LVH, systolic blood pressure, and body mass index)[28] at baseline as a priori determined covariates. Secondary unadjusted analyses were also performed to validate the adjusted results. The risk reduction for losartan vs atenolol was calculated as 100 × (1−RR). Numbers needed to treat were calculated as 1/absolute risk reduction (1/ARR). Event rates over time are pre-

sented as Kaplan-Meier curves: the numbers below curves represent the number of event-free patients remaining in follow-up at the corresponding time point. Adjustment for blood pressure was based on Cox regression models with blood pressure values throughout the trial as time-varying covariates. Differences between groups in changes in ECG-LVH were analyzed with the Wilcoxon rank-sum test and frequencies of adverse experiences were analyzed with the Fisher exact test. All tests were performed at 2-sided 5% significance levels using the statistical package SAS version 8.0 (SAS Inc, Cary, NC).

To confirm that randomization was successfully achieved in the ISH subset, we performed 3 supplementary analyses. First, we compared baseline characteristics between treatment groups using the Wilcoxon rank-sum, the Fisher exact, and χ^2 tests as appropriate. Second, we performed a logistic regression analysis[29] in which treatment assignment was the dependent variable and used the *c* statistic (equivalent of area under a receiver operating characteristic curve) to assess whether there was a systematic difference of distributions between the 2 groups. Third, we used the model to generate a propensity score for drug assignment[30] and added that score to the Cox regression analyses.

RESULTS
Follow-up and Blood Pressure Control

Patients assigned to receive either losartan- or atenolol-based treatment were similar in characteristics (TABLE 1). Mean follow-up time (from randomization through death, loss to follow-up, or end of study) was 4.7 years. Patients continued study therapy 83.7% and 74.9% of entire follow-up time in the losartan and atenolol groups, respectively. The distribution of blinded study treatments for patients at the end of follow-up or at occurrence of the first primary end point, if earlier, and the distribution of additional therapy on top of blinded study drug or hydrochlorothiazide were not substantially different in the 2 groups (TABLE 2). The mean

Figure 2. Flow Diagram of the Progress Through Different Phases of the Study
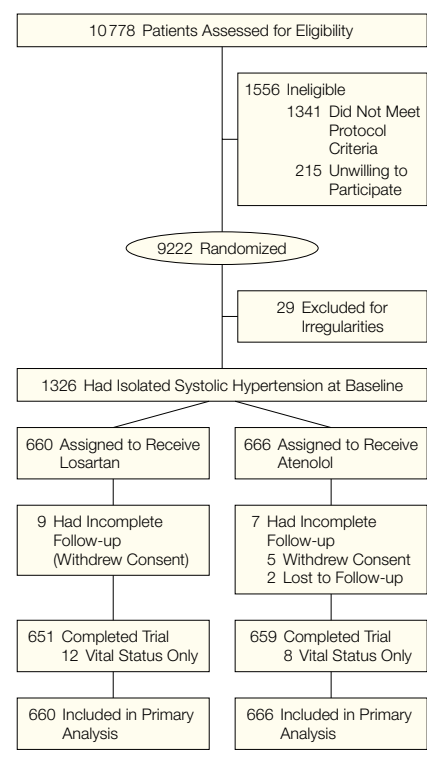
final losartan dose was 79 mg and the mean final atenolol dose was 76 mg. Patients taking losartan were more likely to continue study therapy, and the likelihood of receiving hydrochlorothiazide was the same in both groups.

The mean sitting blood pressures at end of follow-up or at the last visit preceding a primary end point, if one occurred, were reduced by 28/9 in the losartan and 28/9 mm Hg in the atenolol groups (FIGURE 3). The mean blood pressure levels at the last visit were 146/75 in the losartan and 146/74 mm Hg in the atenolol groups (P=.67, systolic; P=.04, diastolic blood pressure). The mean pulse pressure in the losartan group was 71 vs 73 mm Hg in the atenolol group (P=.07), and the mean arterial pressures were 98 and 98 mm Hg (P=.28), respectively.

A blood pressure of less than 140/90 mm Hg was achieved for 44.4% of those taking losartan and 42.9% of those taking atenolol. As expected, heart rate decreased by −6.6/min in patients taking

Table 1. Characteristics of Patients Treated With Losartan and Atenolol*

Characteristics	Losartan (n = 660)	Atenolol (n = 666)
Age, y	70.2 (6.4)	70.4 (6.2)
Women, No. (%)	388 (58.8)	409 (61.4)
Ethnicity, No. (%)		
White	606 (91.8)	616 (92.5)
Black	44 (6.7)	38 (5.7)
Hispanic	5 (0.8)	9 (1.4)
Asian	4 (0.6)	2 (0.3)
Other	1 (0.2)	1 (0.2)
Blood pressure, mm Hg		
Systolic	174 (11)	174 (11)
Diastolic	83 (5)	82 (6)
Heart rate, beats/min	71.5 (10.3)	71.6 (11.3)
Body mass index, kg/m^2	27.2 (4.6)	27.7 (5.2)
Cornell voltage-duration product, mm × ms	2771.1 (1077.8)	2820.6 (1157.9)
Sokolow-Lyon, mm	30.8 (10.5)	31.4 (10.6)
Framingham risk score, arbitrary units	0.230 (0.103)	0.234 (0.098)
Current smoker, No. (%)	95 (14.4)	101 (15.3)
Medical history, No. (%)		
Previously untreated isolated systolic hypertension	230 (34.8)	211 (31.7)
Coronary heart disease	158 (23.9)	140 (21.0)
Cerebrovascular disease	70 (10.6)	86 (12.9)
Peripheral vascular disease	57 (8.6)	55 (8.3)
Atrial fibrillation	28 (4.2)	39 (5.9)
Diabetes	103 (15.6)	132 (19.8)

*Data are presented as mean (SD) unless otherwise indicated.

Table 2. Study Drug at End Point or Termination of Follow-up*

	No. (%)	
Therapy	Losartan (n = 660)	Atenolol (n = 666)
50 mg only	65 (9.8)	56 (8.7)
50 mg plus other therapy with HCTZ	136 (20.6)	148 (22.2)
100 mg with or without HCTZ Therapy	290 (44.1)	246 (36.8)
Alone	14 (2.3)	10 (1.4)
With HCTZ only	107 (16.1)	91 (13.5)
With other therapy only	23 (3.6)	16 (2.6)
With HCTZ and other drugs	146 (22.1)	129 (19.4)
Discontinued therapy	169 (25.5)	216 (32.3)

*HCTZ indicates hydrochlorothiazide.

atenolol vs –0.3/min in those taking losartan (*P*<.001).

Occurrence of End Points

For the primary end point, there was an overall 25% relative risk reduction on losartan (**TABLE 3** and **FIGURE 4**). The Kaplan-Meier curves for CV mortality and for stroke all separated early (**FIGURE 5**) in favor of losartan. There

was no significant difference for myocardial infarction. Adjustment for blood pressure, as a time-varying covariate, did not change the outcome. Among other prespecified end points (Table 3), there was a lower incidence of new-onset diabetes and a lower total mortality rate among those in the losartan group (Figure 4). Non-CV mortality was almost identical in the 2 groups (39 vs 41 deaths).

Outcome data (primary, components of primary and secondary) in patients without ISH are presented in **TABLE 4**. The interaction between treatment and ISH status was not statistically significant (*P*=.21 for the adjusted analysis and *P*=.18 for the unadjusted analysis of primary outcomes). The interactions were also nonsignificant for the components and secondary end points, with the exception of CV death (adjusted, *P*=.02; unadjusted, *P*=.01).

Twenty-three patients with ISH were needed to treat with losartan vs β-blocker atenolol to prevent 1 pri-

mary outcome event during the 4.7-year course of the LIFE study, 25 were need to prevent death; 28, stroke; and 31, new-onset diabetes.

The primary composite end point occurred less often with losartan in patients with diabetes (RR, 0.71; 95% CI, 0.40-1.24; *P*=.22) and in those without diabetes (RR, 0.80; 95% CI, 0.56-1.14; *P*=.22). Risks for events in patients with and without ISH are provided in Table 3 and Table 4. The event rates were generally higher with ISH than without ISH.

Adverse Events and Safety Profile

Losartan was better tolerated with fewer overall and drug-related discontinuations (**TABLE 5**). Descriptive laboratory values are reported at baseline and end of study in **TABLE 6**.

Change in ECG-LVH

At end of study, mean Cornell voltage-duration product was reduced by 211 × ms in the losartan and 63 mm × ms in the atenolol groups (*P*<.001) and Sokolow-Lyon voltage was reduced by 3.9 and 2.3 mm, respectively (*P*<.001).

Confirmation of Randomized Assignments

In supplementary analyses, we constructed a logistic regression model in which treatment assignment was the dependent variable and the baseline characteristics listed in Table 1 were the independent variables. The *c* statistic for the model was only 0.579, suggesting that there was little if any association between the baseline characteristics and treatment assignment. Furthermore, a log-likelihood test showed that a model for treatment assignment with the 16 covariates was no better than a model with no covariates (*P*=.14). We also created a propensity score by summing for each patient the products of baseline characteristics and their coefficients from this logistic regression model. When we added the propensity score into the Cox regression models for analyses of the study end points, there were no material changes in the results.

COMMENT

This substudy showed that losartan treatment resulted in a 25% reduction in the main outcome, the predefined primary composite end point of CV morbidity and mortality (CV death, stroke, and myocardial infarction) vs atenolol, in 1326 LIFE patients with ISH. Interaction analysis (treatment and ISH status) suggested that losartan prevented CV death particularly well in ISH patients. Baseline blood pressure and pulse pressure reductions were similar with both therapies. Adjustment for changes in blood pressures had no appreciable effect on the outcome.

The results of the main LIFE study[18] contrast with recent hypertension studies comparing angiotensin-converting enzyme inhibitors, calcium-antagonists, and α-blockers to β-blocker or diuretic therapy, in which there have been no differences in primary outcome between treatment groups.[2] In this article we extend the main study findings to patients with ISH. This is the first demonstration in patients with ISH that a treatment modality better reduces CV morbidity and mortality than another proven antihypertensive therapy without a meaningful difference in pressure reduction. It appears that in non-

Figure 3. Systolic, Diastolic, and Mean Arterial Blood Pressure During Study Follow-up in Intention-to-Treat Analysis
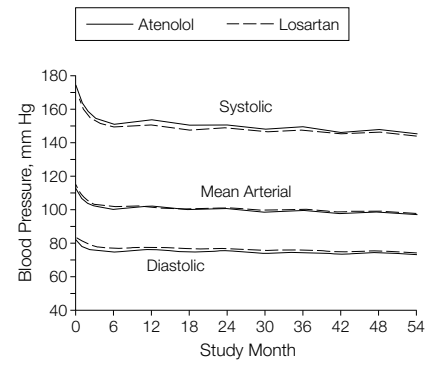
Table 3. End Points in Patients With Isolated Systolic Hypertension

End Point	Losartan (n = 660)		Atenolol (n = 666)		Unadjusted RR (95% CI)	P Value	Adjusted RR (95% CI)†	P Value
	Rate	No. (%)	Rate	No. (%)				
Primary Composite	25.1	75 (11.4)	35.4	104 (15.6)	0.71 (0.53-0.95)	.02	0.75 (0.56-1.01)	.06
Components								
Cardiovascular mortality	8.7	27 (4.1)	16.9	52 (7.8)	0.51 (0.32-0.81)	.004	0.54 (0.34-0.87)	.01
Stroke	10.6	32 (4.8)	18.9	56 (8.4)	0.56 (0.36-0.86)	.008	0.60 (0.38-0.92)	.02
Myocardial infarction	10.2	31 (4.7)	11.9	36 (5.4)	0.86 (0.53-1.39)	.54	0.89 (0.55-1.44)	.64
Other prespecified								
Total mortality	21.2	66 (10.0)	30.2	93 (14.0)	0.70 (0.51-0.96)	.03	0.72 (0.53-1.00)	.046
Hospitalization								
Angina pectoris	11.3	34 (5.2)	7.6	23 (3.5)	1.48 (0.87-2.51)	.15	1.48 (0.87-2.51)	.15
Heart failure	8.5	26 (3.9)	13.3	40 (6.0)	0.64 (0.39-1.05)	.08	0.66 (0.40-1.09)	.11
Revascularization	16.4	49 (7.4)	14.4	44 (6.6)	1.14 (0.76-1.72)	.53	1.17 (0.78-1.77)	.45
Resuscitated cardiac arrest	0.3	1 (0.2)	0	0				
New onset of diabetes‡	12.6	32 (5.8)	20.1	48 (9.0)	0.63 (0.40-0.99)	.04	0.62 (0.40-0.97)	.04

*Rates are based on 1000 patient-years of follow-up. RR indicates relative risk; CI, confidence interval.
†For degree of left ventricular hypertrophy and Framingham risk score at randomization.
‡Among patients without diabetes at randomization (losartan, n = 557; atenolol, n = 535).

Figure 4. Kaplan-Meier Curves for Rates of Primary Composite End Point for Patients in Each Treatment Group
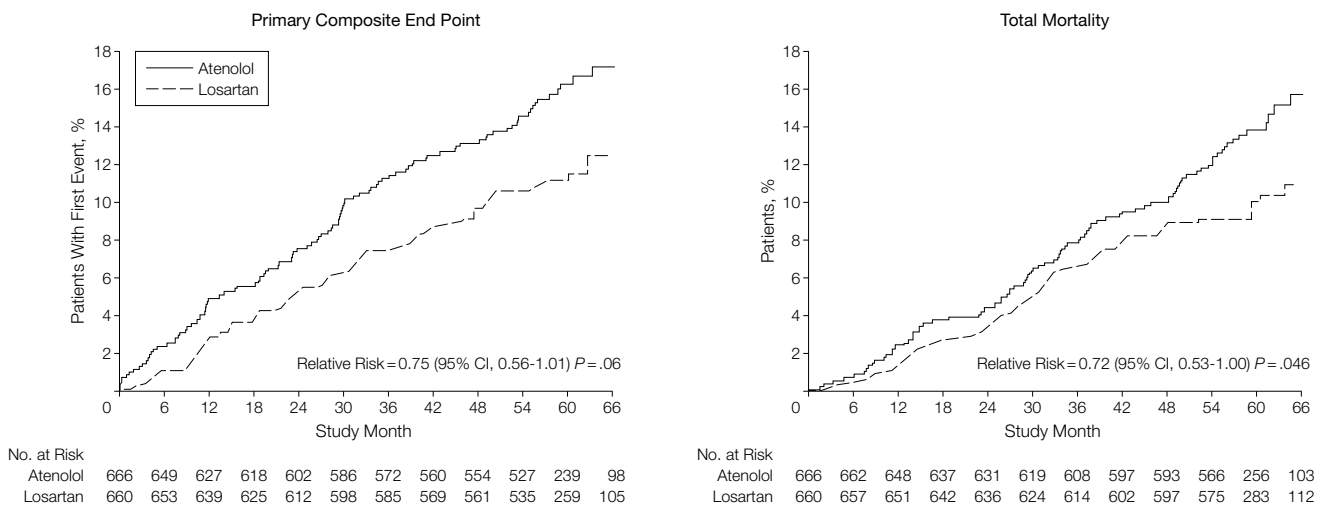
CI indicates confidence interval.

ISH patients, the main findings are reduced stroke and new-onset diabetes while in ISH patients losartan also lowers CV death and all-cause death.

Previous intervention studies in ISH with diuretic or β-blocker or calcium-antagonist or angiotensin-converting enzyme inhibitors have shown 36%,[15] 42%,[16] and 38%[17] reductions in stroke vs placebo. A further 40% reduction in stroke with losartan-based therapy, as demonstrated in this study, is an important finding because stroke is a major cause of death and disability and more common than myocardial infarction in the LIFE study as in all other hypertension trials during the last decade.[31] It was recently emphasized that LVH (both on ECG and echocardiography) is, independent of blood pressure, a strong predictor of cerebrovascular events.[32] This might be even more pronounced in patients with ISH.

The effect of incident myocardial infarction was comparable between losartan and atenolol. Reduction of heart rate, and hence myocardial oxygen demand, is generally thought to contribute to the cardioprotective properties of β-blockers[11,12,33] and might have outweighed additional and potentially beneficial coronary vascular effects of losartan with regard to incident of myocardial infarction. Potentially, the vascular effects of losartan[34] may be more pronounced in stroke protection.

The reduction in CV events by losartan-based therapy in LIFE was further accompanied by better tolerability and fewer drug withdrawals. As a result, more patients in the losartan than in the atenolol groups remained blinded to their therapy until the end of the study. This favorable combination of better prevention and higher tolerability may facilitate the choice of losartan as the first-line antihypertensive medication in patients with ISH.

A major hypothesis of the LIFE study, that losartan would be more effective than atenolol in reversing LVH,[35] was confirmed both in the overall study[18] and among patients with ISH, by greater reduction during the trial of both ECG indices of LVH in losartan-

Figure 5. Kaplan-Meier Curves of Cardiovascular Mortality, Stroke, and Myocardial Infarction
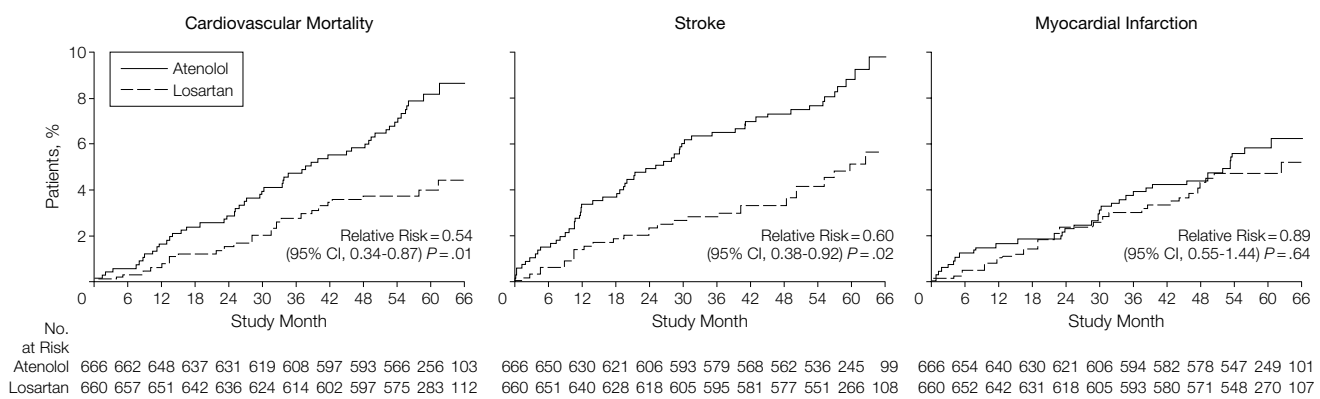
CI indicates confidence interval. Percentage of patients with first event are shown for stroke and myocardial infarction.

Table 4. End Points in Patients Without Isolated Systolic Hypertension

End Point	Losartan (n = 3945)		Atenolol (n = 3922)		Unadjusted RR (95% CI)	P Value	Adjusted RR (95% CI)†	P Value
	Rate	No. (%)	Rate	No. (%)				
Primary composite	23.6	433 (11.0)	26.7	484 (12.3)	0.88 (0.78-1.01)	.06	0.90 (0.79-1.02)	.11
Components								
Cardiovascular mortality	9.3	177 (4.5)	9.6	182 (4.6)	0.97 (0.79-1.19)	.77	0.99 (0.80-1.22)	.90
Stroke	10.8	200 (5.1)	13.8	253 (6.5)	0.78 (0.65-0.94)	.01	0.79 (0.66-0.95)	.01
Myocardial infarction	9.0	167 (4.2)	8.2	152 (3.9)	1.10 (0.88-1.36)	.41	1.12 (0.90-1.40)	.30
Other prespecified								
Total mortality	16.7	317 (8.0)	17.9	338 (8.6)	0.93 (0.80-1.09)	.38	0.95 (0.82-1.11)	.51
Hospitalization								
Angina pectoris	6.8	126 (3.2)	6.5	118 (3.0)	1.06 (0.83-1.37)	.62	1.08 (0.84-1.39)	.54
Heart failure	6.8	127 (3.2)	6.5	121 (3.1)	1.05 (0.82-1.34)	.72	1.06 (0.83-1.36)	.65
Revascularization	11.5	212 (5.4)	13.2	241 (6.1)	0.87 (0.73-1.05)	.15	0.89 (0.74-1.08)	.23
Resuscitated cardiac arrest	0.4	8 (0.2)	0.3	5 (0.1)	1.60 (0.52-4.88)	.41	1.65 (0.54-5.07)	.38
New onset of diabetes‡	13.1	210 (6.1)	17.0	272 (7.9)	0.77 (0.64-0.92)	.004	0.77 (0.64-0.92)	.005

*Rates are based on 1000 patient-years of follow-up. RR indicates relative risk; CI, confidence interval.
†For degree of left ventricular hypertrophy and Framingham risk score at randomization.
‡Among patients without diabetes at randomization (losartan, n = 3462; atenolol, n = 3445).

treated vs patients treated with atenolol. It is possible that the CV protective effect of losartan vs atenolol is due to a more complete blockade of the detrimental effects of angiotensin II effects that extends the benefits beyond blood pressure reduction alone. The more complete protection against angiotensin II with losartan at the AT_1-receptor, whether generated by the circulating renin-angiotensin-system or alternative mechanisms, is a likely contributor, especially in the light of angiotensin II as an independent risk factor for CV disease.[36] Other, molecule-specific actions such as uricosuria, interactions with sympathetic tone, and other as yet unknown mechanisms may possibly be involved as well.

Some limitations of our findings need to be mentioned. First, this study of patients with ISH was a substudy to the LIFE study although this was selected a priori as being of special interest. Second, those evaluated in the LIFE study were predominately white. Third, the patients were higher-risk hypertensive patients with ECG-LVH. Fourth, one could view these results with the contention that β-blockers may have different protective properties in younger patients than in older ones.[37]

In the LIFE study there was no stratification as part of the randomization process, either in the main study or in the ISH subset of patients. However, in any randomized clinical trial, comparisons of the treatment groups within any patient subsets are fully randomized comparisons, provided the subsets are defined based on information available at the time of randomization. Since ISH was defined using prerandomization blood pressure values, we anticipated that the comparison of losartan and atenolol in these patients would in fact be a randomized comparison. To confirm this, we performed a logistic regression with treatment assignment as the dependent variable. The low c statistic of only 0.579 and the lack of any change of findings when adding a propensity score to Cox regression models, along with the similarity of baseline characteristics noted in Table 1, all

argue that randomization was successfully achieved in the ISH subset.

Conclusion

Losartan-based antihypertensive therapy was more effective than an atenolol-based treatment in preventing CV morbidity and mortality, especially stroke and CV death, in a large prespecified subset of LIFE participants with ECG-LVH and ISH. In addition, losartan was associated with a lower incidence of new-onset diabetes and lower total mortality. It is currently not known whether losartan is superior to diuretics[15] or cal-

cium channel blockers[16,17] as a first-line treatment of isolated systolic hypertension.

Author Affiliations: Department of Internal Medicine, Division of Hypertension, University of Michigan, Ann Arbor (Drs Kjeldsen and Julius); Department of Cardiology, Ullevaal University Hospital, Oslo, Norway (Dr Kjeldsen); Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden (Dr Dahlöf); Division of Cardiology, Cornell Medical Center, New York, NY (Dr Devereux); Merck & Co Inc, Whitehouse Station, NJ (Drs Aurup, Edelman, and Snapinn); City Hospital, Birmingham, England (Dr Beevers); Department of Medicine, Division of Cardiovascular Medicine, Karolinska University Hospital, Stockholm, Sweden (Dr de Faire); Department of Medicine (Dr Fyhrquist) and Division of Cardiology (Dr Nieminen), Helsinki University Central Hospital, Finland; Department of Internal Medicine, Glostrup

Table 5. Adverse Events and Discontinuations in Patients Treated With Losartan and Atenolol

	No. (%)		
Variables	Losartan	Atenolol	P Value
Prespecified adverse events			
Angioedema	0.3	0.3	.99
Bradycardia	3.0	14.6	<.001
Cancer	9.8	8.3	.34
Cold extremities	4.1	6.6	.05
Cough	4.1	2.9	.23
Dizziness	19.5	19.7	.99
Hypotension	4.4	2.7	.10
Sexual dysfunction	2.4	3.2	.51
Sleep disturbance	0.9	0.8	.77
Additional common adverse events*			
Dyspnea	11.4	18.9	<.001
Albuminuria	3.5	8.0	<.001
Lower extremity edema	12.4	18.6	.002
Discontinuation due to an adverse event			
All	14.6	22.1	<.001
Drug related	7.1	13.5	<.001
Serious	4.6	6.6	.12
Serious and drug-related	1.2	2.0	.38

*With an incidence of more than 5% and a significant difference between treatment groups.

Table 6. Laboratory Values in Patients Treated With Losartan and Atenolol*

	Losartan (n = 660)			Atenolol (n = 666)		
Laboratory Value	Baseline	Year 4	Change	Baseline	Year 4	Change
Hemoglobin, g/dL	13.9	13.5	−0.4	14.0	13.8	−0.2
Sodium, mEq/L	140.3	139.7	−0.6	140.3	140.1	−0.2
Potassium, mEq/L	4.22	4.21	−0.02	4.22	4.14	−0.08
Glucose, mg/dL	109.9	113.7	3.8	112.6	115.7	3.1
ALAT, U/L	23.6	21.6	−2.0	24.5	23.4	−1.1
Cholesterol, mg/dL						
Total	232.0	217.3	−14.7	232.4	223.1	−9.3
HDL	58.0	57.2	−0.8	57.2	54.1	−3.1
Uric acid, mg/dL	5.4	5.8	0.4	5.4	6.3	0.9
Creatinine, mg/dL	1.0	1.1	0.1	1.0	1.1	0.1

*To convert glucose to mmol/L, multiply by 0.0555. To convert total cholesterol and high-density (HDL) cholesterol from mg/dL to mmol/L, multiply by 0.0259. To convert creatinine from mg/dL to µmol/L, multiply by 88.4. ALAT indicates alanine aminotransferase.

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