

The Effects of Losartan Compared to Atenolol on Stroke in Patients With Isolated Systolic Hypertension and Left Ventricular Hypertrophy. The LIFE Study

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The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study reported that a losartan-based antihypertensive regimen reduced cardiovascular morbidity and mortality (composite of cardiovascular death, stroke, and myocardial infarction) more than therapy based on atenolol in patients with left ventricular hypertrophy and isolated systolic hypertension (ISH). Patients aged 55–80 years with blood pressures 160–200/<90 mm Hg were followed for a mean

of 4.7 years. Blood pressure was similarly reduced in the losartan (n=660) and atenolol (n=666) ISH groups. There were 88 (6.6%) patients who experienced a stroke, 18 of which were fatal. Of patients experiencing strokes, 72.7% had an ischemic stroke. ISH patients in LIFE compared to the non-ISH group had a higher incidence of any stroke and embolic stroke, and similar incidences of fatal, atherosclerotic, and hemorrhagic/other strokes. The incidence of any stroke (40% risk reduction [RR], p=0.02), fatal stroke (70% RR, p=0.035), and atherothrombotic stroke (45% RR, p=0.022) was significantly lower in losartan-treated compared to the atenolol-treated patients. The 36% RR for embolic strokes in the losartan group was not statistically significantly (p=0.33) different from the atenolol group. These data suggest that losartan-based treatment is more effective than an atenolol-based treatment for patients with ISH and a high risk for stroke. (J Clin Hypertens. 2005;7:152–158) ©2005 Le Jacq Ltd.

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Stroke, the second leading cause of death and a major cause of disability worldwide, imposes significant burdens on patients and healthcare systems.^{1,2} It is estimated that 700,000 strokes occur each year in the United States alone.³ As many as 25% of patients who suffer a stroke die within 1 year, and 15%–30% are permanently disabled.³ The incidence and costs of stroke are expected to increase

substantially as the population of industrialized countries ages in the coming decades.⁴ The public health implications of stroke prevention are significant.⁵

Hypertension is a factor in nearly 70% of stroke cases.⁶ Prevention of stroke has focused on reducing blood pressure (BP). Data from clinical trials and meta-analyses have shown a broadly continuous, log-linear association between BP and stroke. Each 10 mm Hg lower systolic BP is associated with a one-third decrease in risk of stroke, consistent across genders, geographical regions, stroke subtypes, and for fatal and nonfatal events.⁷ There is a somewhat weaker association in older patients; for those aged 70 years or older, the risk reduction (RR) was 25%–29%.⁷

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study⁸ reported that a losartan (an angiotensin receptor blocker [ARB]) compared to an atenolol (β blocker)-based antihypertensive regimen was more effective for reducing cardiovascular (CV) morbidity and mortality (the composite of CV death, stroke, and myocardial infarction [MI]) with comparable BP control in patients with hypertension and left ventricular (LV) hypertrophy. The between-group difference was mainly driven by the difference in stroke, the most common component of the primary composite end point.⁸ The risk of fatal or nonfatal stroke was reduced by 25% ($p=0.001$) in the losartan group compared to the atenolol group. There were significant reductions in the risks of fatal stroke ($-35%$, $p=0.032$) and atherothrombotic stroke ($-28%$, $p=0.001$), with RRs that did not achieve statistical significance for hemorrhagic and embolic strokes.⁹

The impact on RR for stroke was evident in the higher-risk groups. The number needed to treat for 5 years to prevent one stroke was 54 for the average patient, 25 for patients with cerebrovascular disease, 24 for patients with isolated systolic hypertension (ISH), and 9 for patients with atrial fibrillation (AF).⁹

ISH is associated with a higher risk for adverse CV outcomes than diastolic BP elevation.^{10,11} Antihypertensive treatment has been beneficial in reduction of CV morbidity and mortality in patients with ISH.^{12–14} This paper examines stroke type and neurological deficit data in LIFE patients with ISH.

METHODS

The LIFE study was an investigator-initiated, prospective, multinational, double-blind, randomized, parallel-group study. The primary objective was to evaluate the long-term effects of once-daily losar-

tan- compared to atenolol-based antihypertensive therapy in patients with essential hypertension and electrocardiogram (ECG)-documented LV hypertrophy on the primary composite end point of CV death, stroke, and MI. The study design, organization, clinical measures, end point definitions, basis for choice of comparative agent, and statistical considerations, as well as baseline characteristics and outcome have been published.^{8,15,16} The trial protocol was approved by all concerned ethics committees, and all patients provided informed consent.

The LIFE study included patients 55–80 years old. Patients had previously treated or untreated hypertension, which in the ISH subgroup of 1326 patients was 160–200 mm Hg systolic with diastolic pressure <90 mm Hg after a 1- to 2-week placebo run-in period. LV hypertrophy was documented by Cornell voltage-duration product and/or Sokolow-Lyon voltage criteria. Patients were followed for 4 years or longer with regular visits and upward titration of medication to reach a goal systolic BP of $<140/90$ mm Hg. Only two patients (0.2%) with ISH were lost to follow-up. Approximately 58% of patients in both groups received hydrochlorothiazide.

Stroke was defined as a new-onset neurological deficit of vascular origin lasting 24 hours or longer or until death. Stroke classification was based on categories developed in the Framingham Study.¹⁷ Ischemic stroke was assigned in the absence of evidence of primary intracranial bleeding, while hemorrhagic stroke required evidence of hemorrhage (i.e., bloody spinal fluid or blood on computed tomography), excluding cases of vessel rupture due to traumatic, neoplastic, or infectious processes. Ischemic stroke was further classified as embolic vs. atherothrombotic. Embolic stroke was based on the presence of a source of an embolus (e.g., chronic or paroxysmal AF, rheumatic mitral stenosis, recent MI, prosthetic heart valve, ulcerated carotid plaque, etc.) and consistent clinical features (e.g., rapid onset and partial clearing, slightly bloody spinal fluid, etc.) or the occurrence of associated peripheral emboli. Atherothrombotic stroke was diagnosed when there was an ischemic stroke without evidence of embolic etiology, as defined above. Strokes for which a distinct etiology could not be ascertained were classified as “other.” Clinical centers provided information on neurologic deficits on end point narrative forms. These were classified as depression of state of consciousness, disturbance of vision, paresis or paralysis of one or more extremities, sensory impairment, speech impairment, central cranial nerve dysfunction, memory defect, ataxia, and movement disorder.

Table I. Baseline Characteristics of Patients With Isolated Systolic Hypertension

	LOSARTAN (N=660)	ATENOLOL (N=666)
Demographic and clinical		
Age (yr)	70.2±6.4	70.4±6.2
Female (%)	58.8	61.4
Ethnic origin (%)		
Non-Hispanic white	91.8	92.5
Black	6.7	5.7
Hispanic	0.8	1.4
Asian	0.6	0.3
Other	0.2	0.2
Baseline systolic blood pressure (mm Hg)	174.2±10.7	174.5±11.0
Baseline diastolic blood pressure (mm Hg)	83.0±5.4	82.3±6.2
Heart rate (bpm)	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 × msec)	2771.1±1077.8	2820.6±1157.9
Sokolow-Lyon criteria (mm)	30.8±10.5	31.4±10.6
Framingham risk score	0.230±0.103	0.234±0.098
Current smokers (%)	14.4	15.3
Medical history (%)		
Previously untreated hypertension	34.8	31.7
Coronary heart disease	23.9	21.0
Cerebrovascular disease	10.6	12.9
Peripheral vascular disease	8.6	8.3
Atrial fibrillation	4.2	5.9
Diabetes	15.6	19.8

Adapted with permission from *JAMA*. 2002;288:1491–1498.¹⁸

The evaluation of end points in the population with ISH in the LIFE study was prespecified. All tests were performed at two-sided, 5% significance levels using the statistical package SAS version 8.0 (SAS Institute, Inc., Cary, NC). Cox proportional hazards models were used to evaluate the relative risk with respect to stroke incidence for the losartan group relative to atenolol group without adjustment for covariates and with adjustment for Framingham risk score and degree of LV hypertrophy. For neurological deficits, the relative risk was based on binomial proportions.

RESULTS

Patient characteristics, BP, and outcomes data for the LIFE ISH group have been published.¹⁸ In the ISH group, 60% of patients were women, average age was 70 years, and mean sitting BP was 174/83 mm Hg. Patients assigned to receive either losartan-based or atenolol-based treatment had similar baseline characteristics (Table I). Mean follow-up was 4.7 years, and study therapy was used for 83.7% and 74.9% of follow-up time in the losartan and atenolol groups, respectively. The

distributions of blinded study treatments were not substantially different in the two groups, with mean losartan and atenolol doses of 79 mg and 75 mg. Hydrochlorothiazide use was similar in the two groups. Mean sitting BPs at the end of follow-up or at the last visit preceding a primary end point, if one occurred, were reduced by 28.4/8.5 mm Hg in the losartan and 28.2/8.8 mm Hg in the atenolol groups. The mean BP levels at the last visit were 145.9/74.5 mm Hg in the losartan group and 146.3/73.5 mm Hg in the atenolol groups ($p=0.67$, systolic; $p=0.04$, diastolic). The mean pulse pressure in the losartan group was 71.4 vs. 72.8 mm Hg in the atenolol group ($p=0.07$), and the mean arterial pressures were 98.3 mm Hg and 97.8 mm Hg ($p=0.28$), respectively.

There were 102 strokes in the ISH group, which occurred in 88 (6.6%) patients, in 18 of whom the stroke was fatal. There were 75 patients with one stroke, 12 patients with two strokes, and one patient with three strokes. Of those experiencing stroke in the ISH group, 72.7% had an ischemic stroke (atherothrombotic or embolic). There were higher incidences in LIFE patients with ISH than in

	WITH ISH (N=1326)	WITHOUT ISH (N=7867)
Patients with stroke	88 (6.6)	453 (5.8)
Fatal stroke	18 (1.3)	84 (1.1)
Ischemic stroke		
Atherothrombotic stroke	64 (4.8)	339 (4.3)
Embolic stroke	21 (1.6)	63 (0.8)
Hemorrhagic and other stroke	6 (0.5)	65 (0.8)

LIFE=Losartan Intervention For Endpoint reduction in hypertension trial; *all values are n (%)

	LOSARTAN (N=660)	ATENOLOL* (N=666)	ADJUSTED RR (95% CI)	P VALUE
Any stroke	32 (4.8%)	56 (8.4%)	0.60 (0.38–0.92)	0.020
Fatal stroke	4 (0.6%)	14 (2.1%)	0.30 (0.10–0.92)	0.035
Ischemic stroke				
Atherothrombotic stroke	22 (3.3%)	42 (6.3%)	0.55 (0.32–0.92)	0.022
Embolic stroke	8 (1.2%)	13 (2.0%)	0.64 (0.26–1.56)	0.33
Hemorrhagic or other stroke	2 (0.3%)	4 (0.6%)	Too few events	

ISH=isolated systolic hypertension; RR=risk reduction; CI=confidence interval; *three atenolol patients had multiple strokes of different types (these patients are counted only once in the patients with any stroke category)

the remainder of the LIFE population without ISH for any stroke and embolic strokes, and a similar incidence of fatal, atherosclerotic, and hemorrhagic/other strokes (Table II).

Relative to the atenolol group, the losartan group had significantly lower risks of any stroke (40% RR, $p=0.02$), fatal strokes (70% RR, $p=0.035$), and atherothrombotic strokes (45% RR, $p=0.022$, Table III). There were fewer embolic strokes in the losartan group (36% RR), but the difference was not statistically significant ($p=0.33$). There were too few strokes in the hemorrhagic/other category to analyze.

When all strokes were considered, each stroke deficit except ataxia was less frequent in losartan-treated patients, with statistically significant differences for less central cranial nerve dysfunction, memory defect, paresis or paralysis, and speech impairment (Table IV).

DISCUSSION

Stroke occurred in 6.6% (20.5% fatal) of the LIFE patients with ISH compared with 5.8% (22.5% fatal) of patients without ISH. Losartan-based treatment was associated with a statistically significant 40% RR ($p=0.02$) compared to atenolol-based treatment for stroke in the 1326 patients with ISH and LV hypertrophy in the LIFE study,¹⁸ a result that drove the 26% ($p=0.06$) adjusted RR in the composite end point. The present analyses show that the risk of stroke was consistent

across different stroke subtypes, with a significant reduction for atherothrombotic (ischemic) stroke. These effects were accompanied by corresponding decreases in the number of specific neurological deficits for fatal plus nonfatal strokes.

Regression of LV hypertrophy might partially explain the cerebrovascular benefit of losartan.^{19–21} Regression of LV hypertrophy as measured by ECG was a secondary end point of the overall LIFE study,¹⁹ and was also measured in patients with ISH.¹⁸ LV hypertrophy was also examined in an echocardiographic substudy of more than 900 patients who had LV mass measured at baseline and follow-up.²⁰ When LV hypertrophy regression was measured by ECG in the overall group, regression was significantly greater in the losartan group from 6 months ($p<0.001$), the first on-treatment measurement, and continued to be significantly greater than with atenolol throughout the study (e.g., annually), despite comparable BP reduction.¹⁹ In the ISH group, LV hypertrophy was significantly reduced in both groups ($p<0.001$); although the magnitudes of regression were greater in the losartan group, between-group comparisons were not reported.¹⁸ Lower in-treatment LV mass was also associated with lower rate of stroke in the echocardiographic substudy of the overall group.²² There was also significantly more echocardiographic LV hypertrophy regression for losartan- compared to atenolol-based treatment.²⁰ There was a strong association between lower

Table IV. Distribution of Individual Neurologic Deficits According to Treatment Assignment in Patients With ISH

	FATAL AND NONFATAL STROKES			
	LOSARTAN (N=660) (N [%])	ATENOLOL (N=666) (N [%])	RR (95% CI)	P VALUE
Ataxia	6 (0.91)	4 (0.60)	1.52 (0.43–5.41)	0.516
Central cranial nerve dysfunction	5 (0.76)	14 (2.10)	0.36 (0.13–0.99)	0.040
Depression of state of consciousness	9 (1.36)	18 (2.70)	0.50 (0.22–1.12)	0.084
Disturbance of vision	5 (0.76)	9 (1.35)	0.56 (0.19–1.67)	0.290
Memory defect	5 (0.76)	14 (2.10)	0.36 (0.13–0.99)	0.040
Movement disorder	15 (2.27)	19 (2.85)	0.79 (0.40–1.57)	0.504
Paresis or paralysis	26 (3.94)	46 (6.91)	0.55 (0.34–0.91)	0.017
Sensory impairment	9 (1.36)	13 (1.95)	0.69 (0.29–1.64)	0.402
Speech impairment	17 (2.58)	38 (5.71)	0.44 (0.24–0.78)	0.004

ISH=isolated systolic hypertension; RR=risk reduction; CI=confidence interval

LV mass index (LVMI) and the reduced rate of the composite end point ($p=0.009$). There were significant, parallel associations between lower LVMI and the primary composite end point and each of its components, independent of systolic BP and assigned treatment. The LV hypertrophy mechanism explained about 20% of the lower stroke rate with losartan in the overall group.²⁰ In an analysis of 127 of the patients with ISH in the echocardiographic substudy, there was a greater reduction in LV mass in the losartan group.²³ The difference between groups was not significant; this was attributed to the small sample size and/or a quantitatively smaller effect on regression of LV mass in patients with ISH compared to those with combined systolic-diastolic hypertension.²³

AF is an important risk factor for stroke, increasing risk five-fold.³ LIFE confirmed a high CV disease and stroke rate in patients with AF and hypertension at baseline.²⁴ Twelve percent ($n=18$) of the patients with AF at baseline who were allocated to losartan experienced a stroke, while 20.5% ($n=38$) of the patients allocated to atenolol had a stroke (adjusted hazard ratio, 0.55, $p=0.039$). Furthermore, in this trial, there was a lower rate of new-onset AF with losartan compared to atenolol-based therapy.²⁵ Among 8804 patients without AF at baseline, 431 (4.9%) developed new-onset AF during the study. New-onset AF increased the risk of fatal and nonfatal stroke (hazard ratio=3.2, $p<0.001$). The AF mechanism was associated with about 35% of the lower stroke rate with losartan.

Antithrombotic^{26–28} and improvement of arterial stiffness²⁹ benefits of treatment with losartan have been described, and may play a role in the beneficial effect of losartan on stroke.^{30,31} Angiotensin II type 2-receptor-mediated brain-anti-ischemic mechanisms have been proposed that

might explain the possible superiority of angiotensin receptor blockers over angiotensin-converting enzyme inhibitors for prevention of stroke.^{30,31} The clinical data supporting risk reduction for stroke with angiotensin-converting enzyme inhibitor treatment come from the Heart Outcomes Prevention Evaluation (HOPE) study in which patients at high risk for cardiovascular events were randomized to ramipril or placebo for a mean of 5 years.^{32,33} There were differences in ambulatory BP between the treatment groups, especially during nighttime, which may complicate the interpretation of the stroke results in the HOPE study.³⁴

Losartan has serum-uric-acid (SUA)-lowering effects that are unique within the angiotensin-II type-1 receptor antagonist class. Baseline SUA was significantly associated with increased occurrence of the primary composite end point in the LIFE study in women, even with adjustment for other CV risk factors, whereas in men, SUA had a weak association when established risk factors were considered separately.³⁵ The contribution of SUA to the treatment effect of losartan on the primary composite end point was estimated to be 29% (14%–107%, $p=0.004$), and tended to be stronger in women than in men.³⁵

In a somewhat older (average age 77.1 years) population with ISH in the Study on Cognition and Prognosis in the Elderly (SCOPE),³⁶ there was a similar reduction of risk for stroke (42%) in candesartan-based compared with placebo-based antihypertensive therapy in the context of 2.00 mm Hg diastolic ($p=0.064$) and 1.2 mm Hg systolic ($p=0.064$) BP differences between the treatment groups favoring candesartan-based therapy.

LIMITATIONS

There are limitations to these analyses. The LIFE study enrolled a predominately older white

population that was at higher risk due to LV hypertrophy. The stroke classification used broad criteria developed in an epidemiological study¹⁷; use of a more detailed classification scheme would have permitted greater refinement in the categorization of stroke subtypes. Differential effects on subtypes such as lacunar vs. large-vessel strokes could not be evaluated. Standard stroke-related disability scales were not used.

The significant RR for stroke with losartan-based therapy in the LIFE study for the overall population and ISH subgroup is an important finding because stroke is a major cause of death and disability. The public health significance of translating the stroke findings in this study to clinical practice is substantial. Use of this type of antihypertensive regimen in the 7.8 million patients with hypertension and ECG LV hypertrophy aged 55–80 years in the European Union is projected to prevent 125,000 first strokes in a 5-year period.³⁷

CONCLUSIONS

In conclusion, consistent with LIFE primary results, these data suggest that losartan-based treatment reduces CV complications, primarily stroke, when compared to atenolol-based treatment for patients with ISH and high CV risk.

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