Stroke Reduction in Hypertensive Adults With Cardiac Hypertrophy Randomized to Losartan Versus Atenolol
The Losartan Intervention For Endpoint Reduction in Hypertension Study


**Abstract**—The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that treatment with the angiotensin II type-1 receptor antagonist losartan reduces overall stroke risk compared with conventional therapy with the β-blocker atenolol. We conducted secondary analyses in LIFE to determine the extent to which the cerebrovascular benefits of losartan apply to different clinical subgroups and stroke subtypes and to assess the dependence of these benefits on baseline and time-varying covariates. Among 9193 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy, random allocation to losartan-based treatment lowered the risk of fatal (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.43 to 0.96; \( P = 0.032 \)) and atherothrombotic stroke (HR, 0.72; 95% CI, 0.59 to 0.88; \( P = 0.001 \)) compared with atenolol-based therapy. Although comparable risk reductions occurred for hemorrhagic and embolic stroke, these were not statistically significant. The number of neurologic deficits per stroke was similar, but there were fewer strokes in the losartan group for nearly every level of stroke severity. Effects were consistent in all clinical subgroups except for those defined by age and ethnicity. The benefits of losartan on all strokes were independent of baseline and time-varying risk factors, including blood pressure. The number needed to treat for 5 years to prevent 1 stroke was 54 for the average participant, declining to 25, 24, and 9 for patients with cerebrovascular disease, isolated systolic hypertension, and atrial fibrillation, respectively. In conclusion, substantial cerebrovascular benefit could be realized with the institution of losartan-based therapy over conventional therapy among hypertensive patients with left ventricular hypertrophy across the spectrum of cardiovascular risk. (*Hypertension.* 2005;45:46-52.)

**Key Words:** population ■ drug therapy ■ clinical trials ■ angiotensin antagonists ■ hypertrophy ■ stroke

**S**troke is a disorder with enormous public health implications, ranking second among leading causes of mortality worldwide and of long-term disability in developed countries.1 The case-fatality rate is \( \approx 20\% \), and among patients alive 6 months after a stroke, one third are dependent on others for activities of daily living.2 From an economic perspective, the disorder imposes a staggering burden, accounting for more than $53.6 billion in yearly costs in the United States alone.3

A number of conditions have been recognized to predispose to stroke, but the preeminent modifiable risk factor for the disorder is hypertension.4 Although hypertension has traditionally been considered a greater risk factor for myocardial infarction than for stroke, in recent randomized trials, the converse has been true, particularly among elderly hypertensives.5 This is of special significance given the growing proportion of people surviving to advanced age worldwide.

Antihypertensive regimens based on thiazide diuretics or β-blockers have proven effective in reducing stroke risk among patients with high blood pressure.6–8 Accordingly, the finding that the angiotensin II type 1 (AT1) receptor blocker losartan effected a substantial reduction in stroke events over the β-blocker atenolol in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study is of great clinical importance.9 The present analyses were undertaken to examine the effects of losartan on stroke outcomes in the LIFE study in greater detail. Specifically, we evaluated whether the benefits of losartan extended to different stroke subtypes and resulting neurological deficits; explored the degree to which they are conditioned by differing baseline

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and time-varying characteristics in the study population; and assessed the public health implications of instituting losartan-based therapy in different subgroups at high risk of stroke.

Methods

Participants
Details of the methods and principal findings of the LIFE study have been reported. Briefly, the study was an investigator-initiated, randomized, multicenter, double-blind, active-control trial that enrolled patients ages 55 to 80 with hypertension and electrocardiographic left ventricular hypertrophy (LVH). Exclusion criteria consisted of secondary hypertension; myocardial infarction or stroke in the preceding 6 months; angina pectoris requiring β-blockers or calcium antagonists; heart failure or ejection fraction ≤40%; important hepatic or renal dysfunction; or a history of a solitary kidney. Eligible patients were assigned to a losartan- or atenolol-based regimen after 1 to 2 weeks of placebo if trough sitting blood pressures were 160 to 200 mm Hg systolic or 95 to 115 mm Hg diastolic.

Procedures
Patients were followed at regular visits and drugs titrated to achieve a target blood pressure <140/90 mm Hg. All ECGs were evaluated for signs of LVH and underwent Minnesota coding at a single center. LVH was defined based on Cornell voltage-duration product and Sokolow-Lyon voltage as described previously. Measurements of serum and urine analytes were performed at 2 central laboratories. An end point classification committee of 2 masked clinicians reviewed records of all cardiovascular events reported by clinical centers to assess fulfillment of end point criteria.

Stroke Definitions
Stroke was defined as a new-onset neurological deficit of vascular origin lasting ≥24 hours or until death. Stroke classification was based on categories developed in the Framingham Study. Ischemic stroke was assigned in the absence of evidence of primary intracranial bleeding, whereas hemorrhagic stroke required evidence of hemorrhage (ie, bloody spinal fluid, blood on computed tomography), excluding cases of vessel rupture attributable to traumatic, neoplastic, or infectious processes. Ischemic stroke was further classified as embolic versus atherothrombotic. Embolic stroke was based on the presence of a source of embolus (eg, chronic or paroxysmal atrial fibrillation, rheumatic mitral stenosis, recent myocardial infarction, prosthetic heart valve, ulcerated carotid plaque, etc.) and consistent clinical features (eg, rapid onset and partial clearing, slightly bloody spinal fluid, etc.), or the occurrence of an associated peripheral emboli. Atherothrombotic stroke was assigned when no evidence of an embolic etiology, as defined above, was present. Strokes for which a distinct etiology could not be ascertained were classified as “other.”

Clinical centers provided information on neurological deficits in end point narrative forms. These were classified as: depression of consciousness; disturbance of vision; paresis or paralysis of ≥1 extremities; sensory impairment; speech impairment; central cranial nerve dysfunction; memory defect; ataxia; and movement disorder.

Statistical Analysis
Comparisons of categorical variables applied the χ² test, whereas those of continuous variables used the Student t or Wilcoxon rank-sum test, as appropriate. Stroke occurrence was a prespecified secondary end point in the LIFE study, and the additional analyses done to further clarify the benefit of treatment on stroke were post hoc. Cox proportional hazards models were used to evaluate unadjusted differences in time to stroke throughout the follow-up period and to adjust for baseline and time-varying risk factors. Effect-measure modification was assessed by inclusion of a first-order interaction term between treatment and major clinical variables. The number needed to treat was calculated as a measure of absolute benefit within various subgroups.

Results

Patient Characteristics, Follow-Up, and Blood Pressure Control
The baseline demographic and clinical characteristics of the 9193 patients constituting the LIFE cohort have been detailed previously. Mean age was 66.9±7.0 years, 54% of participants were women, and 92% were white, 6% were black, and the remainder were of other ethnicities. Mean baseline systolic and diastolic blood pressures were 174.4±14.3 and 97.8±8.9 mm Hg; mean body mass index and total:HDL cholesterol were 28.0±4.8 kg/m² and 4.3±1.4, respectively. Current smokers constituted 16% of the cohort, whereas 13% had diabetes mellitus, and 14% had isolated systolic hypertension. A history of vascular disease was present in 25% of subjects, including 16% with coronary heart disease, 8% with cerebrovascular disease (4% stroke and 4% transient ischemic attack), and 6% with peripheral vascular disease. Atrial fibrillation was noted at baseline ECG in 4% of participants. The treatment groups were well matched with respect to these baseline characteristics.

Participants assigned to losartan or atenolol continued to receive study drug for 86% and 82% of follow-up (mean 4.8 years) and received hydrochlorothiazide as supplementary therapy during 72% and 70% of this period, respectively. The distribution of blinded treatments at termination of follow-up has been detailed previously. Antiplatelet or anticoagulant drugs were used by 23.6% and 23.1% of losartan- versus atenolol-treated patients at baseline and by 36.4% and 37.0%, respectively, at study end.

There were substantial reductions in systolic, diastolic, and mean blood pressures in both treatment arms. Sitting systolic blood pressure was reduced by 30.2 mm Hg in the losartan group and 29.1 mm Hg in the atenolol group at the end of follow-up or last visit before the occurrence of a primary end point (P=0.017 for the difference of 1.1 mm Hg). Corresponding values for diastolic blood pressure were 16.6 mm Hg and 16.8 mm Hg, respectively (P>0.20). At the time of the last visit, blood pressures were 144.1/81.3 mm Hg and 145.4/80.9 mm Hg in the losartan and atenolol groups, respectively. Systolic blood pressure <140 mm Hg was achieved in 50% of losartan-treated and 47% of atenolol-treated patients, whereas diastolic blood pressure <90 mm Hg was achieved by 87% of losartan-treated and 89% of atenolol-treated patients. Systolic and diastolic blood pressure targets were attained by 48% of losartan-treated and 46% of atenolol-treated patients.

Stroke Outcomes
Of the 541 first-incident strokes, stroke diagnoses were based on ≥1 of the following criteria: signs and symptoms in 481 (88.9%), diagnostic imaging (MRI, computed tomography, or angiography) in 426 (78.7%), spinal fluid analysis in 3 (0.6%), and autopsy in 7 (1.3%). First strokes included 395 (73.0%) ischemic atherothrombotic, 81 (15.0%) ischemic embolic, 55 (10.2%) hemorrhagic, and 10 (1.8%) other events. Among these events, 76 (14.0%) were fatal. Atrial fibrillation at baseline or during the study occurred in 55% of
Results of assessment for multiplicative interactions between treatment allocation and subgroups of the study cohort defined by clinical characteristics are shown in the figure. The effects of losartan in some of these subgroups have been documented but are presented for completeness. There was no evidence of effect-measure modification for all but 2 of the 19 subgroups examined, namely, those defined by age and ethnicity. There were significant benefits for patients aged ≥65 years and for white patients. However, in younger patients, losartan-based treatment showed an unfavorable but nonsignificant effect estimate. Among black participants, losartan was associated with a nearly significant increase in stroke events compared with atenolol (unadjusted HR, 1.99; 95% confidence interval [CI], 1.00 to 3.98; \( P = 0.051 \)).

Table 3 presents effect estimates after adjustment for clinical variables capable of confounding the association between treatment and stroke. The effect of losartan-based therapy on stroke incidence was not only independent of degree of electrocardiographic LVH and Framingham risk score, but it was also independent of systolic pressure during follow-up, prevalent and incident atrial fibrillation or coronary heart disease, and treatment with aspirin, warfarin, or statins. As expected, most of the time-varying covariates were associated with an increased risk of stroke. Relative risk reductions for losartan were virtually unchanged after accounting for each potential confounding factor.

The benefit of losartan versus atenolol was also independent of regression of electrocardiographic LVH by Cornell product and Sokolow-Lyon voltage as time-varying covariates, as well as Framingham risk score and baseline and time-varying systolic and diastolic pressures (HR, 0.80; 95% CI, 0.67 to 0.94; \( P = 0.009 \)).

The impact of losartan-based therapy in various groups at high risk of stroke are presented in Table 4. The variability in the magnitude of losartan-associated reductions in the relative risk of stroke in these subgroups was magnified when incidence rates were considered to yield absolute risk reductions. Among patients with previous albuminuria, previous cerebrovascular disease, isolated systolic hypertension, and prevalent atrial fibrillation, absolute risk reductions approached, or well exceeded, that observed for the average patient enrolled in the trial. These absolute risk reductions translated into half or fewer the number of patients requiring losartan-based treatment to prevent a stroke over 5 years.

### Table 2. Number of Neurological Deficits According to Treatment Assignment

<table>
<thead>
<tr>
<th>Severity (No. of Deficits)</th>
<th>Losartan</th>
<th>Atenolol</th>
<th>Difference in No. of Strokes (Losartan-Atenolol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>40 (17)</td>
<td>62 (20)</td>
<td>−22</td>
</tr>
<tr>
<td>≥7</td>
<td>6 (3)</td>
<td>12 (4)</td>
<td>−6</td>
</tr>
<tr>
<td>6</td>
<td>3 (1)</td>
<td>9 (3)</td>
<td>−6</td>
</tr>
<tr>
<td>5</td>
<td>12 (5)</td>
<td>10 (3)</td>
<td>+2</td>
</tr>
<tr>
<td>4</td>
<td>31 (14)</td>
<td>41 (13)</td>
<td>−10</td>
</tr>
<tr>
<td>3</td>
<td>42 (18)</td>
<td>50 (17)</td>
<td>−8</td>
</tr>
<tr>
<td>2</td>
<td>58 (25)</td>
<td>59 (19)</td>
<td>−1</td>
</tr>
<tr>
<td>1</td>
<td>39* (17)</td>
<td>63* (21)</td>
<td>−24</td>
</tr>
</tbody>
</table>

*One patient who suffered a stroke in each arm had no residual deficit.

### Table 1. Incidence of Stroke Subtypes by Treatment Assignment and Corresponding HRs

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Losartan (n=4605)</th>
<th>Atenolol (n=4588)</th>
<th>Adjusted† HR (95% CI)</th>
<th>Unadjusted HR (95% CI)</th>
<th>( P ) Value</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td>232 (5.0)</td>
<td>309 (6.7)</td>
<td>0.75 (0.63–0.89)</td>
<td>0.74 (0.63–0.88)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>203 (4.4)</td>
<td>277 (6.0)</td>
<td>0.73 (0.61–0.88)</td>
<td>0.73 (0.61–0.87)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>170 (3.7)</td>
<td>233 (5.1)</td>
<td>0.73 (0.60–0.89)</td>
<td>0.72 (0.59–0.88)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Embolic</td>
<td>36 (0.8)</td>
<td>48 (1.0)</td>
<td>0.76 (0.50–1.18)</td>
<td>0.75 (0.58–1.15)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>27 (0.6)</td>
<td>34 (0.7)</td>
<td>0.80 (0.48–1.32)</td>
<td>0.79 (0.48–1.31)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Other/unclassified</td>
<td>5 (0.1)</td>
<td>5 (0.1)</td>
<td>1.02 (0.30–3.53)</td>
<td>1.00 (0.29–3.44)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Any fatal stroke</td>
<td>40 (0.9)</td>
<td>62 (1.4)</td>
<td>0.65 (0.43–0.96)</td>
<td>0.64 (0.43–0.95)</td>
<td>0.028</td>
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</table>

*Per 1000 patient ears of follow-up; †for degree of LVH and Framingham risk score at randomization.
Discussion

We provide a detailed assessment of the effects of losartan-based relative to atenolol-based therapy on stroke outcomes in hypertensive patients with LVH in the LIFE study. As reported previously, LIFE found a significant 25% reduction in stroke rate compared with an agent from a class of drugs (β-blockers) that has been documented to afford a significant lowering of stroke risk compared with placebo. The stroke end point is of particular importance in LIFE because it had the greatest cumulative incidence of all cardiovascular end points in the trial, with 6% of participants experiencing a stroke during follow-up. The present analyses show that the substantial lowering of the risk of stroke with losartan-based therapy applied consistently to different stroke subtypes, with significant reductions of fatal stroke and atherothrombotic (ischemic) stroke. These effects were accompanied by corresponding decreases in rates of multiple incident strokes and of specific neurological deficits. Whether losartan-associated benefits in stroke prevention are generalizable to patients without electrocardiographic LVH cannot be determined definitively within the LIFE data set. But a post hoc analysis in the 20% of LIFE participants whose screening ECGs were not confirmed to show LVH by LIFE criteria demonstrated a lower stroke rate in losartan-treated patients (HR, 0.65; 95% CI, 0.45 to 0.93; P = 0.019).

The beneficial effects of losartan were consistent across most clinical subgroups, but statistically significant interactions occurred in 2 instances, suggesting exceptions to the cerebrovascular benefit of losartan among blacks and younger participants. Statistical multiplicity can make subgroup analyses difficult to interpret, and it is uncertain whether the findings in these 2 subgroups represent true differences or chance effects. Younger patients have lower rates of stroke, which might result in less stable estimates of treatment effects, and the reversal in younger participants of the losartan benefit seen in older ones was not significant. Concerning the finding in blacks, race-ethnic differences in the pathophysiology of hypertension have been documented wherein American blacks exhibit a low renin, salt-sensitive
variety of the disorder. Accordingly, it has been suggested that blood pressure in this group responds less well to interruption of the renin-angiotensin system (RAS). However, in LIFE, losartan-based therapy resulted in comparable blood pressure lowering in black and nonblack subgroups, and losartan effected greater LVH regression than atenolol in black and nonblack participants alike. Adjustment for race-ethnic differences in baseline characteristics did not influence the results, and changes in laboratory measures such as glucose or uric acid during the trial were similar in the 2 subgroups. Thus, a mechanistic explanation is lacking for the race-ethnic differences in stroke incidence. Differences in treatment effects observed in blacks within this trial require further investigation.

Despite the slightly greater systolic blood pressure at the end of the study in the atenolol arm, adjustment for systolic pressure during the trial did not meaningfully change the observed risk reduction. The results were likewise not appreciably altered by control for diastolic or pulse pressure as time-varying covariates. Moreover, there was no significant interaction between achieved blood pressure and randomization status. These analyses support the interpretation that the effects of losartan on stroke were independent of differences in blood pressure reduction during the trial.

The finding that RAS blockade exerted beneficial vascular effects irrespective of blood pressure lowering is in line with results of the Heart Outcomes Prevention Evaluation (HOPE) study. In placebo-controlled HOPE, the angiotensin-converting enzyme (ACE) inhibitor ramipril reduced stroke by 32% in high-risk patients, exceeding the effect expected for modest lowering of clinic pressure but perhaps not the greater 24-hour pressure reduction achieved in a substudy. In contrast, 2 recent active-controlled trials comparing ACE inhibitors to thiazide diuretics in hypertensive populations failed to document stroke-specific benefit. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) found a 15% relative-risk increase in stroke for lisinopril compared with chlorthalidone, whereas the second Australian National Blood Pressure (ANBP2) study found no significant effect on this secondary end point. However, in ALLHAT, blood pressure was reduced significantly less in the ACE inhibitor than in the diuretic arm. This observation is likely attributable to the lower efficacy of adding atenolol to lisinopril than to a diuretic, as called for by study design. The smaller blood pressure reduction achieved by the lisinopril-based regimen was especially pronounced among black patients in ALLHAT, and it was the high rate of incident stroke in lisinopril-treated blacks that drove the overall difference observed.

The view that RAS antagonism may lead to cerebral protection beyond antihypertensive effects is buttressed by experimental studies. In stroke-prone hypertensive rats, di-

### Table 3. Stroke Risk for Losartan vs Atenolol Adjusted by Baseline and Time-Varying Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Covariate HR 95% CI</th>
<th>P Value</th>
<th>Treatment HR 95% CI</th>
<th>P Value</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td>0.74 (0.63–0.88)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
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<td></td>
<td>0.76 (0.64–0.90)</td>
<td>0.001</td>
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<td></td>
<td>0.74 (0.62–0.88)</td>
<td>&lt;0.001</td>
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<td></td>
<td>0.76 (0.64–0.91)</td>
<td>0.002</td>
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<td>0.001</td>
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<td></td>
<td></td>
<td>0.74 (0.63–0.88)</td>
<td>&lt;0.001</td>
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</table>

BP indicates blood pressure; FRS, Framingham Risk Score. *Prevalent and incident.

### Table 4. Number Needed to Treat With Losartan vs Atenolol Among Various Subgroups

<table>
<thead>
<tr>
<th>Relative Risk* (95% CI)</th>
<th>Risk Difference†</th>
<th>No. Needed to Treat‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average patient in LIFE</td>
<td>0.74 (0.63–0.88)</td>
<td>3.7</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td>0.84 (0.65–1.10)</td>
<td>3.7</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>0.69 (0.57–0.84)</td>
<td>5.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.78 (0.54–1.13)</td>
<td>5.5</td>
</tr>
<tr>
<td>Micro/macronalbuminuria</td>
<td>0.65 (0.48–0.88)</td>
<td>6.9</td>
</tr>
<tr>
<td>Previous stroke/transient ischemic attack</td>
<td>0.70 (0.46–1.08)</td>
<td>8.1</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>0.56 (0.36–0.86)</td>
<td>8.3</td>
</tr>
<tr>
<td>Previous atrial fibrillation</td>
<td>0.56 (0.31–0.98)</td>
<td>23.0</td>
</tr>
</tbody>
</table>

*Unadjusted. †Per 1000 patient years; ‡to prevent 1 stroke in 5 years.
minishing RAS activity with potassium, captopril, or losartan prevented stroke occurrence without lowering blood pressure. Moreover, studies in a model of acute stroke induced by carotid ligation in gerbils suggest that AT1 receptor stimulation may mediate cerebrovascular anti-ischemic effects. Angiotensin II infusion and losartan, which blocks AT1 and stimulates angiotensin II synthesis by inhibiting AT1 receptor–mediated negative feedback on renin secretion, improved cerebral perfusion and survival in this model more than ACE inhibition. Thus, additional research on possible protective actions of angiotensin II mediated by the AT2 receptor or another as yet undefined receptor could be fruitful.

An additional mechanism that may contribute to the cerebrovascular benefits of losartan is enhanced reduction of LVH, itself an independent risk factor for stroke. Nonetheless, adjustment for regression of electrocardiographic LVH did not meaningfully alter the relative risk for stroke. Furthermore, adjustment for incident atrial fibrillation, of which LVH is an important determinant, did not influence the magnitude of risk reduction. Whether alternative mechanisms, such as the uricosuric effects of losartan, may play an additional role in stroke reduction is unknown.

It is important to emphasize that the predominance of stroke events in LIFE is not a distinctive feature of this study. In a review of major clinical trials in hypertension since 1990, stroke, not myocardial infarction, was the most common cardiovascular complication. Because stroke is a principal morbid, often fatal, event in hypertensive patients, the stroke-specific benefits of losartan among patients with LVH are of considerable importance to public health. The fact that as few as 9 patients, in those with pre-existing atrial fibrillation, would need to be treated for 5 years to prevent 1 stroke indicates that losartan-based therapy could afford impressive clinical benefits. Substantial public health benefits are suggested by a recent calculation that institution of losartan-based therapy could prevent nearly 25 000 strokes per year in Europe among patients meeting LIFE entry criteria.

Two limitations concerning stroke categorization must be acknowledged. First, the stroke classification scheme applied broad criteria from the Framingham Study to determine stroke etiology, and more detailed classification would have refined the categorization of stroke subtypes. Although the impact of AT1 receptor blockade appeared consistent among stroke subtypes, differential effects on lacunar versus large-vessel strokes could not be evaluated. Second, standard stroke-related disability scales were not used, and formal assessment of stroke severity was therefore infeasible.

Perspectives

First-line therapy with losartan substantially reduces the risk of major stroke subtypes compared with atenolol-based therapy among hypertensive patients with LVH. Such benefits are independent of blood pressure reduction and apply across most clinical and demographic groups. The extent to which failure to detect similar stroke-specific benefit for active-control ACE inhibitor trials reflects differences in study populations, choice of active comparator, achieved blood pressure reductions, the play of chance, or biological difference between AT1 receptor blocker– and ACE inhibitor–mediated cerebral protection is uncertain.

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References

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