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Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study

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OBJECTIVES This study was designed to evaluate whether different antihypertensive treatment regimens with similar blood pressure reduction have different effects on new-onset atrial fibrillation (AF).

BACKGROUND It is unknown whether angiotensin II receptor blockade is better than beta-blockade in preventing new-onset AF.

METHODS In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study 9,193 hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy were randomized to once-daily losartan- or atenolol-based antihypertensive therapy. Electrocardiograms were Minnesota coded centrally, and 8,851 patients without AF by electrocardiogram or history, who were thus at risk of developing AF, were followed for 4.8 ± 1.0 years.

RESULTS New-onset AF occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, 95% confidence interval [CI] 0.55 to 0.83, $p < 0.001$) despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer (1,809 ± 225 vs. 1,709 ± 254 days from baseline, $p = 0.057$) than those receiving atenolol. Moreover, patients with new-onset AF had two-, three- and fivefold increased rates, respectively, of cardiovascular events, stroke, and hospitalization for heart failure. There were fewer composite end points (n = 31 vs. 51, hazard ratio = 0.60, 95% CI 0.38 to 0.94, $p = 0.03$) and strokes (n = 19 vs. 38, hazard ratio = 0.49, 95% CI 0.29 to 0.86, $p = 0.01$) in patients who developed new-onset AF in the losartan compared to the atenolol treatment arm of the study. Furthermore, Cox regression analysis showed that losartan (21% risk reduction) and new-onset AF both independently predicted stroke even when adjusting for traditional risk factors.

CONCLUSIONS Our novel finding is that new-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction. (J Am Coll Cardiol 2005;45:712–9) © 2005 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is associated with increased cardiovascular risk, and the incidence of AF is increased in patients with uncontrolled hypertension (1–3). Antihypertensive treatment reduces new-onset AF. However, it is unclear whether there is difference in risk of new-onset AF with different antihypertensive drugs. To our knowledge only one study in post-infarct patients suggests that renin-angiotensin system blockade, compared to placebo, reduces new-onset AF and helps maintain sinus rhythm (4). As this was a placebo-controlled study, it is not known whether this outcome was a result of blood pressure reduction per se or a direct effect of renin-angiotensin system blockade. Several animal and human studies suggest antiarrhythmic properties of renin-angiotensin blockade, but none address whether the beneficial effect is independent of potential blood pressure reduction by angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (5–9). Furthermore, although AF is a frequent complication of hypertension, there is little evidence that choosing what many regard as

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
ECG = electrocardiographic
HF = heart failure
HR = hazard ratio
LV = left ventricular/ventricle
LIFE = Losartan Intervention For Endpoint reduction in hypertension study

first-line therapy, beta-blockade with combined antiarrhythmic and antihypertensive properties, is better than other antihypertensive treatments in preventing AF (10). One striking result of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a 25% reduction of fatal and nonfatal stroke by losartan-based treatment. This result was in part explained by a 45% lower rate of stroke (24.1 vs. 46.5 strokes per 1,000 patient-years of follow-up) on losartan treatment in patients with a history of AF (11), but could also reflect benefits of reduced new-onset AF.

The present study was undertaken to determine whether selective angiotensin II type 1 receptor blockade with losartan was more effective than beta-blockade with atenolol in reducing new-onset AF and associated cardiovascular events in hypertensive patients with electrocardiographic (ECG) left ventricular (LV) hypertrophy.

METHODS

The LIFE study was a prospective, randomized, double-masked, parallel group study (n = 9,193) with double-dummy technique that evaluated the long-term effects of losartan- compared to atenolol-based antihypertensive therapy in patients with hypertension and ECG LV hypertrophy on cardiovascular morbidity and mortality. The main outcome (12) and the complete study protocol with study design, organization, clinical measures, exclusion criteria, basis for choice of comparative agents, statistical considerations, and baseline characteristics (13,14) have been published. We have reported a lower rate of cardiovascular events with losartan- compared to atenolol-based treatment in 342 LIFE patients with AF before or at study baseline (11). The remaining 8,851 patients with ECG-documented sinus rhythm at baseline and no history of AF who were at risk of developing AF during the study are the focus of this study (Fig. 1).

As previously described, patients ages 55 to 80 years, having previously treated or untreated hypertension and ECG signs of LV hypertrophy (12) were randomized to initial therapy with 50 mg/day of losartan or atenolol after one to two weeks taking placebo if they had sitting systolic blood pressure 160 to 200 mm Hg and/or diastolic blood pressure of 95 to 115 mm Hg. In both groups, hydrochlorothiazide was added in case of insufficient pressure lowering. Thereafter the study drug was increased to 100 mg/day

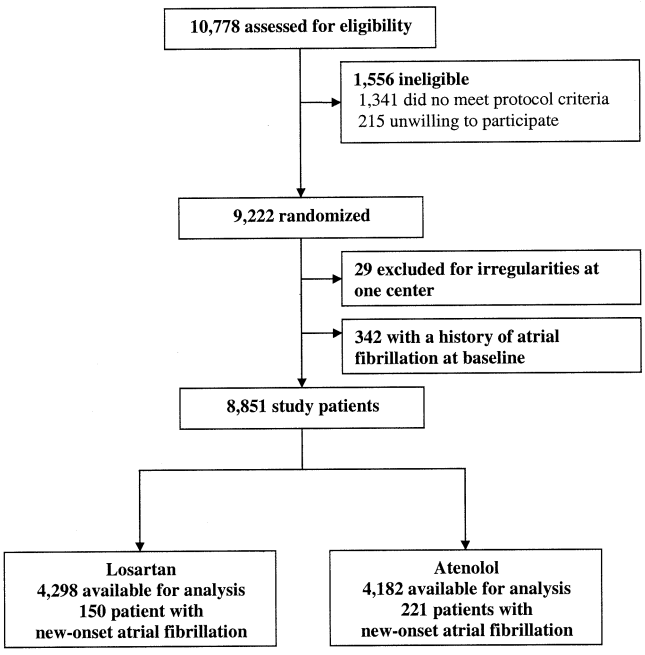

Figure 1. Trial profile.

and supplemented with additional antihypertensive therapy in order to reach target blood pressure of <140/90 mm Hg. Patients were enrolled from June 1995 to May 1997 and were followed ≥4 years (mean 4.8 years) with regular visits. Sitting blood pressure was recorded 24 h postdose (range 22 to 26 h).

New-onset AF was identified from annual in-study ECGs that underwent Minnesota coding for AF at a single ECG core center (13). Care of the patients with new-onset AF was left to the discretion of local investigators. After the stopping date in September 2001, patients had a follow-up clinic visit or at least vital status check within six weeks. Laboratory tests were carried out at two laboratories that assured comparability of measurements by cross-validation.

Echocardiographic assessment of baseline LV systolic function and valvular disease was obtained in approximately 10% of study participants (15,16).

End points and adjudication. This report in 8,851 patients (more than 96% of the entire LIFE population) is based on analysis of a primary composite end point (n = 993), which is the first occurrence of cardiovascular death, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction. Additional end points included all-cause mortality (n = 735) and the first occurrence of each component of the composite end point, whether or not preceded by another component of the primary end point, including 380 cardiovascular deaths, 485 strokes, and 367 myocardial infarctions. All end points were reported by investigators, source data verified by independent monitors, and adjudicated by an independent committee on the basis of prespecified definitions (12). Prevalent coronary, cerebral, or peripheral vascular disease and smoking habits were reported by patients and investigators. Framingham risk score (17) was

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estimated from baseline blood pressure, total and high-density lipoprotein cholesterol, smoking, glucose, and ECG LV hypertrophy.

Statistical methods. SPSS version 12.0 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Potential risk factors (including baseline clinical, demographic, and laboratory data) were assessed for association with new-onset AF. Cox proportional hazards models were used to compare hazard ratios (HRs) between study treatment allocation groups (losartan or atenolol), and to evaluate contributions of differences in the degree of LV hypertrophy (both Cornell voltage-duration product and Sokolow-Lyon voltage as continuous variables), the Framingham risk score (17), and other covariates. For each baseline characteristic, a univariate proportional hazards regression model was used to estimate the HR and its 95% confidence interval (CI). Variables without significant effects were eliminated before developing multivariate models. Multivariate analyses were then performed using Cox regression models with inclusion of remaining variables to identify those independently associated with the end points. Two-tailed $p < 0.05$ was considered significant.

RESULTS

Patient selection and characteristics. Of 9,193 randomized patients, 8,851 patients remained after exclusion of those with AF by history or by Minnesota coding of the baseline ECG (Fig. 1). Rates of new-onset AF in strata defined by baseline characteristics are given in Table 1, dichotomized at median values of continuous variables for display purposes.

In the subset of LIFE echocardiography patients without AF by history or at baseline (n = 911), there were no differences in prevalences of aortic or mitral valve disease (data not shown), LV ejection fraction (61 ± 9% vs. 61 ± 8%, p = 0.889) or left atrial size (3.9 ± 0.6 cm vs. 3.9 ± 0.6 cm, p = 0.752) between losartan- and atenolol-treated patients, respectively.

Patients treated with losartan had, compared to those receiving atenolol, similar baseline characteristics (Table 2) and reductions of systolic (−28.5 ± 18.9 mm Hg vs. −27.3 ± 19.3 mm Hg), mean arterial (−20.0 ± 11.5 vs. −19.7 ± 11.5), and diastolic (−15.8 ± 10.1 mm Hg vs. − 15.9 ± 10.0 mm Hg) blood pressure, but had more reduction in ECG LV hypertrophy by Cornell voltage-duration product (−268 ± 820 mV·ms vs. 122 ± 872 mV·ms, $p < 0.0001$).

There were no differences at baseline or during the study in concomitant treatment with class IA-IC or III antiarrhythmic drugs, digoxin, or non-dihydropyridine calcium channel blockers between losartan- and atenolol-treated patients (data not shown). However, atenolol-treated patients were more likely to receive anticoagulation therapy (5.3% vs. 7.7%, $p < 0.001$).

New-onset AF. New-onset AF occurred in 150 losartan- (6.8 per 1,000 person-years of follow-up) and 221 atenolol-treated patients (10.1 per 1,000 person-years of follow-up, HR = 0.67, 95% CI 0.55 to 0.83, $p < 0.001$). Adjustment for differences in LV hypertrophy by Cornell voltage duration and Sokolow-Lyon criteria and Framingham risk score had only minimal effect on the reduction of new-onset AF associated with losartan (Fig. 2). Furthermore, patients taking losartan tended to stay in sinus rhythm longer from baseline (1,809 ± 225 vs. 1,709 ± 254 days from baseline, p = 0.057) than those taking atenolol.

New-onset AF and outcome. Cardiovascular morbidity and mortality was more frequent in patients with new-onset AF than with persistent sinus rhythm (Table 3). Patients with new-onset AF had an approximately twofold increased risk of cardiovascular events, about threefold higher risk of fatal or nonfatal stroke, and fivefold increased rate of hospitalization for heart failure (HF), even after adjustment for covariates.

Although patients with new-onset AF treated with losartan versus atenolol had similar baseline characteristics (Table 2), losartan-treated patients with new-onset AF had a 40% lower rate of subsequent composite events compared with atenolol-treated patients (n = 31 vs. 51, HR = 0.60, 95% CI 0.38 to 0.94, p = 0.03). There were substantially fewer subsequent strokes (n = 19 vs. 38, HR = 0.49, 95% CI 0.29 to 0.86, p = 0.01), a trend toward fewer myocardial infarctions (n = 9 vs.16, HR = 0.60, 95% CI 0.25 to 1.27, p = 0.16) and no difference in cardiovascular mortality (n = 14 vs. 14, p = NS) in losartan- and atenolol-treated patients with new-onset AF. In contrast, atenolol-treated patients with new-onset AF had fewer hospitalizations for HF (n = 20 vs. 30, HR = 0.43, 95% CI 0.25 to 0.76, p = 0.004) and a trend toward fewer sudden cardiac deaths (n = 2 vs. 6, HR = 0.22, 95% CI 0.05 to 1.10, p = 0.07).

In multivariate analysis that adjusted for differences in age; blood pressure; Framingham risk score; ECG LV hypertrophy; albuminuria; diabetes; and coronary, cerebral, and peripheral vascular disease, both new-onset AF (HR = 2.31, 95% CI 1.70 to 3.14, $p < 0.001$) and atenolol treatment (HR = 1.27, 95% CI 1.05 to 1.54, p = 0.015) were independently associated with fatal and nonfatal stroke among patients free of AF at baseline.

Prediction of new-onset AF. For each baseline characteristic, a univariate proportional hazards regression model was used to estimate the hazard ratio for new-onset AF and its 95% CI (Table 4). Variables with significant associations ($p < 0.05$) were used to develop multivariate models. To identify the most important factors associated with development of new-onset AF, we developed four multivariate prediction models (Table 5). In the first model, which considered baseline characteristics, age was by far the most important predictor of new-onset AF, with each year of age associated with a 9% higher rate of new-onset AF. Age is followed, in order, by male gender (56% increase in risk compared to women), systolic blood pressure (6% increase per 10 mm Hg) and ECG LV hypertrophy by Cornell product (4% increase per 100 mV·ms). In an alternative

Table 1. New-Onset Atrial Fibrillation in Relation to Baseline Characteristics

	New-Onset Atrial Fibrillation, n (%)					
	Losartan-Treated	**p**	**Atenolol-Treated**	**p**	**All**	**p**
Age						
<65 yrs	33 (1.9)		37 (2.2)		70 (2.0)	
≥65 yrs	117 (4.3)	<0.001	184 (6.8)	<0.001	301 (5.5)	<0.001
Gender						
Male	75 (3.7)		115 (5.7)		190 (4.7)	
Female	75 (3.1)	0.263	106 (4.4)	0.051	181 (3.8)	0.026
Race						
Caucasian	143 (3.5)		217 (5.3)		360 (4.4)	
Black	5 (1.9)	0.216	2 (0.8)	0.000	7 (1.3)	0.001
Body-mass index						
<27.5 kg/m^2	68 (3.1)		111 (5.0)		179 (4.0)	
≥27.5 kg/m^2	82 (3.7)	0.231	106 (5.0)	0.936	188 (4.4)	0.434
Systolic blood pressure						
<175 mm Hg	59 (2.6)		92 (4.1)		151 (3.3)	
≥175 mm Hg	91 (4.3)	0.001	129 (6.0)	0.005	220 (5.1)	0.000
Diastolic blood pressure						
<98 mm Hg	70 (3.4)		114 (5.5)		184 (4.5)	
≥98 mm Hg	80 (3.3)	0.855	107 (4.6)	0.148	187 (4.0)	0.205
Heart rate						
<72 beats/min	52 (3.0)		105 (5.7)		157 (4.4)	
≥72 beats/min	98 (3.7)	0.188	114 (4.5)	0.070	212 (4.1)	0.521
Cornell voltage-duration criteria						
<2,668 mV·ms	49 (2.3)		93 (4.3)		142 (3.3)	
≥2,668 mV·ms	101 (4.4)	<0.001	128 (5.7)	0.032	229 (5.0)	<0.001
Sokolow-Lyon criteria						
<29 mV	77 (3.5)		107 (5.0)		184 (4.2)	
≥29 mV	73 (3.2)	0.589	114 (5.1)	0.899	187 (4.1)	0.815
Framingham risk score						
<21%	64 (2.8)		94 (4.2)		158 (3.5)	
≥21%	86 (3.9)	0.044	127 (5.8)	0.017	213 (4.9)	0.002
Diabetes						
No	125 (3.2)		195 (5.1)		320 (4.1)	
Yes	25 (4.5)	0.129	26 (4.6)	0.756	51 (4.6)	0.478
Coronary artery disease						
No	123 (3.2)		192 (5.0)		315 (4.1)	
Yes	27 (4.3)	0.152	29 (5.4)	0.674	56 (4.8)	0.255
Cerebral vascular disease						
No	137 (3.3)		203 (5.0)		340 (4.2)	
Yes	13 (3.7)	0.644	18 (5.5)	0.694	31 (4.6)	0.618
Peripheral vascular disease						
No	139 (3.3)		211 (5.0)		350 (4.2)	
Yes	11 (4.2)	0.477	10 (4.6)	0.874	21 (4.4)	0.815
Potassium						
<4.1 mmol/l	59 (3.7)		90 (5.7)		149 (4.7)	
≥4.1 mmol/l	82 (3.2)	0.429	109 (4.3)	0.036	191 (3.8)	0.037
Total cholesterol						
<6.0 mmol/l	71 (3.4)		102 (5.1)		173 (4.2)	
≥6.0 mmol/l	70 (3.3)	0.809	97 (4.6)	0.524	167 (4.0)	0.527
HDL cholesterol						
<1.44 mmol/l	61 (2.9)		96 (4.7)		157 (3.8)	
≥1.44 mmol/l	80 (3.8)	0.124	103 (5.0)	0.666	183 (4.4)	0.187
Glucose						
<5.4 mmol/l	69 (3.3)		104 (4.9)		173 (4.1)	
≥5.4 mmol/l	75 (3.6)	0.536	98 (4.8)	0.794	173 (4.2)	0.843
Creatinine						
<83 μmol/l	71 (3.4)		112 (5.1)		183 (4.3)	
≥83 μmol/l	73 (3.4)	1.000	90 (4.5)	0.311	163 (3.9)	0.391
Urine albumin/creatinine ratio						
<1.25 mg/mmol	53 (2.6)		81 (4.2)		134 (3.4)	
≥1.25 mg/mmol	81 (4.1)	0.010	109 (5.5)	0.059	190 (4.8)	0.002

HDL = high-density lipoprotein.

Table 2. Baseline Demographic and Clinical Characteristics of Patients With New-Onset Atrial Fibrillation Randomized to Losartan or Atenolol

Characteristic	Losartan (n = 150)	Atenolol (n = 221)	p
Age (yrs)	70.3 ± 6.9	70.7 ± 6	NS
Female gender (%)	75 (50)	106 (48)	NS
Systolic blood pressure (mm Hg)	177.3 ± 14.2	177.8 ± 13.5	NS
Diastolic blood pressure (mm Hg)	97.9 ± 8.8	96.5 ± 8.4	NS
Heart rate (beats/min)	74.3 ± 11.4	72.4 ± 11.6	NS
Body mass index (kg/m^2)	28.8 ± 5.6	28 ± 4.6	NS
Cornell voltage-duration (mV·ms)	2,990 ± 993	2,975 ± 929	NS
Sokolow-Lyon (mV)	30 ± 11.5	30.8 ± 10.9	NS
Framingham risk (%)	23.7 ± 9.5	24.2 ± 9.4	NS
Medical history			
Diabetes mellitus (%)	16.7	11.8	NS
Coronary disease (%)	18.0	13.1	NS
Cerebrovascular disease (%)	8.7	8.1	NS
Peripheral vascular disease (%)	7.3	4.5	NS
Laboratory values			NS
Serum-potassium (mmol/l)	4.1 ± 0.4	4.1 ± 0.4	NS
Total cholesterol (mmol/l)	6 ± 1.3	5.9 ± 1.0	NS
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.5	NS
Glucose (mmol/l)	6.1 ± 2.1	6.1 ± 2.0	NS
Creatinine (μmol/l)	88.9 ± 31	84.8 ± 16.6	NS
Urine albumin/creatinine (mg/mmol)	16.2 ± 53.6	6.8 ± 16.1	0.05

HDL = high-density lipoprotein; NS = not significant.

model (data not shown) lower ECG LV hypertrophy by Cornell product at the annual re-examination was predictive of less new-onset AF.

Addition of study treatment to the second model (Table 5) indicated that randomization to losartan was associated with a 33% lower rate of new-onset AF, independent of other risk factors ($p < 0.001$). Addition of study treatment to the model left the other predictors of new-onset AF from the first model almost unchanged, documenting an independent effect of losartan treatment on prevention of AF. Additional models showed that age and male gender predicted new-onset AF within each treatment group considered separately.

DISCUSSION

This study is, to our knowledge, the first to show that one antihypertensive treatment regimen is more effective than another with equal blood pressure reduction in reducing new-onset AF. That losartan reduced the rate of new-onset AF by 33% compared to atenolol with similar blood pressure reduction is surprising, as many regard beta-blockade a first-line therapy to prevent AF as well as preferred treatment for rate-control in established AF (10). In addition, patients receiving losartan-based therapy tended to stay in sinus rhythm longer.

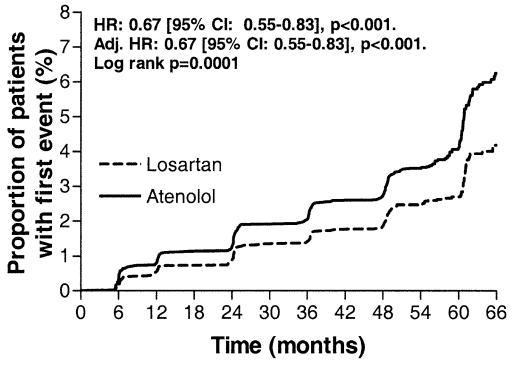

Figure 2. Kaplan-Meier curves illustrating new-onset electrocardiogram-verified atrial fibrillation during follow-up. CI = confidence interval; HR = hazard ratio.

Furthermore, our study demonstrates the clinical relevance of preventing new-onset AF, as it was associated with two-, three-, and five-fold higher rates of cardiovascular morbidity and mortality, stroke, or hospitalization for HF. New-onset AF was associated with increased cardiovascular morbidity and mortality even when taking additional risk factors, as summarized by the Framingham risk score and ECG measures of LV hypertrophy, into account. Furthermore, we found losartan-based treatment significantly reduced cardiovascular events in patients with new-onset AF, with the difference of 19 strokes between the treatment-arms in patients with new-onset AF, comprising about 25% of the 77 fewer strokes associated with losartan- versus atenolol-based therapy in the entire LIFE study (12). However, patients with new-onset AF had fewer hospitalizations for HF when treated with atenolol than losartan. This might be explained by the fact that atenolol showed a better effect on LV ejection fraction in the LIFE echocardiographic substudy, associated with greater reduction in heart rate (18). Of further interest was the trend toward a lower risk of sudden cardiac death associated with new-onset AF in atenolol- than in losartan-treated patients. This is in contrast to findings in the LIFE trial's diabetic subpopulation (19) and merits further research.

Table 3. End Points in Patients With and Without New-onset Atrial Fibrillation

End Point	New-Onset Atrial Fibrillation* (n = 371)			Sinus Rhythm (n = 8,480)			Adjusted Hazard Ratio* (95% CI)	p Value	Unadjusted Hazard Ratio (95% CI)	p Value
	Rate†	n	(%)	Rate‡	n	(%)				
Primary composite end point	47.4	82	22.1	22.5	911	10.7	1.88 (1.50–2.36)	<0.001	2.12 (1.70–2.66)	<0.001
Components										
Cardiovascular mortality	15.2	28	7.5	8.4	352	4.2	1.57 (1.07–2.31)	0.021	1.80 (1.22–2.64)	0.003
Stroke	32.0	57	15.4	10.3	428	5.0	2.82 (2.14–3.72)	0.000	3.12 (2.37–4.12)	<0.001
Myocardial infarction	13.5	25	6.7	8.2	342	4.0	1.49 (0.99–2.24)	0.055	1.65 (1.10–2.47)	0.016
Other end points										
Total mortality	21.8	40	10.8	16.8	695	8.2	1.15 (0.84–1.59)	0.377	1.29 (0.94–1.78)	0.113
Hospitalization for										
Angina pectoris	6.5	12	3.2	5.6	235	2.8	1.04 (0.58–1.86)	0.895	1.15 (0.65–2.06)	0.627
Heart failure	27.0	50	13.5	5.1	215	2.5	4.96 (3.64–6.74)	<0.001	5.55 (4.08–7.55)	<0.001
Revascularization	7.5	14	3.8	4.5	191	2.3	1.47 (0.85–2.53)	0.167	1.66 (0.97–2.86)	0.066
Sudden cardiac death‡	4.3	8	2.2	3.7	156	1.8	1.01 (0.50–2.05)	0.981	1.15 (0.57–2.35)	0.692

*Composed of resuscitated cardiac arrest, cardiac death within 24 h; †for degree of left ventricular hypertrophy, Framingham risk score and treatment allocation; ‡per 1,000 patient-years of follow-up.
CI = confidence interval.

Our study extends previous reports suggesting that renin-angiotensin system blockade by either angiotensin-converting enzyme inhibition (4,20) or angiotensin II receptor blockade (9) reduces incident AF. In the TRACE study new-onset AF was reduced by 45% with trandolapril (4). A subanalysis of the SOLVD study reported that new-onset AF was reduced as much as 78% with enalapril (20). However, both studies were placebo-controlled, and therefore superior antihypertensive effect of the study drug may have contributed to the lower rate of AF. Our study further supports this inference, as higher systolic blood pressure was an independent predictor of new-onset AF, underlining the importance of blood pressure control for prevention of AF.

Furthermore, the present results are consistent with our previous finding that LIFE patients with a history of AF benefited from losartan-based treatment, with 42% reduction of both composite end points and cardiovascular mortality and 45% risk reduction for stroke (11).

Table 4. Univariate Predictors of New-Onset Atrial Fibrillation

Variable	Hazard Ratio (95% CI)	p Value
Age (yrs)	1.09 (1.07–1.10)	<0.001
Male gender	1.3 (1.06–1.60)	0.011
Systolic blood pressure (mm Hg)	1.02 (1.01–1.02)	<0.001
Diastolic blood pressure (mm Hg)	0.99 (0.98–1.00)	0.046
Cornell voltage-duration (mV·ms/100)	1.013 (1.004–1.022)	0.006
Sokolow-Lyon voltage (mV)	1.01 (0.997–1.02)	0.170
Framingham risk score (%)	1.02 (1.01–1.03)	<0.001
Coronary disease (yes/no)	1.28 (0.99–1.67)	0.062
Total cholesterol (mmol/l)	0.89 (0.80–0.98)	0.014
Potassium (mmol/l)	0.78 (0.58–1.04)	0.091
Log UACR (mg/mmol)	1.44 (1.23–1.67)	<0.001
Treatment with losartan	0.67 (0.54–0.82)	<0.001

Heart rate, body mass index, diabetes, cerebral and peripheral vascular disease, high-density lipoprotein cholesterol, plasma glucose, and creatinine were not significant predictors ($p > 0.20$).
CI = confidence interval; UACR = urine albumin/creatinine ratio.

Mechanisms. One explanation for the added benefit of losartan in preventing new-onset AF and events associated therewith in hypertensive patients with LV hypertrophy could be parallel effects of losartan on regression of atrial and ventricular hypertrophy. Our data suggest that sustained LV hypertrophy is an important predictor of new-onset AF. We have recently shown in the LIFE echocardiography substudy (21) that patients with LV hypertrophy also exhibit increased left atrial size, which has been associated with increased stroke risk in normotensive (22) and hypertensive adults (23). The greater regression of ECG and echo LV hypertrophy with losartan- than atenolol-based therapy (24,25) may have been paralleled by greater reduction of left atrial overload and dilatation, thereby reducing stimuli to new-onset AF. A recent animal study showed that angiotensin II receptor blockade prevented the promotion of AF by reducing atrial structural remodeling (5). Furthermore, a recent study suggests that renin-angiotensin system polymorphisms are associated with non-familial AF (26).

Study limitations. Potential limitations of the study include the evaluation of an overwhelmingly Caucasian population from the Nordic countries, the United Kingdom, and the U.S. All patients had ECG LV hypertrophy and hypertension and were thus at high cardiovascular risk. On the other hand, our annual ECG sampling undoubtedly underestimated the incidence of AF and reduced precision of treatment effect estimates.

Although the analysis of AF was not prespecified in the 1995 LIFE study analysis plan, evaluation of treatment effects in the subgroup of patients with new-onset AF was a planned secondary analysis before study termination (September 2001) and unblinding. Furthermore, patients with new-onset AF were recruited for hypertension and ECG LV hypertrophy and randomization within patients with new-onset AF may not be balanced.

Because outcomes were analyzed by the intention-to-

Table 5. Multivariate Predictors of New-Onset Atrial Fibrillation

Variable	Chi-Square	Hazard Ratio (95% CI)	p
Model 1: all patients			
Age (yrs)	105.5	1.09 (1.07–1.10)	<0.001
Male gender	18.0	1.56 (1.27–1.92)	<0.001
Systolic blood pressure (10 mm Hg)	5.5	1.09 (1.01–1.18)	0.019
Cornell voltage-duration (mV·ms/100)	4.1	1.01 (1.00–1.02)	0.035
Model 2: all patients with treatment allocation as a covariate			
Age (yrs)	106.2	1.09 (1.07–1.11)	<0.001
Male gender	17.7	1.56 (1.27–1.92)	<0.001
Systolic blood pressure (10 mm Hg)	5.2	1.09 (1.01–1.18)	0.023
Cornell voltage-duration (mV·ms/100)	4.3	1.01 (1.001–1.02)	0.030
Randomization to losartan	15.1	0.67 (0.54–0.82)	<0.001
Model 3: patients treated with losartan			
Age (yrs)	42.0	1.08 (1.06–1.11)	<0.001
Male gender	5.0	1.45 (1.05–2.00)	0.025
Model 4: patients treated with atenolol			
Age (yrs)	83.2	1.10 (1.08–1.12)	<0.001
Male gender	10.5	1.55 (1.19–2.03)	0.001

CI = confidence interval.

treat principle, without restriction after study drug discontinuation, open-label use of angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor/beta-blocker may have diminished differences between the groups. However, we found no statistical differences in open-label drug usage between losartan versus atenolol arms in patients with new-onset AF. Furthermore, information is unavailable regarding levels of anticoagulation between treatment arms.

Conclusions. Our novel finding is that new-onset AF and subsequent stroke were significantly reduced by losartan- compared with atenolol-based antihypertensive treatment with similar blood pressure reduction. Approximately 25% of the total reduction in stroke associated with losartan- as opposed to atenolol-based antihypertensive treatment in the entire LIFE study occurred in the subset of patients with new-onset AF.

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