ORIGINAL ARTICLE

Valsartan for Prevention of Recurrent Atrial Fibrillation

The GISSI-AF Investigators*

ABSTRACT

BACKGROUND

Atrial fibrillation is the most common cardiac arrhythmia, and no current therapy is ideal for control of this condition. Experimental studies suggest that angiotensin II–receptor blockers (ARBs) can influence atrial remodeling, and some clinical studies suggest that they may prevent atrial fibrillation.

METHODS

We conducted a large, randomized, prospective, placebo-controlled, multicenter trial to test whether the ARB valsartan could reduce the recurrence of atrial fibrillation. We enrolled patients who were in sinus rhythm but had had either two or more documented episodes of atrial fibrillation in the previous 6 months or successful cardioversion for atrial fibrillation in the previous 2 weeks. To be eligible, patients also had to have underlying cardiovascular disease, diabetes, or left atrial enlargement. Patients were randomly assigned to receive valsartan or placebo. The two primary end points were the time to a first recurrence of atrial fibrillation and the proportion of patients who had more than one recurrence of atrial fibrillation over the course of 1 year.

RESULTS

A total of 1442 patients were enrolled in the study. Atrial fibrillation recurred in 371 of the 722 patients (51.4%) in the valsartan group, as compared with 375 of 720 (52.1%) in the placebo group (adjusted hazard ratio, 0.97; 96% confidence interval [CI], 0.83 to 1.14; P=0.73). More than one episode of atrial fibrillation occurred in 194 of 722 patients (26.9%) in the valsartan group and in 201 of 720 (27.9%) in the placebo group (adjusted odds ratio, 0.89; 99% CI, 0.64 to 1.23; P=0.34). The results were similar in all predefined subgroups of patients, including those who were not receiving angiotensin-converting–enzyme inhibitors.

CONCLUSIONS

Treatment with valsartan was not associated with a reduction in the incidence of recurrent atrial fibrillation. (ClinicalTrials.gov number, NCT00376272.)

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Atrial fibrillation is the most common cardiac arrhythmia.[1-5] Antiarrhythmic drugs have only moderate efficacy in preventing recurrences of atrial fibrillation and sometimes cause serious adverse reactions.[6-8] Ablation is a costly procedure, and accepted indications are limited.[9,10] Thus, new approaches to the management of atrial fibrillation continue to be the subject of interest and investigation.

Some studies have shown that the recurrence of atrial fibrillation after cardioversion may be partially related to a biologic phenomenon known as remodeling, in which the electrical, mechanical, and structural properties of atrial tissue and cardiac cells are progressively and irreversibly altered, creating a more favorable substrate for atrial fibrillation.[11-13] The renin–angiotensin–aldosterone system plays a role in atrial remodeling. In animal models of atrial fibrillation, blockade of the renin–angiotensin–aldosterone system with the use of an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin II–receptor blocker (ARB) has been shown to favorably affect electrical and structural remodeling of the atrium.[14-17]

Several clinical studies have suggested that ACE inhibitors or ARBs may have a beneficial effect on either new-onset atrial fibrillation (i.e., primary prevention) or recurrent atrial fibrillation (i.e., secondary prevention). However, in those studies, either atrial fibrillation was assessed as an ancillary variable[18-24] or it was the main end point but the study was too small to definitively establish an effect on the incidence or recurrence of atrial fibrillation.[25-28] Published meta-analyses have reached contrasting conclusions on the effects of inhibitors of the renin–angiotensin–aldosterone system.[29,30] We conducted the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation (GISSI-AF) trial to assess whether the addition of the ARB valsartan to established therapies could reduce the rate of recurrence of atrial fibrillation in patients with a history of that arrhythmia.

Methods

Study Design

The rationale and the design of this study have been described previously.[31] The GISSI-AF study was a prospective, multicenter, randomized, double-blind, placebo-controlled trial. It was designed and supervised by the steering committee (see the Appendix) and approved by the ethics committee at each participating center. Funding was provided by Novartis, which had no role in the design or conduct of the trial; the collection, analysis, or interpretation of the data; or the writing of the report. The authors vouch for the accuracy and completeness of the data and the analysis.

Patients

Patients of either sex were eligible for inclusion in the study if they were at least 40 years of age and had had either two or more episodes of symptomatic atrial fibrillation (as documented on an electrocardiogram) in the previous 6 months or successful cardioversion (electrical or pharmacologic) for atrial fibrillation between 14 days and 48 hours before randomization. All patients had to have been in sinus rhythm for at least 2 days before randomization. In addition, patients had to have at least one of the following conditions: heart failure or a documented history of left ventricular dysfunction (defined as an ejection fraction of less than 40%); a history of hypertension for 6 months or more, with or without left ventricular hypertrophy; type 2 diabetes; a history of stroke or peripheral artery disease; a history of coronary artery disease; or atrial fibrillation without coexisting cardiovascular conditions but with left atrial dilatation (defined as a left atrial diameter of 45 mm or greater in men or 40 mm or greater in women).

Patients were excluded if they required treatment with ARBs for another indication; had contraindications to ARBs; had recently (within the previous 6 weeks) had an acute myocardial infarction, coronary bypass operation, or percutaneous coronary intervention; had clinically significant valvular disease; had thyroid dysfunction; or were scheduled to undergo catheter ablation or implantation of a pacemaker or defibrillator.

All participants had to have been on a stable regimen of treatment for atrial fibrillation and for any underlying cardiovascular disorders for at least 1 month before enrollment. Patients were allowed to continue all previously prescribed treatments for these conditions (including ACE inhibitors, amiodarone, and beta-blockers). All eligible patients provided written informed consent before enrollment.

Randomization and Study Treatment

Eligible patients were randomly assigned to either valsartan or matching placebo by means of a computerized, telephone randomization system, with

the group assignments concealed. Randomization was based on stratification according to site, with blocks of four patients per site. The study drug was initiated at a dose of 80 mg daily for 2 weeks and was then increased to 160 mg daily for another 2 weeks. At the 4-week visit, the dose was increased to 320 mg daily, and this regimen was continued until the end of the follow-up period at week 52.

Upward adjustment of the dose of the study medication was required for all patients unless they presented with a blood pressure below 110/65 mm Hg or symptomatic hypotension. If a patient could not tolerate a daily dose of 160 mg, the dose was reduced to 80 mg, and attempts were subsequently made to increase the dose again. If the patient could not tolerate a dose of at least 160 mg of the study drug within 2 months after enrollment, the study drug was withdrawn.

FOLLOW-UP

Study visits were scheduled at weeks 2, 4, 8, 24, and 52, with the follow-up period concluding at 1 year. A routine clinical examination, including

Table 1. Baseline Characteristics of the Patients According to Study Group.*

Characteristic	Valsartan (N=722)	Placebo (N=720)	P Value
Age — yr	67.5±9.5	68.2±8.9	0.14
Female sex — no. (%)	267 (37.0)	277 (38.5)	0.56
Body-mass index†	28.0±4.5	27.7±4.2	0.19
≤5 yr of education — no. (%)	334 (46.3)	353 (49.0)	0.26
Blood pressure — mm Hg			
Systolic	138.2±16.7	139.0±16.9	0.40
Diastolic	81.5±8.5	81.6±9.0	0.92
Inclusion criteria — no. (%)			
≥2 episodes of atrial fibrillation in previous 6 mo	299 (41.4)	282 (39.2)	0.45
Cardioversion in previous 2 wk	646 (89.5)	630 (87.5)	0.24
Duration of last qualifying episode of atrial fibrillation >7 days	238 (33.0)	225 (31.2)	0.49
Heart failure, LVEF <40%, or both	56 (7.8)	58 (8.1)	0.83
History of hypertension for 6 mo or more	619 (85.7)	612 (85.0)	0.69
Diabetes mellitus	95 (13.2)	116 (16.1)	0.11
History of stroke	32 (4.4)	27 (3.8)	0.51
Peripheral artery disease	37 (5.1)	22 (3.1)	0.047
Documented coronary artery disease	111 (15.4)	68 (9.4)	≤0.001
Atrial fibrillation alone‡	78 (10.8)	94 (13.1)	0.19
Coexisting conditions — no. (%)			
Peripheral embolism	3 (0.4)	7 (1.0)	0.20
Previous transient ischemic attack	28 (3.9)	26 (3.6)	0.79
Renal dysfunction	24 (3.3)	16 (2.2)	0.20
Chronic obstructive pulmonary disease	50 (6.9)	56 (7.8)	0.54
Neoplasia	22 (3.0)	23 (3.2)	0.87
Current smoker	57 (7.9)	64 (8.9)	0.50
Alcohol abuse	6 (0.8)	11 (1.5)	0.22
Electrocardiographic findings at randomization			
Heart rate — bpm	63.5±10.5	63.7±10.5	0.68
QRS interval >120 msec — no. (%)	57 (7.9)	70 (9.7)	0.22
Left ventricular hypertrophy — no. (%)	71 (9.8)	60 (8.3)	0.32
Pathologic Q waves — no. (%)	41 (5.7)	22 (3.1)	0.02

Table 1. (Continued.)

Characteristic	Valsartan (N=722)	Placebo (N=720)	P Value
Concomitant cardiovascular therapies — no. (%)			
Amiodarone	253 (35.0)	248 (34.4)	0.81
Sotalol	53 (7.3)	47 (6.5)	0.54
Class I antiarrhythmic agents	235 (32.5)	232 (32.2)	0.89
ACE inhibitors	420 (58.2)	402 (55.8)	0.37
Calcium-channel blockers	207 (28.7)	221 (30.7)	0.40
Beta-blockers	223 (30.9)	213 (29.6)	0.59
Digitalis	33 (4.6)	30 (4.2)	0.71
Diuretics	268 (37.1)	264 (36.7)	0.86
Aldosterone blockers	43 (6.0)	49 (6.8)	0.51
Statins	196 (27.1)	172 (23.9)	0.16
Oral anticoagulants	398 (55.1)	417 (57.9)	0.29
Aspirin	206 (28.5)	189 (26.2)	0.33

* Plus–minus values are means ±SD. P values were calculated with the use of chi-square tests, with the exception of P values for comparisons of age, body-mass index, blood pressure, and heart rate, which were calculated with the use of t-tests. ACE denotes angiotensin-converting enzyme, and LVEF left ventricular ejection fraction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Atrial fibrillation alone was defined as atrial fibrillation without coexisting cardiovascular conditions but with left atrial dilatation.

electrocardiography and laboratory testing, was performed at each study visit. To increase the likelihood that atrial fibrillation could be detected, all patients were provided with a transtelephonic monitoring device (Cardiobios 1, Telbios). The patients were asked to activate this device, which would transmit a 30-second electrocardiogram to both the coordinating center and the responsible physician, if symptoms occurred and at least once a week whether or not symptoms occurred. If a recurrence of atrial fibrillation was detected, the patient was asked to come in for an office visit to confirm the findings.

STUDY END POINTS

The study was designed with two primary end points: the time to the first recurrence of atrial fibrillation and the proportion of patients who had more than one episode of atrial fibrillation over the 1-year follow-up period. Secondary end points included the total number of episodes of atrial fibrillation per patient, hospitalization for any reason and hospitalization for a cardiovascular event, the composite of death and thromboembolic events, the number of patients in sinus rhythm at the time of each study visit, the duration of and ventricular rate at the first recurrence of atrial fibrillation, and a safety profile. A predefined analysis of the effects of valsartan as compared with placebo on the recurrence of atrial fibrillation was also performed for patients who were in sinus rhythm 15 days after study entry, with the aim of assessing the effect of valsartan after the exclusion of early recurrences of atrial fibrillation. A similar post hoc analysis included patients who were in sinus rhythm at week 8, by which time it was expected that patients would be receiving the target dose of valsartan. An independent end-point committee adjudicated all reports of primary end points, deaths, and hospitalizations.

STATISTICAL ANALYSIS

The estimated sample size was based on the time to the first recurrence of atrial fibrillation. We calculated that for the study to have 88% power to detect a 17.6% relative difference between the valsartan and placebo groups, there would have to be 599 events, assuming an event rate in the placebo group of 50% at 1 year (which corresponds

to a yearly hazard rate of 69%) and a withdrawal rate of 15%. On the basis of these calculations, we planned to enroll 1402 patients.

All analyses were performed in the intention-to-treat population. Comparisons of the first primary end point (time to the first recurrence of atrial fibrillation) between the treatment and placebo groups were performed with the use of a log-rank test. We estimated the size of the effect by calculating hazard ratios with the use of a Cox proportional-hazards model. In a further analysis, we included as covariates all the baseline clinical characteristics that were assessed in the study patients. For the second primary end point (the proportion of patients with more than one recurrence of atrial fibrillation), we assessed the treatment effect by using a logistic-regression model to calculate odds ratios, with and without adjustment for all baseline covariates.

We adjusted the overall significance level of 0.05 to account for the inclusion of two primary end points. The first (time to the first recurrence of atrial fibrillation) was tested at a two-sided significance level of 0.04, and the second (proportion of patients with more than one episode of atrial fibrillation), at a two-sided significance level of 0.01. Thus, confidence intervals of 96% and 99% were calculated for the first and the second primary end points, respectively.

We also calculated hazard ratios with 95% confidence intervals, using the Cox regression model to assess the effect of valsartan on the secondary end points and in the prespecified subgroups. For the between-group comparisons of those secondary end points that were expressed as proportions or mean values, we used a chi-square test or t-test. We performed Cox analyses of the primary outcome to test for an unfavorable outcome in prespecified subgroups by fitting a Cox model with one term representing the treatment group, one term representing the covariate of interest, and an interaction term to test for heterogeneity of the effect of valsartan. Changes in systolic blood pressure were analyzed by means of analysis of variance, with adjustment for baseline values, and were reported as least-square means ±SE.

The reported P values are two-sided and not adjusted for multiple testing. All analyses were conducted with SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

From November 2004 through January 2007, we enrolled 1442 patients at 114 centers; 722 patients were randomly assigned to the valsartan group, and 720 to the placebo group. There were no clinically relevant differences between the two groups in baseline characteristics (Table 1), except for a higher prevalence of coronary artery disease and peripheral arterial disease in the valsartan group than in the placebo group. A total of 85.4% of the patients had a history of hypertension, 14.6% had diabetes, and 7.9% had heart failure, left ventricular dysfunction, or both. At the time of randomization, 34.7% of the patients were receiving amiodarone, 57.0% were receiving ACE inhibitors, 30.2% were receiving beta-blockers, and 56.5% were receiving anticoagulant drugs (Table 1).

The target dose of 320 mg of the study drug was achieved at 4 weeks in 83.1% of the patients assigned to valsartan and in 85.2% of those assigned to placebo, and this dose was maintained in similar proportions of patients until the end of the study. Only five patients in the valsartan group and five in the placebo group had to have the study drug withdrawn because they could not tolerate a daily dose of 160 mg.

By 8 weeks, the least-square mean systolic blood pressure was reduced by 3.91±0.60 mm Hg in the valsartan group and by 1.07±0.60 mm Hg in the placebo group (P<0.001). By the end of the study, the reductions were 4.13±0.63 mm Hg in the valsartan group and 1.96±0.62 mm Hg in the placebo group (P=0.01). The mean heart rate was unchanged from baseline values at 8 weeks and at the end of the study (data not shown). The overall median duration of follow-up was 365 days (interquartile range, 359 to 372). We had follow-up data on survival for all the patients and follow-up data on the first recurrence of atrial fibrillation for almost all the patients (95.5%). More than 80% of expected transtelephonic recordings were actually transmitted.

PRIMARY END POINTS

At 1 year, 51.4% of the patients (371 of 722) in the valsartan group and 52.1% (375 of 720) in the placebo group had had a recurrence of atrial fibrillation (hazard ratio, 0.98; 96% confidence interval

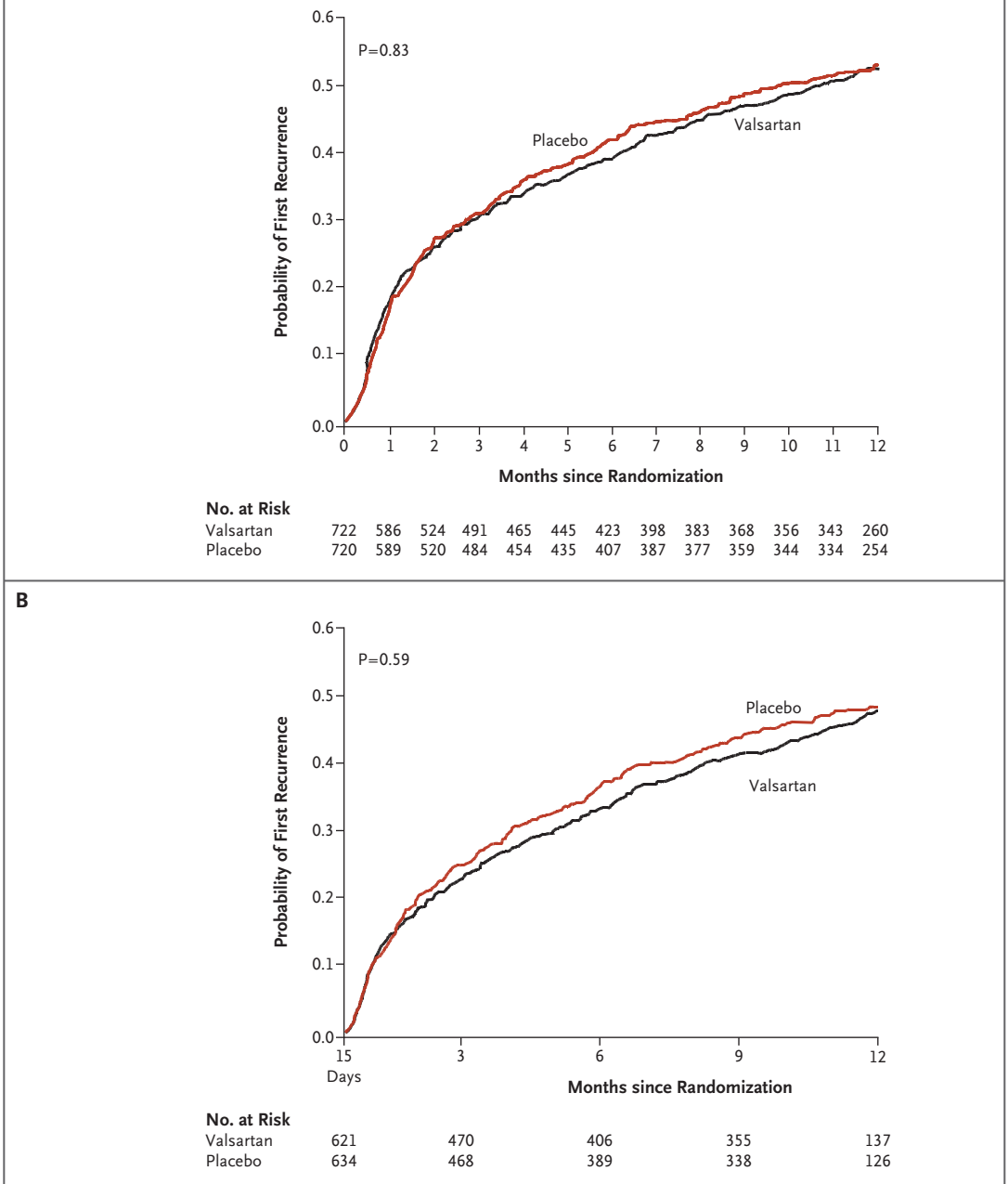

Figure 1. Kaplan–Meier Curves for the Time to the First Recurrence of Atrial Fibrillation.

Panel A includes data from the whole cohort, and Panel B data from the 1255 patients who were in sinus rhythm at 15 days.

[CI], 0.85 to 1.14; P=0.83) (Fig. 1A). After adjustment for all baseline variables reported in Table 1, the adjusted hazard ratio was 0.97 (96% CI, 0.83 to 1.14; P=0.73). Overall, the median times from randomization to the first recurrence of atrial fibrillation were 295 days in the valsartan group and 271 days in the placebo group.

More than one episode of atrial fibrillation occurred in 26.9% of the patients (194 of 722) in the valsartan group, as compared with 27.9% of the

Table 2. Secondary End Points.*

End Point	Valsartan (N=722)	Placebo (N=720)	Hazard Ratio (95% CI)	P Value†
Clinical events — no. of patients (%)				
Hospitalization for any reason	149 (20.6)	143 (19.9)	1.05 (0.83–1.32)	0.70
Hospitalization for cardiovascular event	114 (15.8)	122 (16.9)	0.93 (0.72–1.20)	0.59
Death or nonfatal thromboembolic event	18 (2.5)	9 (1.2)	2.03 (0.91–4.52)	0.08
Death	8 (1.1)	7 (1.0)	1.16 (0.42–3.19)	0.78
Thromboembolic events — no. of patients (%)	10 (1.4)	2 (0.3)	5.06 (1.11–23.11)	0.04
Ischemic stroke	4 (0.6)	0		
Transient ischemic attack	3 (0.4)	1 (0.1)		
Other	3 (0.4)	1 (0.1)		
Episodes of atrial fibrillation — no. of patients (%)				0.88
0	351 (48.6)	345 (47.9)		
1	177 (24.5)	174 (24.2)		
2	67 (9.3)	70 (9.7)		
3–5	87 (12.0)	82 (11.4)		
>5	40 (5.5)	49 (6.8)		
Arrhythmia-related events				
Sinus rhythm at 8-wk visit — no. of patients/total no. (%)	627/684 (91.7)	627/693 (90.5)		0.44
Sinus rhythm at study-end visit — no. of patients/total no. (%)	565/667 (84.7)	559/676 (82.7)		0.32
Ventricular rate at first episode of atrial fibrillation‡	109.6±28.4	107.5±29.6		0.33
Duration of first episode of atrial fibrillation — no. of patients/total no. (%)				
0–7 days	177/371 (47.7)	172/375 (45.9)		0.26
>7 days	89/371 (24.0)	109/375 (29.1)		
Data not available	105/371 (28.3)	94/375 (25.1)		

* Plus–minus values are means ±SD.
† P values for clinical and thromboembolic events were calculated with the use of Cox proportional-hazards models; P values for episodes of atrial fibrillation, sinus rhythm at 8 weeks and at study end, and duration of first episode of atrial fibrillation were calculated with chi-square tests; and the P value for ventricular rate at the first episode of atrial fibrillation was calculated with a t-test.
‡ The total number of patients who had at least one episode of atrial fibrillation was 746 (371 in the valsartan group, and 375 in the placebo group).

patients (201 of 720) in the placebo group (odds ratio, 0.95; 99% CI, 0.70 to 1.29; P=0.66). After adjustment for all baseline variables reported in Table 1, the adjusted odds ratio was 0.89 (99% CI, 0.64 to 1.23; P=0.34).

SECONDARY ANALYSES AND END POINTS

Among the 1255 patients who were in sinus rhythm 15 days after study entry, there was no significant difference between the valsartan and placebo groups with respect to the rates of recurrence of atrial fibrillation (47.7% and 48.4%, respectively; hazard ratio, 0.96; 96% CI, 0.81 to 1.13; P=0.59) (Fig. 1B). Similar results were obtained from a post hoc analysis of data from the 1254 patients who were in sinus rhythm at week 8, by which time the patients would have been receiving the target dose of valsartan (rate of recurrence, 42.7%

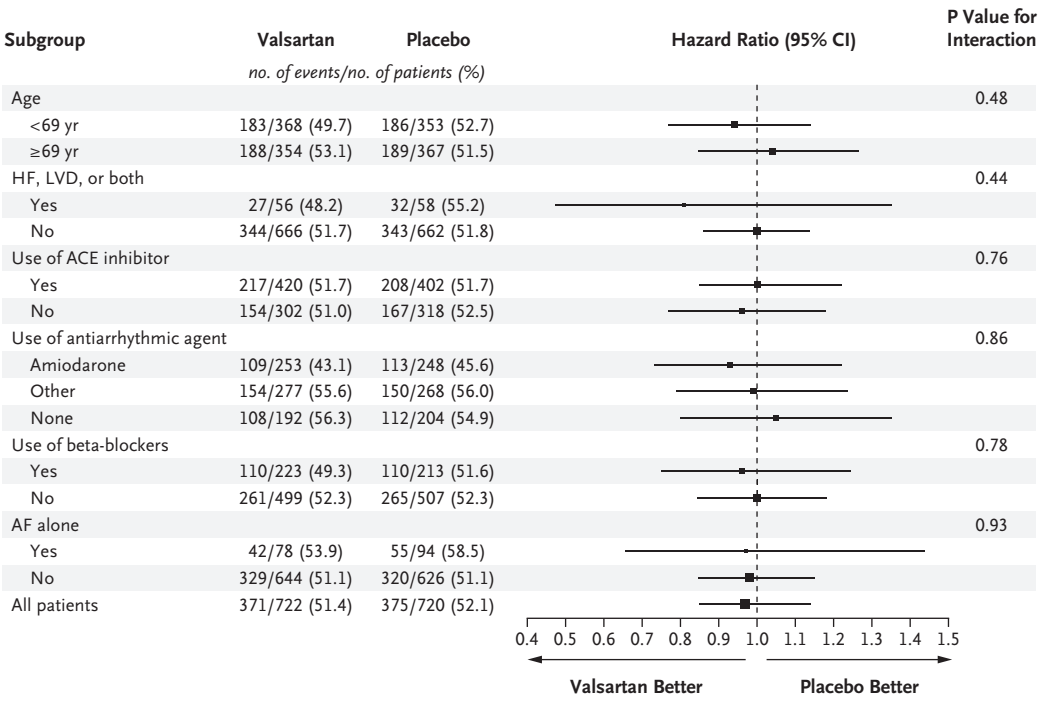

Figure 2. Effect of Treatment with Valsartan on the Risk of a First Recurrence of Atrial Fibrillation (AF) in Prespecified Subgroups.

Hazard ratios are indicated by solid squares, which are proportional in size to the number of people in each group, and horizontal lines represent the 95% confidence intervals, as calculated by a Cox proportional-hazards model, except in the case of the overall population, for which 96% confidence intervals are shown. AF alone refers to atrial fibrillation without coexisting cardiovascular conditions but with left atrial dilatation. ACE denotes angiotensin-converting enzyme, HF heart failure, and LVD left ventricular dysfunction.

in the valsartan group and 44.0% in the placebo group; hazard ratio, 0.96; 96% CI, 0.80 to 1.14; P=0.62). We did not observe significant differences in any of the secondary end points (Table 2), with the exception of thromboembolic events, which occurred in 10 patients in the valsartan group as compared with 2 in the placebo group (hazard ratio, 5.06; 95% CI, 1.11 to 23.11; P=0.04).

When all episodes of atrial fibrillation in a patient were counted, no significant differences were evident between the valsartan group and the placebo group with respect to any number of recurrences of atrial fibrillation per patient (Table 2). About half of the total number of first recurrences of atrial fibrillation were symptomatic, with no significant difference between the two groups in the rate of symptomatic atrial fibrillation (24.0% in the valsartan group and 23.1% in the placebo group, P=0.77).

SUBGROUP ANALYSES

Hazard ratios for the first recurrence of atrial fibrillation were similar in all predefined subgroups of patients (Fig. 2). A nonsignificant trend toward a lower incidence of recurrence of atrial fibrillation was apparent in the valsartan group among the 114 patients who presented with heart failure or left ventricular dysfunction (hazard ratio, 0.81; 95% CI, 0.48 to 1.35; P=0.41).

SAFETY

The study drug was permanently discontinued in 107 (14.8%) of the patients in the valsartan group and 76 (10.6%) of those in the placebo group (P=0.02). Of these discontinuations, 26 in the valsartan group and 12 in the placebo group were attributed to adverse drug reactions (Table 3). Serious adverse reactions occurred in two patients in the valsartan group (severe hypotension in one

Table 3. Adverse Reactions Leading to Permanent Discontinuation of the Study Drug.*

Adverse Reaction	Valsartan (N=722)	Placebo (N=720)
	no. of patients	
Total	26	12
Vertigo	3	1
Asthenia	1	1
Symptomatic hypotension	7	3
Cutaneous allergy	2	2
Hyperkalemia	2	0
Renal dysfunction	3	1
Gastrointestinal disorder	2	1
Hair loss	1	2
Muscle symptoms	0	1
Other†	5	0

* Two serious adverse drug reactions in patients in the valsartan group — hypotension in one patient and renal dysfunction plus hyperkalemia in the other — resolved without sequelae.
† Included in this category are epistaxis in 1 patient, an increase in liver enzyme levels in 1, an allergic reaction in 1, and cough in 2.

patient and renal dysfunction plus hyperkalemia in the other). The proportion of patients who had at least one doubling of the serum creatinine level or who had a serum creatinine level that was higher than 3.5 mg per deciliter (309.4 μmol per liter) during the follow-up period was 0.7% in the valsartan group and 0.9% in the placebo group (P=0.77). The proportion of patients in whom at least one measurement of the serum potassium level was higher than 5.5 mmol per liter during the follow-up period was 5.6% in the valsartan group and 2.4% in the placebo group (P=0.002).

DISCUSSION

In the GISSI-AF trial, we tested the effect of an ARB, valsartan, on the recurrence of atrial fibrillation in patients who had a history of atrial fibrillation associated with cardiovascular disease, diabetes, or left atrial enlargement. In these patients, the addition of valsartan to established therapies for atrial fibrillation and for coexisting cardiovascular conditions did not reduce the risk of either a first recurrence or multiple recurrences of atrial fibrillation. These results were consistent across all predefined subgroups. Our findings do not support the original hypothesis of a beneficial role of blockers of the renin–angiotensin–aldosterone system in the prevention of recurrent atrial fibrillation.

Only four previously published studies, in which a total of 665 patients were enrolled, specifically evaluated the role of ARBs in the secondary prevention of atrial fibrillation.[25-28] The results of three of these studies suggested a beneficial effect; in all three of these trials, amiodarone was given to all patients as part of the trial protocol.[25-27] In contrast, in the subgroup of patients treated with amiodarone in our trial, valsartan did not have a significant beneficial effect.

Our trial did not address the efficacy of agents that block the renin–angiotensin–aldosterone system for the primary prevention of atrial fibrillation. Previous trials and meta-analyses have suggested a more pronounced effect of these agents when they are used for primary prevention,[19-24,29,30] perhaps because of a beneficial influence on the pathophysiological substrate of atrial fibrillation (i.e., structural or electrical remodeling, or both) before the occurrence of irreversible atrial remodeling. We also did not evaluate the efficacy of ACE-inhibitor therapy, which has been reported to be similar to the efficacy of ARB therapy.[29,30]

One limitation of many large clinical trials in which the occurrence of atrial fibrillation is not a primary end point is the method used to detect recurrences of atrial fibrillation. Such trials often rely on the results of electrocardiography performed at scheduled office visits or on the patient's report of symptoms (as in the Losartan Intervention for Endpoint Reduction in Hypertension [LIFE], Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity [CHARM], and Valsartan Antihypertensive Long-term Use Evaluation [VALUE] trials).[21,23,24] As a result, these trials tend to show lower rates of detection of atrial fibrillation than trials, like ours, that use frequent transtelephonic monitoring.

One limitation of our trial is the relatively short duration (1 year) of clinical follow-up. Some of the large trials mentioned above (LIFE, CHARM, and VALUE) had mean follow-up intervals that were longer than 3 years. The time required for the putative effects of ARBs on atrial remodeling is not well defined. However, we did not detect even a modest trend in favor of valsartan therapy during the course of our trial, suggesting that such an effect would not be anticipated with a longer follow-up period.

Conversely, it seems unlikely that the expected benefit of ARB therapy would occur within the

first few days of starting treatment. Early recurrences of atrial fibrillation after cardioversion are probably due to short-term electrical remodeling of atria,[32] which tends to normalize within days or weeks if sinus rhythm is again restored. For this reason, we planned a secondary analysis that was limited to data on patients who were in sinus rhythm at the first follow-up visit, on day 15. This analysis did not show any effect of valsartan on the recurrence of atrial fibrillation. Similar results were obtained from a post hoc analysis of data from patients who were in sinus rhythm at week 8, to account for the time needed to reach the target dose of valsartan.

The significant excess of thromboembolic events in the valsartan group was unexpected, and we believe that this result may be a chance finding. Of note, the rate of thromboembolic events in the placebo group in our trial was much lower than expected and was lower than previously reported rates in similar patient populations.[33,34]

In conclusion, we evaluated the potential benefit of adding 320 mg of valsartan daily to standard therapy in patients who had a history of atrial fibrillation associated with cardiovascular disease, diabetes, or left atrial enlargement. At 1 year, we found no significant reduction in the incidence of recurrent atrial fibrillation among patients receiving valsartan as compared with those receiving placebo.

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APPENDIX

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REFERENCES

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl J Med 1982;306:1018-22.

2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001; 285:2370-5.

3. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. J Am Coll Cardiol 1998;32:197-204.

4. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol 1998;32:695-703.

5. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. Chest 2000; 118:914-22.

6. Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.

7. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. N Engl J Med 2000;342:913-20.

8. Lafuente-Lafuente C, Mouly S, Longás-Tejero MA, Mahé I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. Arch Intern Med 2006; 166:719-28.

9. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005; 111:1100-5.

10. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006;27:1979-2030. [Erratum, Eur Heart J 2007;28:2046.]

11. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995;92: 1954-68.

12. Nattel S, Li D. Ionic remodeling in the heart: pathophysiological significance and new therapeutic opportunities for atrial fibrillation. Circ Res 2000;87:440-7.

13. Daoud EG, Marcovitz P, Knight BP, et al. Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation 1999;99:3024-7.

14. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc Res 2002;54: 456-61.

15. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003; 41:2197-204.

16. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001;104:2608-14.

17. Chen YJ, Chen YC, Tai CT, Yeh HI, Lin CI, Chen SA. Angiotensin II and angiotensin II receptor blocker modulate the arrhythmogenic activity of pulmonary veins. Br J Pharmacol 2006;147:12-22.

18. Pizzetti F, Turazza FM, Franzosi MG, et al. Incidence and prognostic significance of atrial firbrillation in acute myocardial infarction: the GISSI-3 data. Heart 2001;86:527-32.

19. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999; 100:376-80.

20. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003;107:2926-31.

21. Wachtell K, Lehto M, Gerdts E, et al. 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. J Am Coll Cardiol 2005;45:712-9.

22. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005; 149:548-57.

23. Ducharme A, Swedberg K, Pfeffer MA, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 2006;152:86-92.

24. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens 2008; 26:403-11.

25. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation 2002; 106:331-6.

26. Yin Y, Dalal D, Liu Z, et al. Prospective randomized study comparing amiodarone vs. amiodarone plus losartan vs. amiodarone plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation. Eur Heart J 2006;27:1841-6.

27. Fogari R, Mugellini A, Destro M, et al. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol 2006;47:46-50.

28. Tveit A, Grundvold I, Olufsen M, et al. Candesartan in the prevention of relapsing atrial fibrillation. Int J Cardiol 2007; 120:85-91.

29. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005;45:1832-9.

30. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of

renin-angiotensin system prevents new-onset atrial fibrillation. Am Heart J 2006; 152:217-22.
31. Disertori M, Latini R, Maggioni AP, et al. Rationale and design of the GISSI-Atrial Fibrillation Trial: a randomized, prospective, multicenter study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. J Cardiovasc Med 2006; 7:29-38.
32. Tieleman RG, Van Gelder IC, Crijns HJ, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998;31:167-73.
33. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
34. Hart RG, Pearce LA, Anguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.

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