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Original article

Study on the Effect of Irbesartan on Atrial Fibrillation Recurrence in Kumamoto: Atrial Fibrillation Suppression Trial (SILK study)

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ABSTRACT

Background: Experimental studies suggest that angiotensin II-receptor blockers can influence atrial remodeling and may prevent atrial fibrillation (AF). Therefore, we hypothesized that irbesartan may prevent the recurrence of AF following either catheter ablation or electrical cardioversion of AF.
Methods: Study on the Effect of Irbesartan on Atrial Fibrillation Recurrence in Kumamoto (SILK study) is a prospective, multicenter, randomized, and open-label comparative evaluation of the effects of irbesartan and amlodipine on AF recurrence in hypertensive patients with AF who are scheduled to undergo catheter ablation or electrical cardioversion of AF. The primary end point was either AF or atrial tachycardia (AT) recurrence. AF/AT recurrence was evaluated for 6 months using 24-h Holter electrocardiogram and portable electrocardiogram. The secondary endpoints included the change in blood pressure, the interval from the procedure to the first AF/AT recurrence, cardiovascular events, left atrial diameter (LAD), left ventricular ejection fraction (LVEF), and changes in the biomarkers [brain natriuretic polypeptide (BNP), high-sensitivity C-reactive protein (hs-CRP), urinary albumin/creatinine].
Results: The study enrolled 98 patients (irbesartan; $n = 47$, amlodipine; $n = 51$). The recurrence of AF/AT was observed in 8 patients (17.0%) in the irbesartan group and in 10 patients (19.6%) in the amlodipine group. There was no significant difference in the AF/AT recurrence between the irbesartan and amlodipine groups. Blood pressure decreased similarly in both groups. There were no significant differences between the two groups as regards to the interval from the procedure to the first AF/AT recurrence, occurrence of cardiovascular events, changes in LAD and LVEF. BNP and urinary albumin/creatinine significantly decreased similarly in both groups, but no significant difference was found in hs-CRP between the two groups.
Conclusions: In hypertensive patients with AF, treatment with irbesartan did not have any advantage over amlodipine in the reduction of AF/AT recurrence after catheter ablation or electrical cardioversion.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia which is frequently observed associated with hypertension [1]. Antiarrhythmic drugs have had limited efficacy in preventing recurrence of AF [2,3]. Previous experimental studies have suggested that angiotensin II-receptor blockers (ARBs) can influence atrial remodeling [4] and thus may prevent AF [5]. Inhibition of the renin–angiotensin–aldosterone system can prevent structural remodeling and recurrence of AF [6]. Madrid et al. have evaluated the effect of treatment with an ARB, irbesartan, on maintaining sinus rhythm after cardioversion of persistent AF [7]. They showed that patients treated with amiodarone plus irbesartan had a lower rate of recurrence of AF than did patients treated with amiodarone alone following cardioversion of AF [7]. Therefore, we hypothesized that irbesartan may prevent the recurrence of AF following either catheter ablation or electrical cardioversion of AF. Thus, we conducted the Study on the Effect of Irbesartan on Atrial Fibrillation Recurrence in Kumamoto (SILK) to assess the potential benefit on the recurrence of AF by irbesartan when compared with that by a conventional calcium channel blocker, amlodipine, in hypertensive patients with AF who are scheduled to undergo either catheter ablation or electrical cardioversion.

Methods

Study design

The SILK study is a prospective, multicenter, randomized, and open-label study of the effects of irbesartan and amlodipine on AF recurrence in hypertensive patients with AF who are scheduled to undergo catheter ablation or electrical cardioversion of AF. The design of the present study is shown in Fig. 1. After obtaining informed consent, patients were randomly assigned to either the irbesartan or the amlodipine group. After assignment, antihypertensive therapy regimen was started immediately and continued for 2–4 weeks before the procedure. In the irbesartan group, irbesartan was prescribed initially at 50 mg/day (maximal dose 200 mg/day) and in the amlodipine group, the initial dose was 2.5 mg/day (maximal dose 10 mg/day). The target blood pressure (BP) was 130/85 mmHg according to the Japanese Guideline (JSH 2009). If the BP does not reach the targeted value, irrespective of the maximal dose of the assigned drug, other anti-hypertensive drugs may be used to achieve the targeted BP. The antiarrhythmic drugs available for the present study were restricted to class I and class IV anti-arrhythmic drugs. The follow-up period was 6 months from the performance of the catheter ablation or electrical cardioversion procedure. The study visits were scheduled at 1, 3, and 6 months after the procedure (Fig. 1). The 24-h Holter electrocardiogram was performed during the observation period (2–4 weeks before the procedure), 3 months after the procedure, and the 6-month follow-up (Fig. 1). The ultrasound echocardiography and portable electrocardiogram monitoring (OMRON, HCG 901, Kyoto, Japan) were performed during the observation period and at the 6-month follow-up (Fig. 1). Portable electrocardiogram monitoring was provided to each patient for 2–4 weeks and the electrocardiogram was recorded at least three times every day or whenever the patient felt any arrhythmia-related symptoms. Blood tests, urine examinations, and 12-lead surface electrocardiograms were performed at the observation period, 1, 3, and 6 months after the procedure. The study protocol was approved by the ethics committee at each participating hospital.

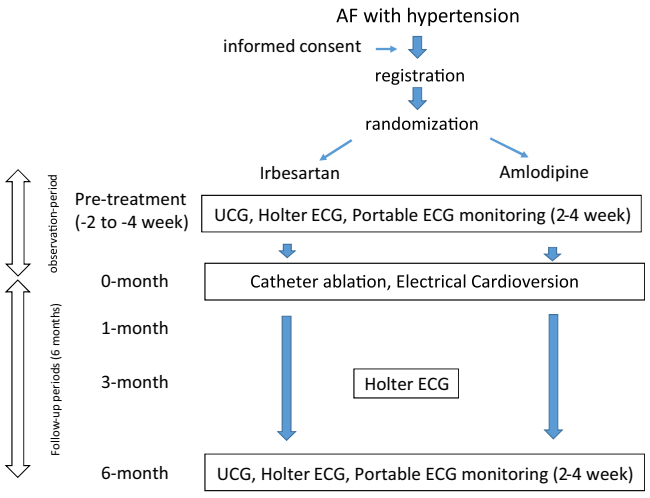

Fig. 1. Design of the SILK study. AF, atrial fibrillation; ECG, electrocardiogram; UCG, ultrasound echocardiography.

Patients

Patients entering the present study needed to meet the following three criteria: (1) age ≥20 years; (2) a history of paroxysmal or persistent AF who are scheduled to undergo catheter ablation or electrical cardioversion of AF; and (3) hypertension, defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg. The exclusion criteria were as follows: (1) contraindication for administration of either irbesartan or amlodipine; (2) history of myocardial infarction within the prior 3 months; (3) history of cardiac surgery within 3 months; (4) bradycardia with a heart rate ≤50 beats/min; (5) prolongation of QT interval ≥480 ms; (6) unstable angina pectoris or congestive heart failure; (7) pregnancy or the possibility of pregnancy; and (8) severe renal or liver dysfunction.

Endpoints

The primary endpoint was the recurrence of AF or atrial tachycardia (AT) recorded on the electrocardiogram during the follow-up period. A three-month blanking period was set for the patients who underwent catheter ablation of AF. The secondary endpoints were as follows: (1) change in BP; (2) the interval from the procedure to the recurrence of AF; (3) cardiovascular events, which included cardiovascular death, acute myocardial infarction, stroke, heart failure, or major bleeding requiring hospitalization; (4) change in the left atrial diameter and left ventricular ejection fraction measured by ultrasound echocardiography; (5) change in the biomarkers [serum brain natriuretic polypeptide level, serum high-sensitive C-reactive protein (hs-CRP) and urinary albumin/creatinine ratio].

Procedures

Electrical cardioversion

Trans-esophageal echocardiography was performed before the procedure in all patients. The cardioversion was performed if no left atrial thrombus was detected. Anticoagulation was achieved before trans-esophageal echocardiography and maintained after cardioversion for at least 4 weeks.

Catheter ablation

Anti-arrhythmic drugs were discontinued five half-life periods before the ablation procedure. Trans-esophageal echocardiography was performed on the day before ablation and identified the

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