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Abstract—It is controversial whether angiotensin II receptor blockers provide better protection than calcium antagonists against atrial fibrillation (AF) recurrence in hypertensive patients. This study was designed to compare the effect of nifedipine- and telmisartan-based antihypertensive treatments for preventing AF recurrence in hypertensive patients with paroxysmal AF. A total of 149 hypertensive patients with paroxysmal AF were randomized to nifedipine- or telmisartan-based antihypertensive treatment groups. The target blood pressure (BP) was <130/80 mm Hg. Clinic BP, ECG, Holter monitoring, and echocardiography were followed up for 2 years. The primary end point was the incidence of overall and persistent AF recurrence. During follow-up, there was no statistical difference in the rate of patients lowering to target BP between both groups, whereas nifedipine group had slightly better BP control but similar heart rate control at 24 months. The incidence of AF recurrence was similar in both groups (nifedipine versus telmisartan: 58.7% versus 55.4%; P=0.742), and Kaplan–Meier analysis showed no significant difference in the freedom from AF recurrence (log-rank test; P=0.48). However, the rate of developing persistent AF in telmisartan group was lower than that in nifedipine group (5.4% versus 16.0%; P=0.035). Patients in telmisartan group had lower values of left atrial diameter, left atrial volume index, and left ventricular mass index at the end of follow-up. The effects of telmisartan in preventing AF recurrences in hypertensive patients with paroxysmal AF after intensive lowering BP is similar to that of nifedipine, but telmisartan has more potent effects on preventing progression to persistent AF. **(*Hypertension.* 2013;61:00-00.)** ● **Online Data Supplement**

Key Words: angiotensin II receptor blocker ■ atrial fibrillation ■ calcium antagonist ■ hypertension

Atrial fibrillation (AF) and hypertension are 2 prevalent and often coexisting conditions for which the incidence increases with age, and both are responsible for considerable cardiovascular morbidity and mortality.[1] Hypertension is the most prevalent and independent risk factor of developing AF.[2,3] Previous studies demonstrated that hypertension was associated with left ventricular hypertrophy (LVH), impaired ventricular filling, left atrial (LA) structural changes, and slowing of atrial conduction velocity.[4] Meanwhile, antihypertensive treatment could reduce the risk of AF by reversing structural cardiac damage caused by hypertension.[5,6] All antihypertensive drugs reduce left ventricular and LA filling pressures and wall stress. However, preventing structural changes may be an effect specific to angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Recently, angiotensin II has been recognized as a key factor in atrial structural and electric remodeling associated with AF.[7] There are many potential mechanisms by which inhibition of the renin–angiotensin system (RAS) may reduce AF. Besides reducing the blood pressure (BP), per se, RAS blockers may prevent LA dilatation, atrial fibrosis, dysfunction, and conduction velocity slowing, and thereby have a greater effectiveness in patients with heart failure and LVH as seen in the meta-analysis by Schneider et al.[8] Furthermore, previous studies suggested that the ARB was more effective than the dihydropyridine calcium channel blocker in ameliorating atrial structural remodeling.[9] Hence, RAS blockers might have more benefit beyond BP control than the dihydropyridine calcium channel blocker for hypertensive patients with paroxysmal AF.

The present study was aimed to evaluate whether telmisartan-based treatment was superior to nifedipine-based treatment in hypertensive patients with paroxysmal AF after intensive BP control.

Patients and Methods

Study Population

The Nifedipine versus Telmisartan on Prevention of AF recurrence in hypertensive patients with AF trial (NTP-AF study, NCT01435161) was a prospective, randomized, open-label, parallel trial and was conducted from April 2006 to December 2011. All hypertensive patients with paroxysmal AF who were referred to the second affiliated Hospital of Chongqing Medical University were invited to participate in this study. All patients underwent history acquisition, physical examination, standard 12-lead ECG, 24-hour Holter monitoring, echocardiogram, chest X-ray, and thyroid and renal function tests before

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recruitment. Paroxysmal AF was defined as self-terminating AF episodes lasting <48 hours, alternating with periods of sinus rhythm.

The inclusion criteria were as follows: (1) essential hypertension, clinic systolic BP ≥140 and ≤180 mm Hg and diastolic BP ≥90 and ≤110 mm Hg; (2) documented paroxysmal AF (documentation of AF in at least 1 ECG recorded during the 6 months before randomization).

The exclusion criteria were as follows: (1) taking antiarrhythmic agents of class I or class III within the last 3 months; (2) persistent AF with a duration ≥1 week, and permanent AF; (3) undergoing current cardioversion, symptomatic bradycardia, implanted pacemaker or converting defibrillator; (4) cardiac surgery or catheter ablation within the last 3 months; (5) valvular disease, a history of angina pectoris, diabetes mellitus, hypertrophic cardiomyopathy, and congenital heart disease; (6) congestive heart failure or left ventricular ejection fraction <50%; (7) stroke, renal dysfunction, or hyperthyroidism; (8) patient aged ≤18 years, pregnancy or fertile female.

Among the 201 patients screened for the study, 149 were eligible for randomization. The flow of participants in the study was presented in Figure 1.

The study protocol was approved by the ethical committee of the second affiliated hospital of Chongqing medical university (study CR2006-9), and informed consent was obtained from each participant at time of enrollment.

Study Protocol

All participants underwent a 2-week washout period, during which all antihypertensive drugs were discontinued. Thereafter, 149 patients were randomized: 75 in nifedipine-based treatment group (initial therapy with nifedipine gastrical intestinal therapeutic system 30 mg/d, Bayer) and 74 in the telmisartan-based treatment group (initial therapy with telmisartan 80 mg/d, Boehringer-Ingelheim). The randomization sequence was generated by computer. The drugs were given in an open-label fashion. At the 2-week follow-up, hydrochlorothiazide 12.5 to 25 mg once daily were added to the trial drugs to achieve a target BP of <130/80 mm Hg. Those patients who did not achieve the target BP at the 4-week follow-up, metoprolol 50 to 100 mg once daily were added. If the BP was still >130/80 mm Hg at the 8-week follow-up visit, the trial drugs were increased to nifedipine 60 mg once daily or telmisartan 160 mg once daily. Thereafter, the dosages and types of antihypertensive drugs were adjusted according to the level of BP. The flow diagram of the protocol was shown in online-only Data Supplement.

Follow-Up

All patients were given a questionnaire to investigate the presence of palpitations, symptomatic hypotension, and dizziness, study drug compliance, and side effects. Patients were required to follow-up at 1-month interval within the first 6 months and 3 months interval thereafter. Follow-up review included clinical assessment, clinic BP measurements, 12-lead ECG, 24-hour Holter monitoring, and echocardiography. More detailed descriptions were available in online-only Data Supplement.

Echocardiography Examination

Echocardiography was performed before randomization and every 6 months during follow-up. More detailed descriptions were available in online-only Data Supplement.

Study End Points

The primary end point was the incidence of AF (including paroxysmal and persistent) recurrence. The development of persistent AF implied AF had continued for >7 days but was terminated after pharmacological and electric conversion. The secondary end points included the time to a first electrocardiographically confirmed relapse of AF and cardiovascular events, including cardiovascular death, acute myocardial infarction, stroke, and congestive heart failure.

Statistical Analysis

The sample size calculation was based on an 80% power of detecting a 30% reduction in the rate of AF recurrence in telmisartan group compared with nifedipine group, and the resulting sample size was 71 patients for each group. Data were expressed as mean values±SD for continuous variables, and frequencies were measured for categorical variables. The study analysis was performed on the basis of the intension-to-treat principle. Variables were compared between groups with the use of t test for continuous measures and χ^2 test for categorical variables. ANOVA was performed to analyze the differences in means between groups. The Kaplan–Meier method was used to estimate the AF recurrence-free survival. Differences in the AF recurrence-free survival were assessed by the log-rank test. The Cox proportional hazards regression method was used to determine the relationship of clinical characteristics to the rate of developing persistent AF during follow-up. The following variables were considered potential predictors of developing persistent AF: left atrium volume index (LAVI; or left ventricular mass index, LVMI), as a time-dependent or standard covariate, age, sex, AF duration, history of hypertension, and treatment group. Variables were then analyzed in a stepwise fashion to develop Cox models. A 2-sided $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed using SPSS statistical software (version 17.00, Chicago, IL).

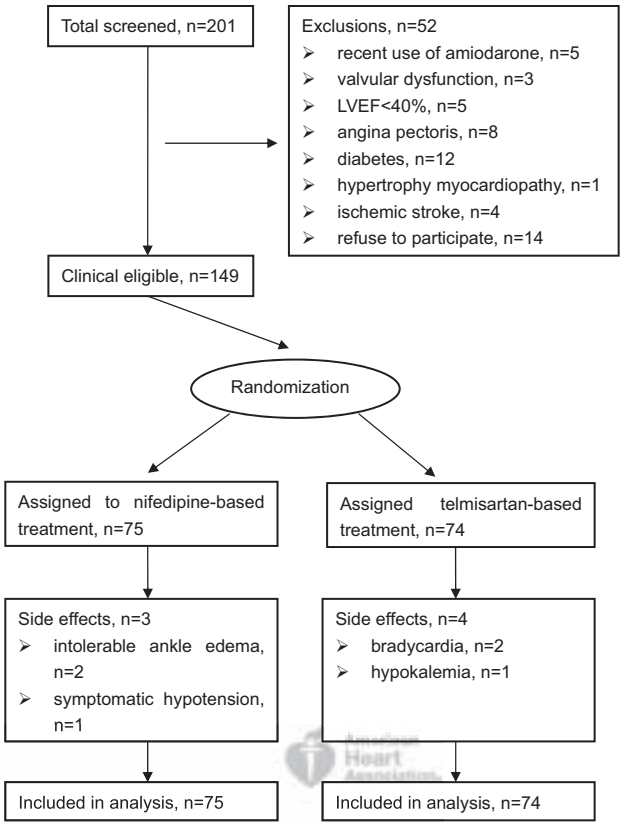

Figure 1. Flow diagram of patient's enrollment. LVEF indicates left ventricular ejection fraction.

Results

The baseline clinical characteristics in both groups are shown in Table 1. The mean age was 61.8±6.5 years old, and 61.7% of the patients were men. The duration of AF was 1.6±0.9 years in the nifedipine group and 2.1±1.2 years in the telmisartan group ($P=0.007$). No significant differences were found between groups in terms of age, sex, body mass index, duration of hypertension, frequency of AF occurrence, and left ventricular ejection fraction. All patients completed 2 years follow-up.

The change of BP, heart rate, and the proportion of patients receiving metoprolol were presented in online-only Data Supplement. In both groups, there were substantial reductions in systolic BP and diastolic BP values at 24 months ($P<0.001$).

Table 1. Main Demographic and Baseline Characteristics of Included Patients

Variables	Nifedipine (n=75)	Telmisartan (n=74)	*P*
Age, y	62.0±7	61.5±6	0.670
Sex (men), %	65.3%	58.1%	0.364
Body mass index, kg/m^2	24.9±1.8	25.6±2.7	0.09
History of hypertension, y	9.0±4.5	8.9±4	0.846
Atrial fibrillation duration, y	1.6±0.9	2.1±1.2	0.007
Frequency of atrial fibrillation occurrence, times/mo	1.6±0.7	1.5±0.7	0.503
Systolic blood pressure, mm Hg	159.2±8.9	161.4±9.5	0.160
Diastolic blood pressure, mm Hg	91.9±8.1	93.3±6.4	0.233

There was no significant difference in the rate of patients lowering to target BP (130/80 mm Hg) at 12 and 24 months. During the 24 months, both groups had no difference in heart rate and the proportion of patients receiving metoprolol.

The main results of this study were reported in Table 2. At the end of the follow-up, the incidence of AF recurrence was slightly less in the telmisartan group than that in the nifedipine group by intention-to-treat analysis, (55.4% versus 58.7%; *P*=0.742). Median time to AF recurrence was 349 days in the nifedipine group and 341 days in the telmisartan group, respectively (*P*=0.48). Kaplan–Meier analysis showed no difference in the survival free of AF (log-rank test had a χ^2 of 0.504; *P*=0.48; Figure 2). The rate of developing persistent AF was lower in the telmisartan group (4 patients, 5.4%) than that in the nifedipine group (12 patients, 16%), the difference being statistically significant (*P*=0.037). The absolute rate of reduction in persistent AF by telmisartan is 10.6%, so the number needed to treat to prevent 1 episode of persistent AF was 9.4 (95% confidence interval [CI], 8.6–10.4). In the multivariate Cox regression analysis, after adjustment for age, sex, AF duration, history of hypertension, and LVMI, treatment with telmisartan was found to be an independent negative predictor of developing persistent AF (hazard ratio, 0.297; 95% CI, 0.090–0.974; *P*=0.045). Moreover, treatment with nifedipine and LAVI were found to be independent positive predictors of developing persistent AF (hazard ratio, 3.37; 95% CI, 1.03–11.08; *P*=0.045; hazard ratio, 1.265, 95% CI, 1.111–1.440; *P*<0.001, respectively); however, treatment with telmisartan tended to be the only independent negative predictor of developing persistent AF (hazard ratio, 0.351; 95% CI, 0.11–1.11; *P*=0.075), whereas LAVI (or) LVMI was entered in the Cox model as a time-varying covariate.

Table 2. Main Results of the Study

Main Results	Nifedipine (n=75)	Telmisartan (n=74)	*P*
Rate of atrial fibrillation recurrence, n (%)	44 (58.7)	41 (55.4)	0.742
Days to first recurrence (median), days	341	349	0.48
Development of persistent atrial fibrillation, n (%)	12 (16)	4 (5.4)	0.037
Cardiovascular events, n (%)			
Cardiovascular death	0 (0)	0 (0)	—
Acute myocardial infarction	0 (0)	0 (0)	—
Stroke	0 (0)	1 (1.4)	0.312
Heart failure	0 (0)	0 (0)	—
Concomitant drugs*			
Hydrochlorothiazide, %	82.7	86.5	0.676
Metoprolol, %	73.3	74.3	0.961

*All patients receiving metoprolol during the whole follow-up period, whether administered with a long or short period, were incorporated in statistical analysis.

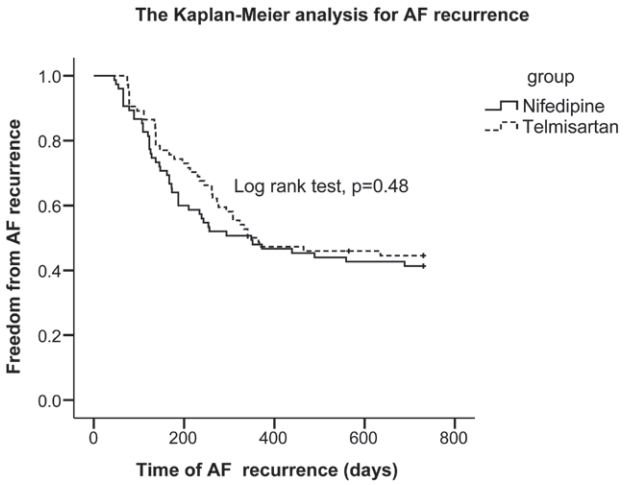

Figure 2. The log-rank test demonstrated that survival distribution of atrial fibrillation (AF) recurrence between the nifedipine and telmisartan groups was not significant (*P*=0.48).

Difference between both groups had no significance in terms of all echocardiographic parameters at baseline, as shown in Table 3, but patients in telmisartan group had lower values of LA diameter (LAD), LAVI, left ventricular posterior wall thickness and LVMI at the end of follow-up. Changes in LVMI correlated well to changes in LAVI at 24 months (*r*=0.599; *P*<0.001). As presented in Table 4, compared with patients with no recurrence of AF or paroxysmal AF, patients who progressed to persistent AF had longer history of hypertension, high body mass index and BP rate at 24 months, and higher baseline and final values of LAD, LAVI, left ventricular posterior wall thickness, and LVMI. All echocardiographic measurements during follow-up were significantly improved by both treatments (*P*<0.001) with the exception of left ventricular systolic diameter (Table 3). The baseline characteristics and ultrasonic cardiography indexes of patients with or without AF recurrence were also presented in online-only Data Supplement.

In the present study, 1 patient receiving telmisartan was diagnosed with cerebral infarction by MRI because of dizziness, not associated with other neurological deficit. All other participants were not diagnosed as cardiovascular death, acute myocardial infarction, and heart failure (Table 2).

At the end of the study, the average daily dose was 30.0 mg and 84.1 mg for nifedipine and telmisartan, respectively. Total adverse effects requiring discontinuation of treatment occurred in 3 patients (4.0%) in the nifedipine group and 4 patients (5.4%) in the telmisartan group (*P*=0.985). In the nifedipine group, nifedipine was discontinued in 2 patients because of intolerable ankle edema, and in 1 patient because of symptomatic hypotension. In the telmisartan group, 2 patients discontinued

Table 3. Change of Echocardiographic Parameters

Parameters	Group	Baseline	6-month	12-month	24-month	*P*†
IVS, mm	Nif	13.3±0.8	12.2±0.8	11.8±1.0	11.2±0.8	<0.001
	Tel	13.4±1.0	12.1±1.0	11.2±1.0	11.8±1.0	<0.001
LVPWT, mm	Nif	13.1±0.9	12.8±0.8	12.4±0.8	12.3±1.1*	<0.001
	Tel	13.1±0.8	12.8±0.8	12.4±0.9	11.7±0.9	<0.001
LAD, mm	Nif	40.3±3.9	38.6±3.1	38.0±3.0	37.9±3.0**	<0.001
	Tel	40.1±3.8	37.9±2.8	37.5±2.5	37.0±2.3	<0.001
LVDD, mm	Nif	52.6±2.9	50.6±2.1	49.7±1.9	49.4±1.5	<0.001
	Tel	52.4±2.5	50.3±2.0	49.8±1.8	49.1±1.7	<0.001
LVSD, mm	Nif	33.9±4.2	32.7±4.1	32.3±4.1	31.9±4.0	0.022
	Tel	32.5±4.2	31.7±3.8	31.4±4.0	31.1±4.0	0.180
LVEF, mm	Nif	64.7±3.1	65.7±2.7	65.8±2.6	66.2±2.4	0.004
	Tel	64.9±4.9	65.0±4.2	65.6±3.9	66.2±3.4	0.261
LVMI, g/m^2	Nif	164.2±22.8	140.7±17.9	130.8±15.7	124.7±14.7***	<0.001
	Tel	159.7±22.4	138.7±18.2	130.9±16.7	118.5±16.1	<0.001
LAVI, mL/m^2	Nif	25.3±4.1	23.5±3.7	22.9±3.6	22.7±3.7****	<0.001
	Tel	25.3±4.8	22.7±3.3	22.3±3.0	21.7±2.9	<0.001

† refers to the probability value of 1-way ANOVA; comparing nifedipine vs telmisartan, *P=0.044, **P<0.001, ***P=0.016, ****P=0.070.

IVS indicates interventricular septum; LAD, left atrial diameter; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; and LVSD, left ventricular systolic diameter.

metoprolol because of bradycardia, and another 2 patients discontinued hydrochlorothiazide because of hypokalemia.

Discussion

Main Findings

In the present study, we aimed to evaluate whether telmisartan could provide more benefits beyond the BP-lowering effect than nifedipine in hypertensive patients with paroxysmal AF, but no overt cardiovascular diseases. All enrolled patients had no evidence of dysfunction and did not receive antiarrhythmic drugs and ACEIs with the exception of metoprolol. The present results showed that although the nifedipine group had slightly better BP control but similar heart rate control at 24 months, telmisartan had more potent effects than nifedipine on preventing the development of persistent AF, despite their effects on overall AF recurrences were similar.

Ang-II blockade has important beneficial effects on atrial stretch, interstitial fibrosis, inflammation, and eventually structural remodeling, all of which serve as a substrate for the persistence and recurrence of AF.[7] Previous meta-analyses based on several post hoc analyses of randomized controlled trials have shown that RAS blockers significantly reduced the risk of new-onset AF ranging from 28% to 49%, but this benefit was limited to patients with systolic left ventricular dysfunction or hypertension with LVH.[10,11] For secondary prevention of AF, several relatively small prospective randomized studies[12–14] have demonstrated that therapies with ACEI/ARBs conferred an additional benefit on risk of recurrent AF in these patients when coadministered with antiarrhythmic drug therapy, usually amiodarone, compared with antiarrhythmic drug alone. Whether RAS blockade could prevent recurrent AF in paroxysmal AF patients with minor underlying cardiac pathology, who are not undergoing cardioversion and do not receive antiarrhythmic drugs therapy or ACEIs, remains controversial.

For ARBs in the secondary prevention of AF, 3 prospective randomized studies must be mentioned. First, the J-RHYTHM II (The Japanese Rhythm Management Trial II for Atrial Fibrillation) study,[15] enrolling patients with hypertension and paroxysmal AF, had a design similar to the present study and aimed to assess the potential benefit of BP control by RAS blockers when compared with that by calcium channel blocker. It showed no benefit of treatment with candesartan compared with amlodipine on the frequency (days/month) and duration of AF recurrence or progression to persistent AF during 1-year follow-up. Additionally, unlike the present study, a total of 70.4% of the patients in the J-RHYTHM II study received antiarrhythmic drugs. Second, the angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) study,[16] which enrolled 430 patients with paroxysmal AF without structural heart disease and randomly assigned to placebo or 40 mg olmesartan per day, showed that 1 year of ARB therapy did not reduce the number of AF episodes. Of note, in the ANTIPAF study, 43% of patients had hypertension, and both the systolic BP and diastolic BP did not change significantly in either group up to the end of follow-up. Finally, the GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation) trial[17] randomized 1442 patients with mixed paroxysmal and persistent AF who were in sinus rhythm at the time of enrolment to treatment with valsartan (titrated up to 320 mg) or placebo on top of optimal medical therapies, including antiarrhythmic drugs. The study also failed to demonstrate any beneficial effect of an ARB-based regimen on the primary end point of time to first AF recurrence and number of patients with >1 AF recurrence. Likewise, the GISSI-AF study also included patients with heart failure or left ventricular dysfunction, coronary or peripheral artery disease, and diabetes mellitus. Moreover, the majority of the GISSI-AF patients had undergone cardioversion for AF within 2 weeks before randomization and were taking an antiarrhythmic

Table 4. Baseline Characteristics and Echocardiographic Parameters of Patients With No AF Recurrence, Paroxysmal AF Recurrence, and Persistent AF

Variables	Patients With No AF Recurrence (n=64)	Patients With Paroxysmal AF Recurrence (n=69)	Patients With Persistent AF Recurrence (n=16)	*P**
Clinical characteristics				
Age, y	61.6±6.2	62.2±6.7	60.6±7.1	0.662
Sex (male), %	57.8	63.8	62.5	0.764
BMI, kg/m^2	24.8±1.8	25.7±2.6	25.2±2.5	0.063
History of hypertension, y	9.6±4.2	8.0±3.8	10.2±5.6	0.032
AF duration, y	2.0±1.0	1.8±1.2	1.4±0.8	0.114
Frequency of AF occurrence, times/mo	1.5±0.7	1.6±0.7	1.5±0.6	0.780
SBP at 24-month, mm Hg	126.3±4.7	126.6±4.6	127.6±4.7	0.581
DBP at 24-month, mm Hg	76.0±4.4	75.8±4.2	77.2±5. 1	0.527
Target BP rate at 24-month, %	75.0%	73.9%	87.5%	<0.001
Heart rate at 24-month, bpm	68.3±3.9	68.1±4.5	70.6±4.6	0.091
Echocardiographic parameters				
IVS, mm				
Baseline	13.2±0.9	13.4±0.8	13.9±0.9	0.007
24-month	11.3±0.9	11.0±0.7	11.9±1.1	0.002
LAD, mm				
Baseline	39.2±3.7	40.3±3.7	43.8±2.4	<0.001
24-month	36.6±2.7	37.7±2.5	39.8±2.2	<0.001
LVEF, %				
Baseline	64.8±4.1	65.3±4.2	62.6±3.4	0.062
24-month	65.4±3.1	67.0±2.6	65.6±2.5	0.005
LVDD, mm				
Baseline	52.0±2.9	52.5±2.5	54.3±2.1	0.007
24-month	48.7±1.5	49.7±1.5	50.1±1.6	<0.001
LVSD, mm				
Baseline	32.3±4.5	33.7±3.9	34.5±3.8	0.070
24-month	32.1±4.0	31.1±4.1	31.1±3.6	0.300
LVPWT, mm				
Baseline	12.8±0.6	13.3±1.0	13.5±0.6	0.001
24-month	11.6±0.9	12.1±1.0	12.9±0.8	<0.001
LVMI, g/m^2				
Baseline	154.8±21.9	164.5±21.6	179.8±18.0	<0.001
24-month	116.6±13.6	123.2±15.5	134.7±16.0	<0.001
LAVI, mL/m^2				
Baseline	24.0±4.1	25.6±4.5	29.2±3.0	<0.001
24-month	21.2±3.1	22.6±3.4	24.6±2.8	<0.001

* denotes the probability value of 1-way ANOVA comparing the 3 subgroups.

AF indicates atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; IVS, interventricular septum; LAD, left atrial diameter; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; LVSD, left ventricular systolic diameter; and SBP, systolic blood pressure.

drug (78% of patients), or an ACEI (58%), which might dilute the potential beneficial effect of valsartan on AF.

The main highlight of this study was that telmisartan-based antihypertensive treatment was superior to nifedipine-based antihypertensive treatment in preventing progression to persistent AF. On the contrary, both the J-RHYTHM II and the ANTIPAF studies showed no benefit of treatment with ARB compared with calcium channel blockers or placebo after a relative short period of follow-up. Furthermore, in the present study, although nifedipine group had slightly better BP control at 24 months, patients with telmisartan had lower values of LAD, LAVI, left ventricular posterior wall thickness, and LVMI at 24 months, associated with lower rate of progression to persistent AF. This suggested more potent effects of telmisartan on reversal of atrial and ventricular remodeling induced by long-standing arterial hypertension. Compared with patients with no recurrence AF or paroxysmal AF, patients who progressed to persistent AF had higher baseline and final values

of LAD, LAVI, left ventricular posterior wall thickness, and LVMI, which suggested that more prominent atrial and ventricular remodeling had developed during follow-up in these patients. It is generally thought that LA dilation response to LVH in patients with hypertension, as one of the most important indicator of LA structural remodeling, precedes or appears early after the onset of AF and is one of the important factors in perpetuating the arrhythmia.[18,19] We observed such changes in LVMI correlated well with changes in LAVI at 24 months. Increased LV mass and enlargement of left atrium have been identified as independent determinants of new-onset AF, whereas antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may reduce LAD (or LA size) and the incidence of new-onset AF.[6,20] Although to what extent such prevention and reversal of atrial remodeling will translate into a reduction in the burden of AF and other adverse clinical outcomes remains to be seen, we cautiously speculate that the primary mechanism for the benefit of telmisartan on decreasing progression to persistent AF is that telmisartan has more potent effects on the reversal of LVH and LA remodeling, despite both groups achieving optimal BP control.

The relationship between BP control and the incidence of AF remains to be determined. Some researchers[5,21–23] reckon that BP control and the reduction of LA overload was essential for controlling AF. Recent European Society of Cardiology guidelines pointed out that,[24] for patients with uncomplicated hypertension, an optimal BP control to prevent LVH and LA enlargement with effective antihypertensive drugs rather than specific class of agents seem to be more important to prevent further development of AF. Recently, a prospective cardiovascular survey[25] further demonstrated that even upper normal BPs was the long-term predictor of incident AF in initially healthy middle-aged men. In the present study, most patients reached the target BP of 130/80 mm Hg at the 12- and 24-month follow-up by intensive BP control. Relatively speaking, we applied a stricter BP control strategy compared with the J-RHYTHM II study. Moreover, despite more substantial reduction of BP values but identical heart rate response while added on metroprolol in the nifedipine group, therapy with telmisartan showed more benefit with respect to improvement of LVH and LA dilation, and consequently preventing the progression to persistent AF independent of metoprolol or heart rate effects. Furthermore, Cox regression showed that treatment with telmisartan tended to be the only independent negative predictor of developing persistent AF, whereas LAVI (or) LVMI was entered in the Cox model as a time-varying covariate. Therefore, our findings, to a certain degree, do support the concept that the blockade of RAS may have favorable effects on the occurrence of persistent AF beyond the control of BP.

There are inconsistent data from previous retrospective studies about the association of the type of AF with stroke risk and survival. Some studies[26,27] reported that nonvalvular AF was not associated with the risk of stroke/transient embolism, bleeding or all-cause mortality, whereas others[28–30] found that patients with paroxysmal AF have lower recurrence and mortality compared with those with persistent and permanent AF.

Moreover, a large prospective study conducted by de Vos et al[31] enrolling 1219 patients with paroxysmal AF in the Euro Heart Survey on AF has reported that patients with AF progression had more adverse cardiovascular events and were more often admitted in the hospital. Therefore, we reckon that the prevention of progressing from paroxysmal AF to persistent AF has potential benefits. However, the relatively small sample size in the present study has limited the power to detect the potential benefits of keeping patients a bit longer in paroxysmal versus persistent AF.

Study Limitations

Several limitations may have influenced our results: (1) In the absence of placebo-control group, this study could not clarify the relationship between the incidence of AF relapse and BP control; (2) although periodic 12-lead ECG and Holter recording were routinely monitored throughout the follow-up period, short of implantation of a loop recorder in asymptomatic hypertensive patient, which is expensive and not always practical in daily practice, AF recurrences might have been missed in some patients, which, however, were equally affected in both groups; and (3) ambulatory and central BP measurements may be needed to dissect the differential drug effects between telmisartan versus nifedipine independent of BP (average and central BP) lowering. Further research works on these issues are awaited with great interest. Moreover, this study did not check the difference in AF frequency between the pretreatment period and the final month of the follow-up to evaluate the effects of 2 treatments on AF burden.

Perspectives

In summary, the present results show that although nifedipine-based antihypertensive treatment had slightly better BP control at 24 months, telmisartan-based antihypertensive treatment had more potent effects on preventing progression to persistent AF, but similar effects on overall AF recurrences in hypertensive patients with paroxysmal AF. The potential reason for the benefit of telmisartan is possibly attributed to its more prominent effects on reversal of LVH and atrial remodeling. However, to what extent these will translate into a reduction in the burden of AF and other adverse clinical outcomes remains to be seen.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Few studies have investigated which antihypertensive drugs would get more benefit on risk of recurrent atrial fibrillation (AF) in those patients with hypertension and paroxysmal AF. Although some studies, such as the J-RHYTHM II and ANTIPAF study, focused on this issue, a substantial proportion of patients had a history of overt structural heart disease and received antiarrhythmic drug therapy and angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

What Is Relevant?

- For the first time, this study aimed to evaluate whether telmisartan could provide more benefits beyond the blood pressure-lowering effect than nifedipine in hypertensive patients with paroxysmal AF without overt cardiovascular diseases in the absence of angiotensin converting enzyme inhibitors and ion-channel–blocking antiarrhythmic drug therapy.

Summary

The present study showed that although nifedipine-based antihypertensive treatment had slightly better blood pressure control at 24 months, telmisartan-based antihypertensive treatment had more potent effects on preventing progression to persistent AF, but similar effects on overall AF recurrences in hypertensive patients with paroxysmal AF. The potential reason for the benefit of telmisartan is possibly attributed to its more prominent effects on reversal of left ventricular hypertrophy and atrial remodeling. However, to what extent these will translate into a reduction in the burden of AF and other adverse clinical outcomes remains to be seen.

The effect of Nifedipine versus Telmisartan on Prevention of Atrial Fibrillation recurrence in hypertensive patients with atrial fibrillation (NTP-AF study)

ClinicalTrials.gov Identifier: NCT01435161

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Drs Du and Fan have the same contribution to the paper.

Expanded method

Follow-up

All patients were given a questionnaire to investigate the presence of palpitations, symptomatic hypotension, and/or dizziness, study drug compliance and side effects. Patients were required to follow-up at 1 month interval within the first 6 months and 3 months interval thereafter. Follow-up review included clinical assessment, clinic BP measurements, 12-lead ECG, 24-hour Holter monitoring and echocardiography. Clinic BP measurements (3 times per study visit after being seated for ≥5 minutes, on the same day just before intake of the study drugs) were always obtained by the same investigator with a validated automatic oscillometric device (HEM-737, Omron Health Care Inc). Furthermore, patients were prompted to perform a 12-lead ECG as soon as possible when they experienced palpitations. To evaluate asymptomatic AF episodes, 24-hour Holter monitoring was performed every 3 months. Any episode of ECG-documented AF of at least 30s duration that occurred beyond 1 month after randomization was classified as a recurrence.

Echocardiography

Echocardiography was performed before randomization and every 6 months during follow-up, using IE33 ultrasound systems (Philips Netherlands). All echocardiographic studies were performed according to the American Society of Echocardiography standards[1]. The LA diameter (LAD) was measured as the maximum dimension along the parasternal long-axis view from two-dimensionally guided M-mode tracings. The LA volume (LAV) was measured using single plane Simpson's method in the apical view showing the largest LA area. The LAV was corrected for body surface area (LA volume index, LAVI). LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were obtained using a modified biplane Simpson's method from apical four- and two-chamber views, and the LV ejection fraction (LVEF) was calculated by the following formula: (LVEDV-LVESV)/LVEDV×100 (%). The LV mass index (LVMI) was calculated using Devereux's formula[2].

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Expanded result

Table S1. The change of BP, heart rate, and the proportion of patients receiving metoprolol. **(Page 6 of the Manuscript)**

variable	group	Baseline	6-month	12-month	24-month
SBP (mmHg)	Nif	159.2±8.9	126.6±4.4*	125.6±5.4**	125.6±4.4**
	Tel	161.4±9.5	128.8±3.3	127.2±4.0	127.6±4.8
DBP (mmHg)	Nif	91.9±8.1	77.5±4.7	77.1±4.8	75.3±4.1†
	Tel	93.3±6.4	77.9±4.4	77.6±4.0	76.7±4.6
ΔSBP (mmHg)	Nif	—	-32.6±7.4	-33.6±7.7	-33.6±9.7
	Tel	—	-32.6±8.8	-34.1±7.8	-33.8±8.8
ΔDBP (mmHg)	Nif	—	-14.3±6.6	-14.8±7.6	-16.5±8.1
	Tel	—	-15.4±4.8	-15.7±5.6	-16.6±6.1
Target BP rate (%)	Nif	—	66.7	77.3	84.0
	Tel	—	59.5	85.1	85.1
Heart rate (bpm)	Nif	76.3±5.2	73.6±8.0	68.5±4.3	68.6±4.6
	Tel	76.5±5.0	72.7±4.9	68.1±4.4	68.3±4.1
Metoprolol@ (%)	Nif	—	68.0	65.3	56.8
	Tel	—	70.3	64.9	46.7

Nif: Nifedipine group; Tel: Telmisartan group; ΔSBP: the decrease values of SBP between at baseline and 24 months; ΔDBP: the decrease values of DBP between at baseline and 24 months; @: the proportion of patient received metoprolol

Comparing nifedipine vs telimsartan: * p<0.001, ** p=0.036, *** p=0.010, † p=0.052

Table S2. Baseline characteristics and UCG indexes of patients with or without AF recurrence

variable		Patients with no AF recurrence (n=64)	Patients with AF recurrence (n=85)	P value
Age (years)		61.6±6.2	61.9±6.8	0.833
Gender (male, %)		57.8	63.5	0.590
BMI (kg/m^2)		24.8±1.8	25.6±2.6	0.025
History of hypertension (years)		9.6±4.2	8.4±4.3	0.072
AF duration (years)		2.0±1.0	1.7±1.2	0.120
Frequency of AF occurrence (times/month)		1.5±0.7	1.5±0.7	0.515
HR (bpm)	baseline	76.2±5.0	76.6±5.2	0.632
	24-month	68.3±3.9	68.3±3.9	0.645
SBP (mmHg)	baseline	160.4±9.3	160.2±9.2	0.873
	24-month	126.3±4.7	126.8±4.7	0.491
DBP (mmHg)	baseline	91.1±6.6	93.7±7.6	0.035
	24-month	76.0±4.4	76.0±4.4	0.889
Echocardiographic parameters				
IVS (mm)	baseline	13.2±0.9	13.5±0.9	0.034
	24-month	11.3±0.9	11.2±0.9	0.466
LAD (mm)	baseline	39.2±3.7	41.0±3.8	0.004
	24-month	36.6±2.7	38.1±2.6	<0.001
LVEF(mm)	baseline	64.8±4.1	64.8±4.2	0.996
	24-month	65.4±3.1	66.7±2.6	0.005
LVDD (mm)	baseline	52.0±2.9	52.8±2.5	0.056
	24-month	48.7±1.5	49.7±1.6	<0.001
LVSD (mm)	baseline	32.3±4.5	33.9±3.9	0.028
	24-month	32.1±4.0	31.1±4.0	0.120
LVPWT(mm)	baseline	12.8±0.6	13.3±0.9	<0.001
	24-month	11.6±0.9	12.2±1.0	0.001
LVMI (g/m2)	baseline	154.8±21.9	167.4±21.7	0.001

	24-month	116.6±13.6	125.4±16.1	0.001
LAVI (ml/m2)	baseline	24.0±4.1	26.3±4.4	0.001
	24-month	21.2±3.1	23.0±3.4	0.001

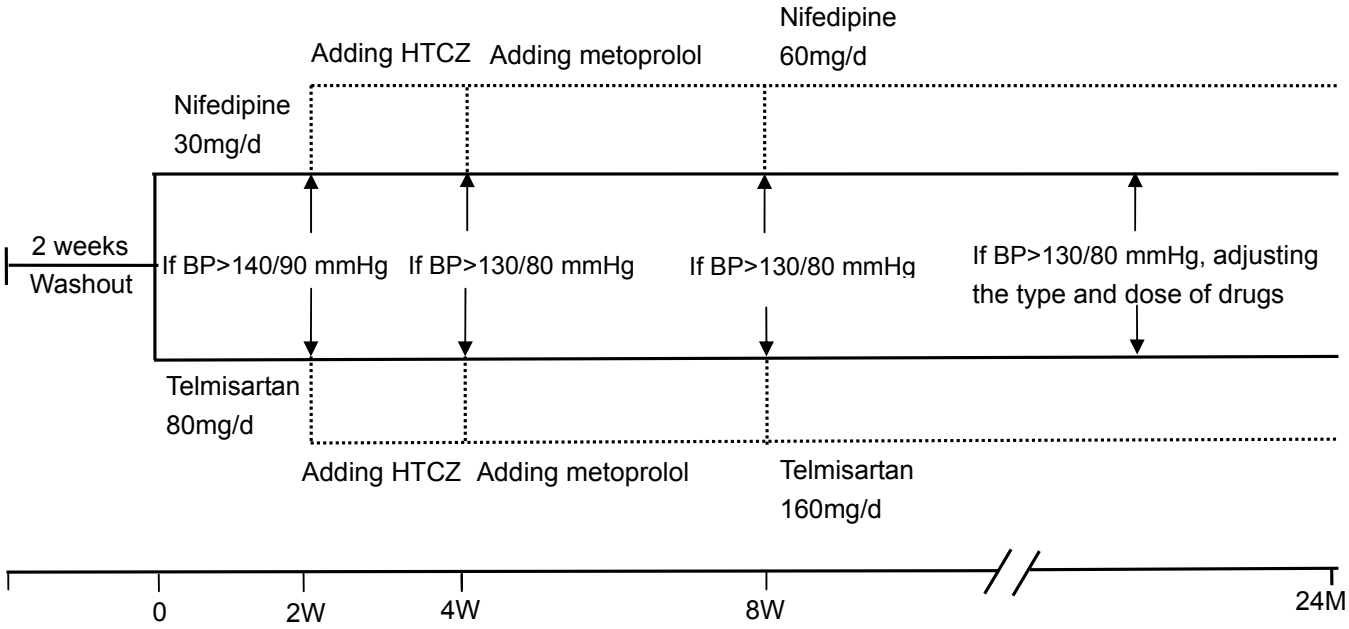

Figure S1. Flow diagram of the nifedipine- and telmisartan-based antihypertensive therapeutic protocol.

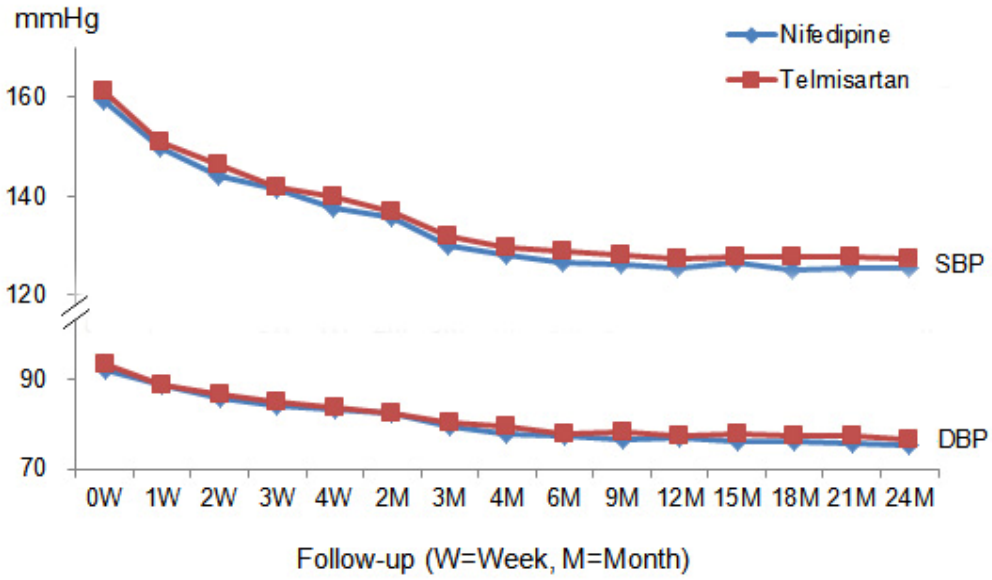

Figure S2. The time-course of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in nifedipine-based treatment group and telmisartan-based treatment group. (Page 6 of the Manuscript)