

Olmesartan Reduces New-onset Atrial Fibrillation and Atrial Fibrillation Burden after Dual-chamber Pacemaker Implantation in Atrioventricular Block Patients

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Abstract

Background: Atrial fibrillation (AF) is the most frequent tachyarrhythmia in patients with a permanent pacemaker. Angiotensin II receptor antagonists have a protective effect against the occurrence of AF in patients with heart diseases. This study aimed to assess the effectiveness of olmesartan in the prevention of new-onset AF and AF burden in atrioventricular block (AVB) patients with dual-chamber (DDD) pacemaker implantation.

Methods: This was a single-center, prospective, randomized, single-blind, controlled clinical study. A total of 116 AVB patients, who received DDD pacemakers implantation with the percentage of ventricular pacing (VP%) $\geq 40\%$ from April 22, 2011 to December 24, 2012, were prospectively randomized to olmesartan group (20 mg per day; $n = 57$) or control group ($n = 59$). Patients were followed up using pacemaker programming, 12-lead electrocardiography in the intrinsic sinus rhythm, laboratory examinations, and transthoracic echocardiography at 24 months. Atrial high rate events (AHREs) were defined as 180 beats/min over a minimum of 5 min. AF burden was calculated by the number of hours with AHREs divided by the number of measurement hours.

Results: Ten (17.5%) patients in the olmesartan group and 24 patients (40.7%) in the control group occurred new-onset AF, and the difference between two groups was statistically significant ($P = 0.04$). AF burden was lower in olmesartan group than that in control group ($8.02 \pm 3.10\%$ vs. $13.66 \pm 6.14\%$, $P = 0.04$). There were no significant differences in mean days to the first occurrence of AHREs and mean cumulative numbers of AHREs between two groups ($P = 0.89$ and $P = 0.42$, respectively). Moreover, olmesartan group had smaller values of maximal P-wave durations and P-wave dispersion (PD) after 24 months follow-up compared with the control group (109.5 ± 7.4 ms vs. 113.4 ± 7.1 ms, $P = 0.00$; and 40.6 ± 4.5 ms vs. 43.3 ± 4.4 ms, $P = 0.02$, respectively). Left ventricular end-diastolic diameter and left ventricular ejection fraction were not significantly different between two groups (both $P > 0.05$).

Conclusion: This study suggested that 24-month of olmesartan therapy could reduce new-onset AF and AF burden in patients with DDD pacemakers.

Clinical Trial Registration: ChiCTR-TRC-12004443; <http://www.chictrdb.org>.

Key words: Angiotensin II Receptor Antagonist; Atrial Fibrillation; Olmesartan; Pacemaker; Ventricular Pacing

INTRODUCTION

Atrial fibrillation (AF) is the most frequent tachyarrhythmia in patients with a permanent pacemaker, occurring in up to 88.6% of patients with prior history of AF and 53.8% of patients without prior AF history at 24 months postimplant.^[1] Atrial high rate episodes (AHREs) may be brief, infrequent, and asymptomatic, and may be detected before clinical arrhythmia is apparent. These subclinical device-detected AHREs are associated with an increased stroke risk, similar to, but to a lesser degree than, clinically apparent AF detected by routine methods.^[2] The only therapeutic strategy that has been

demonstrated to be effective in reducing the occurrence of AF in these patients is minimizing ventricular pacing (VP).^[3] However, minimal VP algorithms are not suitable for patients with advanced atrioventricular block (AVB). Recently, several

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clinical and experimental studies have reported a protective effect of the angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists against the occurrence of AF in patients with heart diseases (e.g., hypertension, heart failure, cardiac hypertrophy, and so on).^[4,5] However, these results have not been consistently replicated in the cohort of pacemaker patients.

In the present study, we examined patients without previous history of AF, who were implanted dual-chamber (DDD) pacemakers, to assess the effectiveness of olmesartan in the prevention of new-onset AF and AF burden in AVB patients with high VP% ($\geq 40\%$).

METHODS

Patients selection

This was a single-center, prospective, randomized, single-blind, controlled clinical study. Patients with the age of ≥ 40 years and < 80 years, who had AVB and met the indication for a permanent dual-chamber cardiac pacing, were consecutively recruited from April 22, 2011 to December 24, 2012, in Nanjing First Hospital. After a 1-week run-in period, the patients with the VP% $\geq 40\%$ were included in the study.

Patients were excluded if they had received an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI) in the past month or had received therapy with antiarrhythmic agents (sodium or potassium channel blockers within 4 half-lives; amiodarone within the past 3 months). Other exclusion criteria included heart failure with reduced ejection fraction, proteinuria, serum potassium level ≥ 5 mmol/L, known bilateral renal artery stenosis, serum creatinine level ≥ 30 mg/L, established paroxysmal AF (documentation of AF in at least one electrocardiography [ECG] recorded before randomization), left atrial (LA) diameter ≥ 6 cm, hyperthyroidism, heart surgery within 3 months, and participation in another clinical trial within the past 30 days.

The study was approved by the Ethical Committee of Nanjing First Hospital and was conducted according to the *Declaration of Helsinki*. A written informed consent was obtained from the patients before participation.

Study design

The trial was designed to detect a 50% relative reduction in the risk of AF from a rate of 50% in the control group to 25% in the treatment group. Using a two-tailed test, a type I error of 0.05, a power of 90%, and a 10% drop-out rate to fulfill the criteria of intention-to-treat analysis, we calculated that we need 120 patients, 60 in each group, to show the superiority of olmesartan over placebo.

Seven days after implantation of the pacemaker, the patients with the VP% $\geq 40\%$ were randomized to olmesartan group (20 mg olmesartan per day) or control group (no olmesartan) at 1:1 ratio according to the computer generated random number by one certain researcher. The patients were

nonblinded in the study. In case of suspected intolerance of the study medication, study medication was terminated. Each patient was followed up for a period of 24 months after enrollment according to the schedule.

Follow-up visits were scheduled at 1 month, 6 months, 12 months, 18 months, and 24 months. Patients were asked to record actual medication, physical examination, arterial blood pressure, 12-lead ECG in the intrinsic sinus rhythm, sodium, potassium, creatinine, transthoracic echocardiography, and pacemaker programming. All the physicians, pacemaker interrogators, and the data recorders involved in follow-up did not know the grouping. Two investigators performed the analyses for each participant separately using the same protocol. We used the mean values of the parameters from the two investigators for statistics. The study design is illustrated in Figure 1.

Pacemaker programming

All the pacemakers Relia RED(R), Sensia SED(R), Adapt DDD(R) (Medtronic Inc., Minnesota, USA) and Identity™ 5286, Victory™ 5816, and 5826 (St. Jude Medical, Minnesota, USA) implanted in this study have high sensitivity and specificity for the detection of AF or AHREs. The algorithm was recommended to optimize AF detection and minimize VP. The detection threshold for AHRE was set to be 180 beats/min over a minimum of 5 min. It was essential that the devices were programmed appropriately to avoid far-field R-wave oversensing and atrial undersensing to ensure a high sensitivity and specificity for AF detection. Validation of appropriate detection of AHRE or AF was also carried out by looking at atrial electrograms to exclude false-positive detection. While the pacemakers offer automatic atrial overdrive in response to high intrinsic atrial rates, this feature was not used during the study to permit assessment of a simpler approach to preventing AF.

VP% and atrial pacing (AP%) were recorded. The new-onset AF, the days to the first occurrence of documented AHRE, cumulative numbers of AHREs in the follow-up were also recorded. The AF burden was calculated by the number of hours with AHREs divided by the number of measurement hours.

P-wave dispersion

P waves on all derivations were synchronously recorded on standard 12-lead surface ECGs at 50 mm/s paper speed and 20 mm/mv standardization in the intrinsic rhythm. The onset of the P-wave was defined as the point of first visible upward slope from baseline for positive waveforms and as the point of the first downward slope from baseline for negative waveforms. The return to the baseline was considered as the end of the P-wave. The average P-wave of three consecutive beats from each lead was determined. Maximum P-wave duration (Pmax) was defined as the longest P-wave duration, and minimum P-wave duration (Pmin) was defined as the shortest P-wave duration in all derivations. P-wave dispersion (PD) was defined as the difference between Pmax and Pmin.

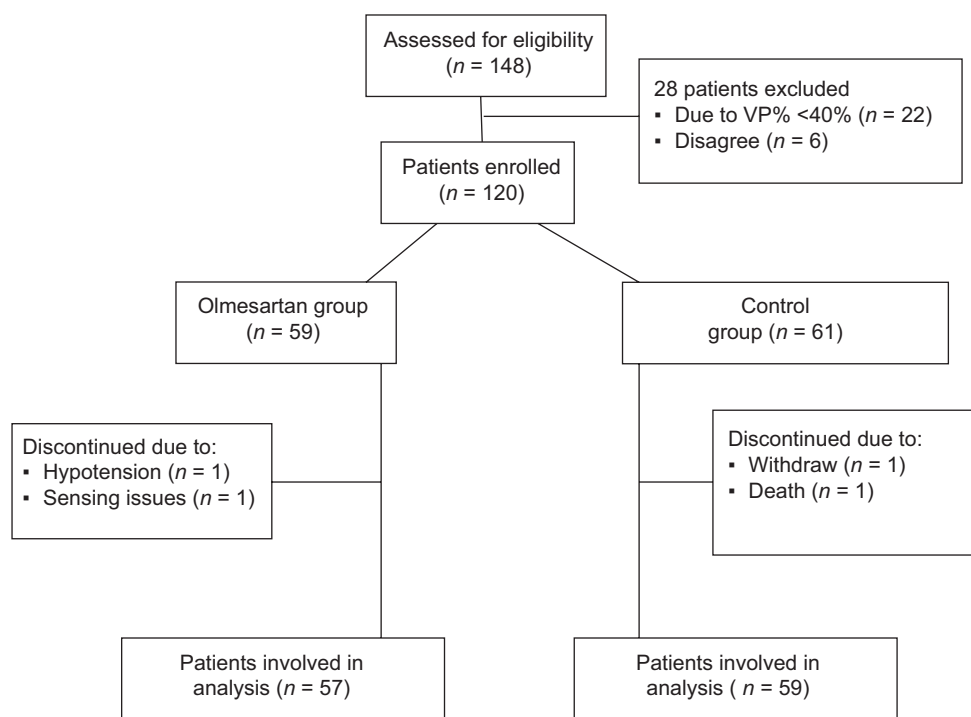


Figure 1: Flowchart of study selection process. VP: Ventricular pacing.

Echocardiographic examination

All echocardiographic examinations were performed with GE Vivid 7 (GE Healthcare, Wisconsin, USA) using cardiac ultrasound scanner 2.0–3.5 MHz transducers. One lead ECG was recorded continuously. All the patients were in sinus rhythm. LA end-systolic diameters, left ventricular end-systolic, and end-diastolic dimensions were measured from M mode in the parasternal long axis views according to the American Society of Echocardiography’s guideline. Ejection fractions were measured according to the Simpson method.

Study endpoints

The primary endpoint was the presence of new-onset AF confirmed by pacemaker programming during 24-month follow-up. Secondary end-points of the study were AF burden, PD, and echocardiographic findings for LA size.

Statistical analysis

Data are expressed as mean \pm standard deviation (SD) or percent. Student’s *t*-test was used for comparing continuous variables. Differences in portions were judged by Chi-square test. The two-tailed paired *t*-test was used to compare the data before and after pacemaker implanting. The significance of the different variables in the prediction of new-onset AF was assessed using univariable analysis, and then significant factors were inserted in a multivariable logistic regression analysis. Relative risks were estimated using exposure odds ratios (ORs) from cross-tabulation. A $P < 0.05$ was considered to be statistically significant. Analyses were performed using the SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 116 patients (68 males and 48 females) were enrolled in this study, with the mean age of 65.1 ± 10.5 years (range: 43–80 years); and there were 57 patients in olmesartan group and 59 patients in control group. No statistically significant difference was observed between the two groups when basic clinical parameters of the patients were compared [Table 1].

The AP% and VP% were not significantly different between two groups after 24-month follow-up ($P = 0.18$ and $P = 0.89$, respectively). Among the 116 patients, 34 patients (23 males and 11 females, mean age: 70.0 ± 9.0 years, range: 54–79 years) developed new atrial tachyarrhythmia during 24-month follow-up. The numbers of patients occurring new-onset AF were 3, 6, 7, 4, and 4 in the control group and 2, 3, 2, 1, and 2 in the olmesartan group at 1 month, 6 months, 12 months, 18 months, and 24 months, respectively and the difference between two groups was statistically significant ($P = 0.04$). AF burden in the olmesartan group was lower than that in the control group after 24 months follow-up (8.02 ± 3.10 vs. 13.66 ± 6.14 , $P = 0.04$) [Figure 2].

Intracardiac electrograms of every recorded AHRE were assessed and classified (AF vs. no AF) by two experienced cardiologists who were blinded to the groups. During 24 months follow-up, 1239 AHRE were recorded and classified in 34 patients. Among 1239 episodes, 1170 episodes (94.4%) were true AHREs. Our results were based on the true AHREs. After 24 months follow-up, there was no significant difference in days to the first occurrence of AHREs between two group, which was 293.8 ± 197.5 days

in the olmesartan group and 286.7 ± 191.7 days in the control group ($P = 0.89$); there was also no significant difference in cumulative numbers of AHREs between the two groups ($P = 0.42$) [Table 2].

Table 3 shows the hemodynamic, ECG, and echocardiographic parameters between two groups before and 24 months after treatment. According to the parameters before and 24 months after treatment, blood pressure was reduced from $132.2 \pm 14.4/81.1 \pm 8.8$ mmHg (1mmHg=0.133 kPa) to $128.3 \pm 20.1/75.1 \pm 6.3$ mmHg in the olmesartan group, while stayed at $130.3 \pm 15.1/80.2 \pm 10.4$ mmHg to $128.5 \pm 11.1/78.2 \pm 10.6$ mmHg in the control group. The parameters of Pmax and PD changed significantly before and 24 months after treatment in control group (104.2 ± 7.3 ms vs. 113.4 ± 7.1 ms, $P = 0.00$; and 38.5 ± 3.6 ms vs. 43.3 ± 4.4 ms, $P = 0.00$, respectively). The parameter of PD showed no remarkable change before and 24 months after treatment in the olmesartan group (38.9 ± 3.4 ms vs. 40.6 ± 4.5 ms, $P = 0.14$). LA end-systolic diameter at 24-month follow-up tended to be smaller than that before

treatment in the olmesartan group (40.8 ± 4.3 mm vs. 41.5 ± 5.1 mm); however, the difference failed to achieve statistical significance ($P = 0.08$). LA end-systolic diameter also had no remarkable change before and 24 months after treatment in the control group ($P = 0.06$).

According to the parameters between two groups, olmesartan group had smaller values of Pmax and PD after 24 months follow-up compared to the control group (109.5 ± 7.4 ms vs. 113.4 ± 7.1 ms, $P = 0.00$; 40.6 ± 4.5 ms vs. 43.3 ± 4.4 ms $P = 0.02$, respectively). However, the values of LA end-systolic diameter and left ventricular ejection fraction (LVEF) had no changes between two groups before treatment and after 24 months follow-up.

Multivariable logistic regression analyses showed that the predicted factors for new-onset AF were male ($OR: 3.865$, 95% confidence interval [CI]: 1.342–11.127; $P = 0.01$), LA diameter ($OR: 1.146$, 95% CI: 1.050–1.250; $P = 0.00$), and olmesartan recipe ($OR: 0.327$, 95% CI: 0.109–0.978; $P = 0.04$).

Table 1: Baseline characteristics of all patients in this study

Characteristics	Olmesartan group (n = 57)	Control group (n = 59)	P
Age (years), mean \pm SD	64.8 \pm 10.9	65.3 \pm 10.3	0.89
Male, n (%)	35 (61.4)	33 (55.9)	0.58
Smoking, n (%)	17 (29.8)	15 (25.4)	0.68
Diabetes mellitus, n (%)	15 (26.3)	13 (22.0)	0.67
Coronary artery disease, n (%)	14 (24.5)	10 (16.9)	0.69
Hypertension, n (%)	25 (43.8)	24 (40.7)	0.85
Medications, n (%)			
β -blocker	7 (12.3)	8 (13.6)	0.87
Dihydropyridine calcium antagonist	20 (35.1)	21 (35.6)	0.96
Diltiazem	2 (3.5)	2 (3.3)	1.00
Verapamil	1 (1.8)	0	0.49
Diuretics	10 (17.5)	8 (13.6)	0.61
Nitrate	13 (22.8)	12 (20.3)	0.82
Statins	12 (21.1)	12 (20.3)	0.92
Aspirin	17 (29.8)	18 (30.5)	0.94
Oral anticoagulants	1 (1.8)	0	0.49

SD: Standard deviation.

DISCUSSION

This study showed that the use of 20 mg olmesartan per day reduced the prevalence of new-onset AF and AF burden in

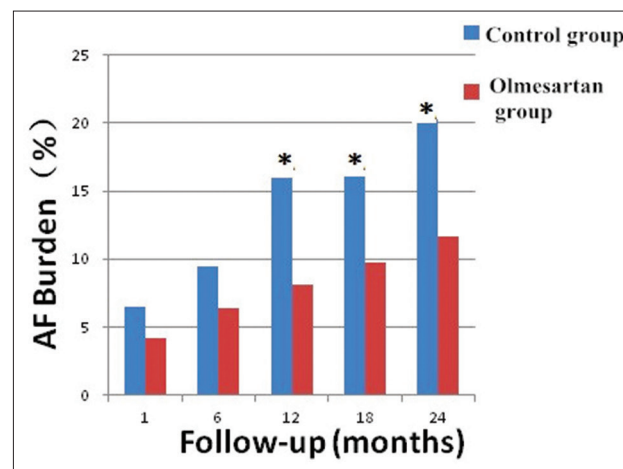


Figure 2: Atrial fibrillation burden of olmesartan and control groups during follow-up period. * $P < 0.05$, vs. olmesartan group at same time-point. AF: Atrial fibrillation.

Table 2: Pacemaker parameters after 24-month follow-up in olmesartan and control groups in this study

Parameters	Olmesartan group (n = 57)	Control group (n = 59)	Statistical values	P
AP (%)	12.6 \pm 7.3	13.9 \pm 5.2	-1.10*	0.18
VP (%)	71.6 \pm 22.0	72.2 \pm 18.7	-0.09*	0.89
Patients occurred new-onset AF	10 (17.5)	24 (40.7)	5.19†	0.04
Days to the first occurrence of AHREs (days)	293.8 \pm 197.5	286.7 \pm 191.7	-0.14*	0.89
Cumulative numbers of AHREs (episodes/patient)	22.8 \pm 19.2	28.4 \pm 18.4	0.13*	0.42
Duration of AHRE episodes (h/day)	1.93 \pm 0.75	3.29 \pm 1.45	2.78*	0.04
AF burden (%)	8.02 \pm 3.10	13.66 \pm 6.14	-	0.04

Data are shown as mean \pm SD or n (%). * t value; † χ^2 value. AF: Atrial fibrillation; AP: Atrial pacing; VP: Ventricular pacing; AHREs: Atrial high rate episodes; SD: Standard deviation; -: Not applicable.

Table 3: Comparison of parameters between olmesartan and control groups before and 24 months after treatment

Variables	Olmesartan group (n = 57)	Control group (n = 59)	t	P
Heart rate (beats/min)				
Before	60.6 ± 12.6	57.9 ± 13.6	1.120	0.27
At 24-month	66.0 ± 5.2	68.5 ± 6.5	-2.230	0.06
t	-3.46	-7.02		
P	0.00	0.00		
Systolic BP (mmHg)				
Before	132.2 ± 14.4	130.3 ± 15.1	2.210	0.16
At 24-month	128.3 ± 20.1	128.5 ± 11.1	2.090	0.71
t	3.57	1.83		
P	0.04	0.52		
Diastolic BP (mmHg)				
Before	81.1 ± 8.8	80.2 ± 10.4	1.090	0.59
At 24-month	75.1 ± 6.3	78.2 ± 10.6	1.910	0.05
t	3.82	1.62		
P	0.03	0.78		
SCr (μmol/L)				
Before	96.4 ± 8.7	94.3 ± 12.1	1.410	0.28
At 24-month	94.7 ± 7.6	95.7 ± 8.1	1.120	0.61
t	2.05	1.57		
P	0.32	0.56		
Pmax (ms)				
Before	101.9 ± 7.6	104.2 ± 7.3	-1.602	0.11
At 24-month	109.5 ± 7.4	113.4 ± 7.1	-2.886	0.00
t	-7.32	-7.34		
P	0.00	0.00		
PD (ms)				
Before	38.9 ± 3.4	38.5 ± 3.6	0.624	0.54
At 24-month	40.6 ± 4.5	43.3 ± 4.4	-3.208	0.02
t	-1.55	-3.45		
P	0.14	0.00		
LA end-systolic diameter (mm)				
Before	41.5 ± 5.1	42.0 ± 6.0	-0.910	0.37
At 24-month	40.8 ± 4.3	43.6 ± 5.9	-2.919	0.06
t	0.51	-0.47		
P	0.08	0.06		
LVEF (%)				
Before	58.7 ± 6.9	60.6 ± 6.9	-1.372	0.17
At 24-month	59.2 ± 7.1	59.1 ± 7.1	-1.997	0.57
t	1.71	2.58		
P	0.12	0.05		

Data are shown as mean ± SD. BP: Blood pressure; SCr: Serum creatinine; Pmax: Maximal P-wave duration; PD: P-wave dispersion; LVEF: Left ventricular ejection fraction; SD: Standard deviation; LA: Left atrial.

patients with DDD implantation 24 months after treatment. Olmesartan group showed significantly lower PD and Pmax values, which indicated that receiving olmesartan treatment was a protective factor for new-onset AF.

In our study, the percentage of the progression to new-onset AF in all the included AVB patients was 29.3% at 24-month follow-up, with 17.5% in the olmesartan group and 40.7% in the control group, respectively. Although

DDD pacing remains AV synchrony, long-term right VP coursed intraventricular and interventricular asynchrony.^[6] AF occurring during the course is accompanied by atrial electrical and structural remodeling, including atrial dilation, contractile dysfunction, and fibrosis.^[7] Current pacemakers have enhanced monitoring features that allow determination of the time of occurrence and overall burden of atrial tachycardia/AF.^[8] AHREs lasting >5 min were detected in more than 65% patients aged older than 70 years with complete AV block after 18 months DDD pacemaker implantation, due to LA enlargement and P-wave duration expansion.^[9,10] In a retrospective observational study of 160 patients with DDD pacemakers, mainly (69%) for AVB, the incidence of new-onset AF at 1 year was lower in the ACEIs- or ARBs-treated group compared with no ACEIs/ARBs group (5% vs. 10%).^[11]

Our data suggested the beneficial effects of 24 months of olmesartan therapy for the reduction of new-onset AF and AF burden were similar between two groups. Previous studies have suggested that ACEIs or ARBs prevented the development of AF in patients with LV dysfunction.^[4,5,12] As well, the Losartan Intervention For Endpoint reduction in hypertension study demonstrated losartan-based therapy significantly reduced new-onset AF by 33% compared to atenolol-based therapy, with similar blood pressure reduction.^[13] The target for therapy with the renin-angiotensin-aldosterone system inhibitors was to prevent LA stretch and dilatation secondary to left ventricular dyssynchrony and dysfunction caused by long-term right VP.^[14] In particular, olmesartan can effectively inhibit pressure overload-induced cardiac hypertrophy even in angiotensinogen-knockout mice lacking endogenous angiotensin II.^[15] However, angiotensin II-antagonist in paroxysmal AF trial failed to prove that 1 year of olmesartan therapy reduced the number of AF episodes in patients with documented paroxysmal AF without structural heart disease.^[16]

P-wave duration by signal-averaged ECG has been shown to be useful for identifying patients at risk for AF. PD appeared to be related to the LA size and function.^[17] Demir *et al.*^[18] reported that in patients with DDD pacemakers, increased LA dimension, Pmax value of 120 ms, and PD value of 40 ms were associated with significantly increased risk of persistent AF. Our study observed that pacing prolonged the values of Pmax and PD. Therapy of 20 mg olmesartan per day for 24 months significantly reduced adverse electrical remodeling caused by pacing. It is one of the possible mechanisms of olmesartan reducing AF in pacemaker patients. However, there was a minimal decrease in the LA size at 24-month follow-up in the olmesartan group, which was parallel with a minimal increase in the size in the control group, without statistical significance. Maybe a longer follow-up or larger study samples can reveal the difference of structure remodeling among patients with pacemaker implantation.

Our study had some limitations that should be taken into consideration. First, this was only a single-center and nonblinded study. Second, six different pacemaker models

from two different companies were used in the study. Even there were no significant differences in device mix between the two study groups, the possibility of the different detection algorithms affecting the results could not be ruled out.

In conclusion, this study proved that 24-month of olmesartan therapy could reduce new-onset AF and AF burden in patients with DDD pacemakers.

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Conflicts of interest

There are no conflicts of interest.

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