Original Article

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Association of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists use with risk of atrial fibrillation after pacemaker implantation among very old patients

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SUMMARY It remains unknown whether and to what extend the angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can play a role in the development of atrial fibrillation (AF) after pacemaker implantation in very old patients. Therefore, we aimed to investigate the association between oral ACEIs or ARBs and the risk of developing AF in very old patients after pacemaker implantation. Patients above 80 years old with pacemaker implantation and without baseline history of AF were included and their real-world information about ACEIs or ARBs use was extracted from electronic medical records. New AF cases were confirmed *via* the records of outpatient visits. The multivariable Cox proportional-hazards model was used to evaluate the associations between oral ACEIs or ARBs and risk of AF after pacemaker implantation. Among a total of 388 identified patients aged 80 to 98 years, 118 used ACEIs, 174 had ARBs therapy, and 115 AF were identified after pacemaker implantation during a median follow-up time of 3.1 years. After adjustment for potential confounders, patients with daily use of ARBs had a relatively lower risk of AF after pacemaker implantation (HR: 0.627, 95% CI: 0.425, 0.926; $P = 0.019$) compared with those non-users, whereas ACEIs therapy didn't show a significant relation with AF risk (HR: 1.335, 95% CI: 0.894, 1.995; $P = 0.157$). In conclusion, for very old patients with a permanent pacemaker, daily use of oral ARBs was associated with a relative lower risk of AF after pacemaker implantation, however, daily use of ACEIs was not related with AF risk.

Keywords atrial fibrillation, pacemaker implantation, very old patients, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists

1. Introduction

Pacemaker implantation is a common and effective treatment to control all kinds of bradycardia arrhythmias (*1*). In recent years, an augmented life expectancy and enhanced therapeutic options for heart diseases have increased the proportion of the elderly (≥ 80 years) requiring pacemaker implantation. However, a significant amount of researches have described that the incidence of atrial fibrillation (AF) in pacemaker implanted population increased from 3% to 15-30%, and very old patients were associated with a higher risk of AF (*2-5*). Indeed, AF induced by artificial pacing is widely considered to be directly related to atrial pathological remodeling, which includes structural pathological remodeling and electrical remodeling. In addition, sympathetic activation, inflammation, and pacing mode are associated with AF development after pacemaker implantation (*6-8*). Factors influencing the occurrence of AF after pacemaker implantation remain elusive, especially among elderly patients, and related evidence is limited.

Previous studies have revealed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are primarily related to alleviating cardiac structural pathological remodeling and electrical remodeling. Besides, a certain proportion of very old patients take ACEIs or ARBs daily to regulate blood pressure, alleviate heart failure and other diseases. Therefore, the potential association between ACEIs or ARBs use and the occurrence of AF after pacemaker implantation in the elderly patients warrants further investigation.

The mechanisms of action of ACEIs and ARBs are slightly distinct. Previous studies have demonstrated that ARBs essentially inhibited the local systemic

renin-angiotensin-aldosterone system (RAAS) activity and alleviated the atrial remodeling. In contrast, ACEIs mainly play a role of RAAS in circulation but with limited function in the regional heart. Therefore, it is reasonable to hypothesis that ARBs and ACEIs might have an effect on the occurrence of AF after pacemaker implantation. Thus, we conducted a real-world study to explore the effect of ACEIs and ARBs on the occurrence of AF after pacemaker implantation among very old patients, thereby providing evidence for cardiovascular drugs selection.

2. Methods

2.1. Study subject

After de-identification of personal information, patients who received pacemaker implantation in Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine from 2012 to 2018, aged more than 80 years old and without a known baseline history of AF, were included in this study. Real-world information of daily oral ACEIs or ARBs use was extracted from the prescribed medication information. Exclusion criteria were as follows: (*i*) Previous history of cardiac surgery, (*ii*) Abnormal thyroid function (hyperthyroidism), (*iii*) Congenital heart disease, (*iv*) Severe liver and renal dysfunction, (*v*) Severe valvar heart disease, (*vi*) Patients with AF (either paroxysmal or permanent) before the study, (*vii*) Patients who were diagnosed with AF within 3 months after pacemaker implantation were also excluded since it has been widely accepted that at least 3 months were needed for cardiac remodeling in inducing AF, and related studies also commonly excluded such individuals (*2,9*).

2.2. Medication information collection

The main exposure of interest was the use of ACEIs or ARBs, which was identified from the prescription records. We collected detailed information about the prescribed ACEIs and ARBs. The main purpose of this study was to compare the risk of subsequent development of AF after pacemaker implantation in patients with or without ACEIs/ARBs use, as well as the contrasting roles they played in subjects.

2.3. Primary outcomes

New AF cases were defined by EMR checks and confirmed by professional physicians during either an ambulatory visit, discharge diagnosis, or during post-operation follow up appointments. AF cases were further diagnosed based on the International Classification of Diseases, 10th Revision, with the diagnosis code of (ICD-10: I48).

2.4. Covariates

For each patient, we conducted a retrospective review of their EMR and database information, including hypertension, diabetes mellitus, heart failure, left ventricular ejection fraction (LVEF), and NYHA Functional Classification as covariates. Data on other related prescribed medications, including β-blockers, calcium-channel blockers (CCBs), statins, and diuretics were also abstracted.

2.5. Statistical Analyses

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as frequencies. The Kolmogorov-Smirnov test was used to examine whether the continuous variables were normally distributed. Student's *t*-tests or otherwise the Mann-Whitney *U* tests were used to compare the normal distributed continuous data in two groups. Categorical variables were compared by using the chi-square test. Cox proportional models were applied to calculate the hazard ratio (HR) and 95% confidence interval (CI) to evaluate the association between oral ACEIs or ARBs and AF risk after pacemaker implantation, after adjustment for age, gender, documented comorbidities and concomitant medications. Kaplan-Meier curve and log-rank test was employed to compare the AF-free survival in ACEIs/ARBs users and non-users.

All statistical analyses were performed by using the STATA 15.1 software. The *P*-value less than 0.05 was considered as statistical significance.

3. Results

3.1. Patient characteristics

A total of 388 patients aged over 80 years (80-98 years) were included for analyses. 115 AF cases were identified after pacemaker implantation during a median follow-up time of 3.1 years. Among them, 118 (30.4%) patients received ACEIs therapy and 42 AF cases were identified, whereas 174 (44.9%) took ARBs, and 43 AF cases were observed. Baseline characteristics of all subjects are summarized in Table 1 and Table 2. Compared with ACEIs non-users, ACEIs users were more likely to receive cardioprotective medications including β-blocker (73.7% *vs*. 63.0%, $P = 0.039$), statins (74.6% *vs*. 54.8%, $P < 0.001$). Meanwhile, the ACEIs users had higher prevalence of hypertension (83.1% *vs*. 70.4%, $P = 0.009$) and heart failure (61.0% *vs*. 44.8%, $P = 0.003$) (Table 1). ARBs users presented with an increased use of CCB (75.1% *vs*. 56.1%, $P < 0.001$), and were more likely to suffer from hypertension (79.3% *vs*. 70.1%, $P = 0.039$) and

Table 1. Baseline characteristics of ACEIs users and non-users

Characteristics	ACEIs users $n = 118$	Non-users $n = 270$	*P* value
Male	64 (54.2)	145 (53.7)	0.92
Age (year)	85.9 ± 3.6	86.1 ± 4.0	0.63
Current smokers	35 (29.7)	44 (16.3)	0.003
Current drinkers	13 (11.0)	12 (4.4)	0.015
History of hypertension	98 (83.1)	190 (70.4)	0.009
History of heart failure	72 (61.0)	121 (44.8)	0.003
NYHA functional class			
1	46 (39.0)	149 (55.2)	< 0.001
2	28 (23.7)	75 (27.8)	
3	33 (28.0)	40 (14.8)	
4	11 (9.3)	6 (2.2)	
History of diabetes	28 (23.7)	65 (24.1)	0.94
β-blocker users	87 (73.7)	170 (63.0)	0.039
CCB users	84 (71.2)	168 (62.2)	0.089
Diuretics users	98 (83.1)	185 (68.5)	0.003
Statins users	88 (74.6)	148 (54.8)	< 0.001
LVEF (%)	60.36 ± 9.55	62.52 ± 8.86	0.095
LAD, mm	40.29 ± 5.37	38.56 ± 4.62	0.019
AF	42 (35.6)	73 (27.0)	0.090
TFPAF (month)	27.9 ± 17.9	29.6 ± 15.0	0.59
Follow-up months	35.9 ± 18.2	37.0 ± 18.0	0.58

Abbreviation: NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; AF, atrial fibrillation; TFPAF, time from pacemaker implantation to atrial fibrillation occurrence. Values were given as mean ± standard deviation, or frequency (percentage).

Table 2. Baseline characteristics of ARBs users and non-users

Characteristics	ARBs users $n = 174$	Non-users $n = 214$	*P* value
Male	94 (50.4)	115 (53.7)	0.96
Age (year)	86.3 ± 4.0	85.9 ± 3.8	0.33
Current smokers	33 (19.0)	46 (21.5)	0.54
Current drinkers	10 (5.7)	15 (7.0)	0.61
History of hypertension	138 (79.3)	150 (70.1)	0.039
History of heart failure	82 (47.1)	111 (51.9)	0.35
NYHA functional class			
1	92 (52.9)	103 (48.1)	0.22
2	50 (28.7)	53 (24.8)	
3	27 (15.5)	46 (21.5)	
4	5 (2.9)	12 (5.6)	
History of diabetes	50 (23.7)	43 (20.1)	0.047
β-blocker users	123 (70.7)	134 (62.6)	0.094
CCB users	129 (74.1)	123 (57.5)	< 0.001
Diuretics users	132 (75.9)	151 (70.6)	0.24
Statins users	111 (63.8)	125 (58.4)	0.28
LVEF (%)	62.66 ± 8.07	61.10 ± 9.94	0.20
LAD, mm	38.53 ± 4.43	39.59 ± 5.29	0.12
AF	43 (24.7)	72 (33.6)	0.055
TFPAF (month)	32.3 ± 15.4	27.0 ± 16.2	0.086
Follow-up months	40.1 ± 18.2	33.9 ± 17.4	< 0.001

Abbreviation: NYHA, New York Heart Association; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; AF, Atrial fibrillation; TFPAP, time from pacemaker implantation to atrial fibrillation occurrence. Values were given as mean ± standard deviation or frequency (percentage).

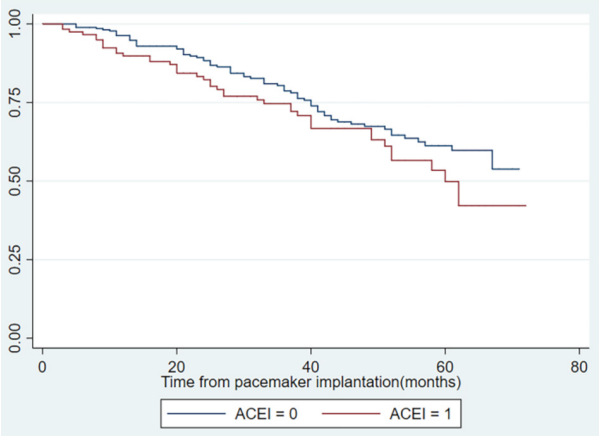

Figure 1. Kaplan-Meier curve of AF-free survival for 72-month follow-up after pacemaker implantation in ACEIs users and non-users.

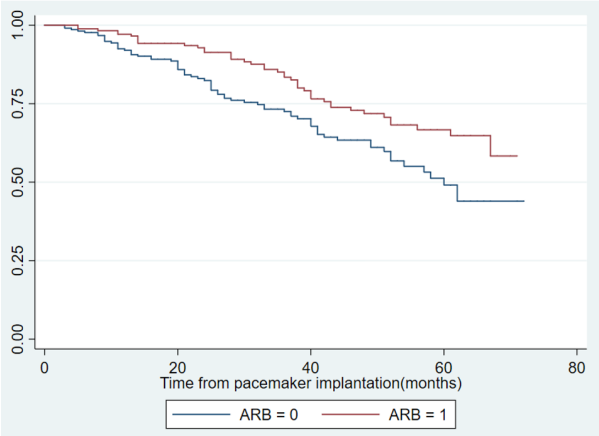

Figure 2. Kaplan-Meier curve of AF-free survival for 72-month follow-up after pacemaker implantation in ARBs users and non-users.

diabetes (23.7% *vs*. 20.1%, $P = 0.047$) (Table 2).

3.2. Primary outcome: AF after pacemaker implantation

Among a total of 388 patients aged more than 80 years old, 115 AF cases were identified after pacemaker implantation during a median follow-up time of 3.1 years. Among the enrolled individuals, 292 patients ($n = 388$) used ACEIs or ARBs. Kaplan-Meier curve indicated that the ACEIs users related with a non-significant increased risk of developing AF after pacemaker implantation ($P = 0.157$) (Figure 1), whereas patients taking ARBs had a benefit on AF-free survival after pacemaker implantation ($P = 0.019$) (Figure 2).

Consistent results were detected by using a multivariable Cox regression. Patients with daily use of ARBs had a relatively lower risk of AF after pacemaker implantation (HR: 0.627, 95% CI: 0.425, 0.926; $P = 0.019$), which remained statistically significant after adjusting for other clinical confounders: age, gender, smoking status and drinking status, medication use (β-blocker, CCBs, statins, and diuretics), and history

Table 3. Associations between ACEIs or ARBs users and risk of atrial fibrillation after pacing in Chinese very old patients

Variables	Case/N	HR (95% CI)	*P* value
ACEIs users	42/118	1.335 (0.894, 1.995)	0.157
Non-users	73/270	Referent	
ARBs users	43/174	0.627 (0.425, 0.926)	0.019
Non-users	72/214	Referent	

Model adjustment: age, gender, current smoking status, current drinking status, medication use (β-blocker, CCB, statins, diuretics), history of chronic diseases (hypertension, NYHA functional class, and ischemic stroke). Abbreviations: HR, hazard ratio; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker.

of chronic diseases (hypertension and ischemic stroke), New York Heart Association functional classification for HF. ACEIs use shown to be non-related with AF risk (HR: 1.335, 95% CI: 0.894, 1.995, $P = 0.157$) (Table 3).

4. Discussion

Pacemaker implantation is currently a common and effective method to treat all kinds of bradycardia arrhythmias. Due to the progressive increase of life expectancy in recent years, the trend has remained stable over the past few years that the patient's age of receiving a permanent pacemaker implantation has been increasing. For example, the mean age of pacemaker implantation has increased from 77 years in 2012 to 77.8 years in 2016, and about 50% of total pacemaker implantation individuals are above 80 years old in Spain (*10*). Moreover, the incidence of AF has been observed in the pacemaker implanted population, especially in the geriatric patients, which accounted for 30% of total AF patients and was nearly twice higher than the young patients (*11*). However, most available studies on AF developing after pacemaker implantation are usually conducted on middle-aged patients, especially those below the age of 80 years old. Some of these trials even exclude this subgroup of patients. Therefore, among very old patients, ways to decrease the risk of AF after pacemaker implantation merits further investigation.

Basic studies have demonstrated that AF induced by artificial pacing is directly related to atrial remodeling, including structural pathological remodeling and electrical remodeling. On the other hand, as an independent risk factor for the development of AF, aging may inevitably lead to myocardial hypertrophy and fibrosis for their excitable state of RAAS. Thus, factors that inhibit the local RAAS activity induced by pacemaker implantation in very old patients may decrease the risk of AF. This study mainly focused on potential factors that decrease AF risk in very old patients with a permanent pacemaker.

A high proportion of very old patients take daily ACEIs/ARBs for heart diseases. Previous studies have corroborated that ACEIs and ARBs are related to alleviating cardiac structural pathological and electrical remodeling. Interestingly, ACEIs/ARBs have been reported to be more effective among the elderly than in young patients since they can inhibit the excitable state of RAAS in the regional heart in those very old patients. Furthermore, multiple studies have confirmed that ARBs and ACEIs can prevent AF episodes. For example, ARBs are more effective than ACEIs in reducing the risk of AF in old patients with a history of hypertension (*12*); Olmesartan can reverse moderate myocardial hypertrophy, reduce structural remodeling caused by AF, and prevent recurrence of AF (*13*); Enalapril can also reduce the sensitive index of AF through inhibition of atrial remodeling to reduce the occurrence of AF (*14*). Therefore, ACEIs/ARBs may affect AF development in patients with a permanent pacemaker, especially in very old individuals.

Compared to ACEIs in preventing AF episodes after pacemaker implantation in oldest old patients, ARBs might be more effective as they can alleviate cardiac pathological structural and electrical remodeling by functioning on cardiac local angiotensin receptors (activating the AT2 receptor and antagonizing AT1 receptor). By inhibiting the activation of the AT1 receptor, a feedback mechanism increases angiotensin II synthesis, leading to AT2 activation. The latter counter-regulates the effects of the AT1. In addition, AT2 receptor stimulation attenuates the progression of myocardial fibrosis and advances antifibrotic process, mediating vasodilation and inhibiting cellular growth and connective tissue deposition. Past studies have established that ACE2 expression and activity increased in hearts with losartan treatment, and contributes to the increase of Ang-(1-7) activity, while higher Ang1-7 expression levels in left atrial myocardial tissues may lead to lower expression levels of TGF-β1, which then inhibit myocardial fibrosis. In addition, a serine protease with an extremely high affinity for the angiotensin-producing enzyme AngI, which is sensitive to hemagglutinin, was identified in the human heart (*15*). Thymidine has higher specificity and catalytic activity for the conversion of AngI to AngII than ACE, accounting for 6% of captopril in normal human heart and animal tissue extracts. The heart of dogs with chronic volume overload hypertrophy suggests that chymotrypsin, rather than ACE, is the main source of AngII *in vitro* (*15,16*). However, subsequent studies have shown that intracoronary infusion can inhibit 60% of the formation of AngII in the entire myocardial circulation of the body.

ARBs was reported to inhibit chymase function, which is typically increased in the pacing heart. Therefore, ARBs may be more effective in decreasing Ang II induced by pacemaker implantation, which then

attenuates pathological remodeling of heart structure, finally decreasing the risk of AF in elderly pacing patients. ARBs may also prevent AF developing in very old patients with a permanent pacemaker implantation through attenuating alterations in electrical remodeling. The shortening of the atrial effective refractory period (AERP) caused by pacing may promote atrial fibrillation, which is subsequently attributed to the reduction of the action potential duration (APD), resulting in a gradual decrease in the transient outward current (Ito) and L-type Ca^{2+} current (ICa, L). This implies that the direct arrhythmic effect of AngII is predominantly mediated through AT1R signaling. The possible cellular mechanisms of this direct arrhythmic effect of AngII may be due to the alteration of sarcoplasmic reticulum (SR) Ca^{2+} release. In isolated human atrial myocytes, AngII increases the frequency of spontaneous ryanodine receptors (RyR) that mediate basic Ca^{2+} release events (*17*). That effect is mediated by AT1Rs since it is blocked by candesartan. While effects of ACEIs on the ICa,L remains controversial. Recently, a rabbit model recently demonstrated that ACEIs increases the ICa,L current density but do not prevent its down-regulation from tachy-pacing. In addition, the remodeling of connexin 43 (*CX43*) and connexin 40 (*Cx40*) induced by pacemaker implantation may serve as a potential mechanism for the occurrence of AF in the elderly pacing population. For instance, Shyu *et al*. (*18*) observed an increase in *CX43* mediated by the activation of AT1 in cultured rat cardiomyocytes. Additionally, an earlier study described the crucial role of AT1 in gap-junctional remodeling. Connexins are intercellular channels and may form ascendant coupling regions, therefore they are instrumental in the electrical and structural remodeling of the atrium. Interestingly, studies have pointed out that *Cx43* and *Cx40* gene therapies can inhibit the electrical remodeling of the atrium to prevent AF. While dephosphorylation of *Cx43* caused by ARBs use is associated with the downward remodeling of *Cx43* (*19*), thus ARBs may function through reducing *Cx43*. Generally, ARBs may attenuate pathological remodeling of the cardiac structure and electrical remodeling and decrease the risk of AF in the oldest old pacing patients. Consequently, they may seem more effective, since they act on cardiac local angiotensin receptors. These findings are consistent with the results of our study in the sense that with ARBs use, there would be a lower risk of AF after pacemaker implantation in very old population.

Multiple guidelines have recommended ACEIs/ARBs use for very old patients suffering from hypertension or heart failure, while ignoring the fact that these RAAS-activity inhibiting drugs which may also be effective for treating AF by alleviating atrial remodeling. Lately, attention to treating AF has been transformed from anti-arrhythmic drugs to upstream therapy. Owing to the growing experimental evidence demonstrating the impact of Ang II on the atrial myocardium, several studies have been published on the possible therapeutic effect of ACEIs and ARBs in patients with AF (*20*). However, there are no studies about ACEIs or ARBs use in elderly pacing individuals. Therefore, whether ACEIs or ARBs use can reduce AF occurrence after pacemaker implantation in oldest old patients remain controversial, and it should be resolved. The results of our present study suggested that in very old patients with a permanent pacemaker, ARBs may be preferred over ACEIs, given that they reduce the risk of AF developing after pacemaker implantation.

Overall, our results demonstrated that very old individuals with daily oral ARBs consumption after pacemaker implantation were associated with a lower risk of developing new-onset AF than those without ARBs using, which remained statistically significant after adjusting for related clinical covariates. In contrast, individuals receiving ACEIs therapy did not show a protective effect against AF development. Our findings might contribute to the idea that the daily use of ARBs is associated with a less risk of inducing subsequent AF in very old pacing patients, while ACEIs users related with a non-significant increased risk of developing AF after pacemaker implantation. Therefore, it might provide evidence for the selection of the clinical drugs for very old pacing individuals.

Our study has some limitations. Firstly, we only transferred the retrospective data in a single center based on case records, so the final sample size of the group is small. Secondly, the definition of the onset time of AF may have a small range of bias because it is generally difficult to accurately define the onset time of AF by inquiring about symptoms, and asymptomatic AF may have been missed and are likely underrepresented in this study. Thirdly, the factors leading to the occurrence of AF are very complex. We have considered the correction factors as far as possible, but inevitably, there would still be some omissions. Fourthly, the effect of ACEIs therapy is related to dose, while according to electronic medical records, ACEIs were prescribed at conventional dose. Thus, the does weren't classified clearly. In addition, the pacing mode may also affect the incidence rate of AF after pacemaker implantation. We did not categorize different pacing modes or conduct subgroup analyses, because most of the included individuals received ventricular single chamber pacing (VVI mode).

In conclusion, our real-world data found that among very old pacing patients, daily oral ARBs might be associated with a lower risk of AF after pacemaker implantation but ACEIs use was not related with AF. However, our findings need to be reconfirmed by further well-designed randomized controlled trials.

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. All data generated and analyzed during this study are included in this published article.

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