Atrial Fibrillation in Primary Aldosteronism

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ABSTRACT

Primary aldosteronism (PA) is the most common cause of secondary hypertension. Increasing evidence has demonstrated an increased cardiovascular risk in patients with PA compared to those with essential hypertension (EH), including atrial fibrillation (AF), the most prevalent arrhythmia among adults that is associated with an elevated risk of subsequent cerebro-cardiovascular adverse events. The mechanisms of increased prevalence of AF in PA patients are complex. Excessive aldosterone production is regarded to be a key component in the pathogenesis of AF, in addition to arterial hypertension and electrolyte imbalance. In addition, several translational and clinical studies have reported that structural remodeling with atrial fibrosis and electrical remodeling with arrhythmogenicity induced by an excess of aldosterone also play major roles in AF genesis. Clinical studies from several registries and meta-analysis have reported an increased prevalence and risk of AF in PA patients compared to EH patients. Recent trials have further demonstrated a reduction in the risk of new-onset atrial fibrillation (NOAF) after adrenalectomy, while the results of medical treatment with mineralocorticoid receptor antagonists (MRAs) have been inconsistent. This review outlines the current evidence of the relationship between PA and AF, and highlights recent progress in the management of PA with regards to the development of AF.

Introduction

Primary aldosteronism (PA) manifests as secondary hypertension and is defined as excessive autonomous endogenous aldosterone production unresponsive to renin regulation, further leading to elevated blood pressure and electrolyte imbalance. PA has a prevalence of 4.3–9.5 % in all patients with hypertension, 13 % of those with stage 3 hypertension, and 17–23 % of those with resistant hy-

pertension [1]. Higher rates of long-term mortality and co-morbidities have been reported in PA patients compared to patients with essential hypertension (EH) [1–3]. Atrial fibrillation (AF) is the most common arrhythmia in adults, and has a prevalence of 3 % in adults aged over 20 years, and more in the elderly and patients with chronic illnesses, and it has been shown to increase the risk of all-cause mortality and major cardiac and cerebrovascular complications [4]. In patient with PA, AF is the most common seen arrhythmia with a prevalence of 7.1–7.3 % [2, 5]. In German Conn's study, AF occurred in 7.1 %; other atrial or ventricular arrhythmia occurred in 5.2 % of the patients [5].

The pathogenesis of AF is complex, and involves abnormal cardiac electrical activity from the atrium and adjacent structures with subsequent cardiac electrical, structural, neural and autonomic remodeling [6]. The progressive remodeling and degradation with fibrosis of the atrium and other cardiac structure combined with AF has been shown to increase the risk of thromboembolism [7].

Previous studies on the association between aldosterone and AF have mostly been conducted on clinical patients with heart failure and related mineralocorticoid receptor antagonists (MRAs) treatment as upstream or conjunctional therapy. In addition, several animal and cell experiments have reported aldosterone-induced cardiac structural changes or electrophysiological alterations at the pathological or molecular level [8]. The pro-fibrotic and pro-arrhythmogenic effects of aldosterone and mineralocorticoid receptor (MR) activation have been proposed in these studies. This implies that excessive aldosterone in PA patients may be associated with the development of AF, and that effective treatment of PA may decrease the risk of further occurrences of AF.

This review evaluates the current evidence of the relationship between PA and AF, from the pathogenesis of AF with a clinical or basic approach to concurrent clinical trials about PA treatment.

Pathophysiology of the occurrence of AF in PA patients

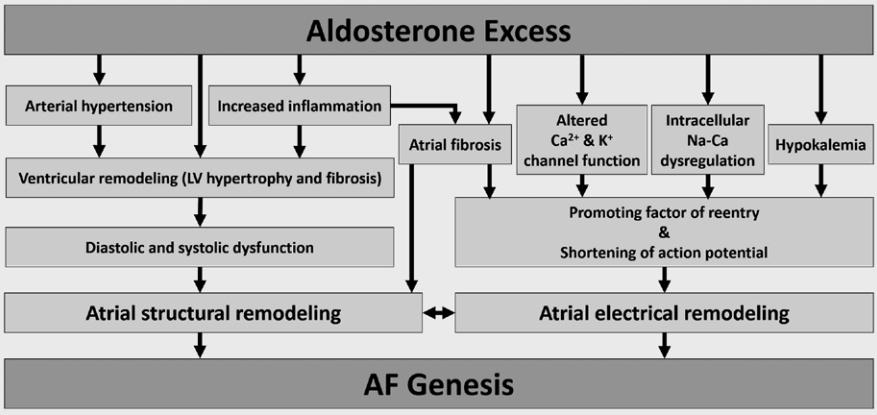
AF genesis

The leading hypothesis for the genesis of AF is initiation by ectopic firing and perpetuation by reentry [6]. The molecular basis for focal ectopic firing from myocyte sleeves within the pulmonary veins [9] and atrial tissue as the disease progresses [6] is attributed to a diastolic leak of Ca^{2+} from the sarcoplasmic reticulum, resulting in Na^{+} inward current via Na^{+}–Ca^{2+} exchange, and subsequently spontaneous myocyte depolarization [10]. There are two main possible mechanisms of AF reentry, including reentrant rotors or multiple independent wavelets [6]. Slow conduction wavefront velocity, indicating structural remodeling, and short effective refractory periods (ERPs) of the atrium, indicating electrical remodeling, promote and perpetuate the reentry [6]. In addition, fibrotic changes, abnormalities of atrial cardiomyocytes or interstitial matrix of the atrium all also contribute to reentry [6].

For patients with PA, there are several possible mechanisms for the development of AF, including arterial hypertension and ventricular remodeling, hypokalemia, atrial structural and electrical remodeling caused by excess aldosterone (▶ **Fig. 1**).

Atrial structural remodeling

Cardiac fibrosis results from excessive activation of cardiac fibroblasts and myofibroblasts [11], and atrium-specific fibrosis presents with fibrotic atrial cardiomyopathy and promotes AF with an elevated risk of thromboembolism [7]. Excess aldosterone has been shown to cause cardiac fibrosis in many previous studies [12, 13]. Prior to the development of fibrosis, aldosterone and MR activation facilitate inflammation by inducing the production of reactive oxygen species (ROS), which activate proinflammatory transcription factors [14] in macrophages [15] and the heart [16]. Furthermore, aldosterone



▶ **Fig. 1** Pathogenesis of atrial fibrillation in primary aldosteronism. Primary aldosteronism (PA) is characteristic of aldosterone excess, which causes atrial fibrillation (AF) by the following mechanisms. Aldosterone excess causes arterial hypertension and hypokalemia, both related to increased risk of AF. Direct effect of excessive aldosterone working on cardiac structure favoring could be summarized into two: atrial structural remodeling and atrial electrical remodeling. Atrial structural remodeling is caused by increased left ventricle and atrium fibrosis with systemic inflammation involved, through the emergence of diastolic and systolic dysfunction; atrial electrical remodeling is caused by aldosterone-induced atrial fibrosis, altered calcium and potassium channel function, intra-cellular sodium-calcium dysregulation, further promotion of reentry and shortening of action potential to cause AF.

causes cardiac interstitial macrophage infiltration [17], and activates the MRs on macrophages to promote the expressions of profibrotic genes, including transforming growth factor β1 (TGF-β1) [18] and plasminogen activator inhibitor-1 (PAI-1) [19]. PAI-1 inhibits plasmin-dependent matrix metalloproteinase (MMP) activation to limit collagen degradation and thus increase fibrosis [20]. TGF-β can enhance the formation of myofibroblasts, which express alpha-smooth muscle actin (α-SMA), to drive collagen formation [21]. Myofibroblasts, which are derived from fibroblasts, play a particularly crucial role in cardiac fibrosis due to a nearly two-fold higher capacity of collagen synthesis and higher capacity of synthesizing many cytokines and chemokines [22]. Aldosterone has been shown to induce the transdifferentiation of neonatal rat cardiac fibroblasts to myofibroblasts via Keap1/Nrf2 signaling pathways [23].

Atrial structural remodeling is a major promoting factor of reentry [6]. An excess of aldosterone can cause increased atrial fibrosis [24] and further conduction interference. Reil et al. found that aldosterone-infused rats had increased atrial size, fibroblasts and interstitial collagen, but reduced active MMP-13, a collagen degrading enzyme in both atriums [25]. They also found that P-wave duration, total right atrium activation time, and anisotropy of local conduction time, as an index of atrial structure remodeling, were all prolonged in aldosterone-infused rats compared with controls [25]. Heterogeneous pathways of slow conduction and atrial dilatation both provide larger pathways that are more ready for sustained reentrant circuits [26]. The effects of structural atrial remodeling on the development of AF were most clearly demonstrated in a cardiac myocyte-specific transgenic mouse model overexpressing TGF-β1. This model resulted in atrial fibrosis, and the increase in atrial fibrosis significantly increased susceptibility to AF [21].

Atrial electrical remodeling

Aldosterone-induced atrial fibrosis-related re-entry circuits are another possible mechanism of AF in PA patient. Fibrotic tissue decreases gap junction coupling and causes muscle bundle discontinuities which reduce and promote re-entry circuits [27]. Electrophysiological changes have also been documented with aldosterone-treated cells and animal models. In an aldosterone infusion rat model, Lammers et al. reported prolonged duration of AF after transesophageal atrial burst stimulation [28]. Interestingly, aldosterone infusion did not affect ventricular function or atrial pressure in their study, but lengthened P-wave duration. P-wave duration is a marker of atrial conduction time and is associated with a higher risk of AF [29, 30]. Furthermore, aldosterone infusion has been associated with a significant shortening of action potential and increased protein expressions of Kir2.1 and Kv1.5 [28]. Inwardly-rectifying potassium channels (Kir) are characterized by the property of inward-rectification, which is defined as the ability to allow large inward currents and smaller outward currents. The activation of Kir would therefore promote the formation of AF. This implies that electrical condition abnormalities and hypokalemia may cause AF in patient with PA.

Ouvrard-Pascaud et al. reported that aldosterone increased L-type Ca^{2+} channels in neonatal rat atrial mouse cells, and decreased the activity of the rapidly activating delayed rectifier potassium current IKr and transient outward K^+ current Ito1 [31]. Aldosterone has also been shown to promotes the prolonged release of Ca^{2+} from the sarcoplasmic reticulum due to opening of ryanodine receptors, finally leading to Ca^{2+} overload and thereby promoting AF [32]. Aldosterone has also been shown to increase ICaT and induce calcium overload [33]. This aldosterone-induced calcium overload will produce a positive feedback vicious cycle of atrial electrical remodeling and leading to AF.

In a special group of PA patients (familial hyperaldosteronism type III) who were characterized by having germline mutation of *KCNJ5* (potassium inwardly-rectifying channel, subfamily J, member 5) [34], *KCNJ5* mutation is also a possible cause of AF genesis. Loss of function of *KCNJ5* may result in long QT syndrome and AF [35]. A previous study revealed that germline *KCNJ5* mutations are also associated with early-onset lone AF in Caucasians [36], while novel molecules targeting mutant *KCNJ5* potassium channels are under development to treat bradyarrhythmia and AF [37].

Arterial hypertension and ventricular remodeling

Chronic hypertension results in left ventricular hypertrophy [38] and diastolic dysfunction and consequently elevation of left ventricular end diastolic pressure [39], and it is a major risk factor for AF [40]. Left ventricular diastolic dysfunction and elevated left ventricular end diastolic pressure result in elevated left atrial pressure, structural changes, and subsequently an increased occurrence of AF [41]. In animal models, hypertension has been shown to cause left atrial remodeling, including atrial dilatation, hypertrophy, inflammatory infiltrates, interstitial fibrosis, conduction slowing and heterogeneity [42]. In clinical studies, the Framingham Heart Study revealed that levels of systolic and pulse pressures were significantly associated with increased left atrial size [43], and an increased left atrial size has been shown to contribute to the development of AF [44]. Furthermore, even after adjusting for age and sex, hypertension has been reported to remain a significant predictor of AF [45].

Hypokalemia

Hypokalemia is defined as a low serum potassium level, and it has been reported in cases and series of AF in patients with PA [46, 47]. An epidemiological study reported that a low serum level of potassium was associated with a higher risk of AF among the general population [48] or patients after cardiac surgery [49]. The electrophysiological effects of hypokalemia include resting membrane hyperpolarization, Na^+–K^+ ATPase inhibition, and suppression of K^+ channel conductance, resulting in action potential duration prolongation, reduced repolarization reserve, early afterdepolarization, delayed afterdepolarization, and automaticity [50], which may all contribute to the genesis of AF. Clinically, previous study from the German Conn's Registry reported that atrial arrhythmia was found more common in those with the hypokalemic variant (12.3 %) than in those with normokalemic PA (7.8 %), although the difference was not statistically significant [5].

PA and AF: Clinical studies and implications

Epidemiology

Incidence of AF in PA

In 2005, Milliez et al. reported a 12.1-fold elevated risk and a prevalence of 7.3 % of AF among 124 PA patients compared to 465 EH controls with a prevalence of 0.6 % [2]. Their study followed the patients for 3 years, after which the PA patients also held a 4.2-fold higher risk of stroke than the EH controls. Although the sample size

was relatively small, the study provided initial and early evidence of the additional cardiovascular risk of PA over EH after blood pressure had been matched between the two groups. In 2008, Catena et al. reported an elevated odds ratio of 4.93 for sustained arrhythmia among 54 PA patients compared with EH controls, although the definition of sustained arrhythmia included arrhythmia other than AF [51]. In 2009, the German Conn's Registry reported a prevalence rate of AF of 7.1 % among 553 of 640 PA patients, and atrial arrhythmia was more common in those with the hypokalemic variant (12.3 %) than in those with normokalemic PA (7.8 %) without statistical significance [5]. In addition, Savard et al. reported a significantly higher prevalence of AF of 3.9 % with an adjusted odds ratio of 5.0 among 459 PA patients compared to 1290 EH controls in whom the prevalence was 1.1 % [52]. Moreover, Mulatero et al. reported that sustained arrhythmias (AF, atrial flutter, sustained ventricular tachycardia, and ventricular fibrillation) were significantly more common among 270 PA patients after 12 years of follow-up with an odds ratio of 2.2 compared to EH patients [53]. In 2018, the JPAS Study Group further reported a prevalence of AF of 2.8 % in a multi-center, nationwide, and large cohort of 2582 PA patients over a 10-year period [54]. Furthermore, Monticone et al. reported a 3.52-fold higher risk of AF in 3838 PA patients compared to 9284 EH controls in a meta-analysis of 31 studies over a median period of 8.8 years [3]. These data provide evidence of the strong association between aldosterone and AF in addition to the results reported in the aforementioned basic studies.

Incidence of PA in AF

An elevated risk of AF in patients with PA has been reported in numerous clinical studies as discussed above, however, the risk and prevalence of PA among patients with AF has been less studied. Mourtzinis et al. reported that screening for PA using the aldosterone to renin ratio resulted in the diagnosis of four cases of PA in 149 AF patients (2.6 %) in 2017 [55]. In 2018, the same group reported a prevalence of PA of 0.056 % among 713 569 AF patients, compared with 0.024 % in AF-naive controls using a Swedish national registry [56]. A multicenter prospective study (PAPPHY) further reported increased prevalence of PA among hypertensive patients with unexplained AF [57].

Clinical evidence associated with the occurrence of AF in PA

Left atrium structure and function

Since electrical abnormalities often originate from the left atrium, AF is associated with left atrial function [7, 58]. Left atrium function is evaluated using echocardiographic studies, from left atrium diameter, left atrial volume index (LAVI), or left atrial strain analysis [59]. Dilatation of the left atrium and an increase in volume has been positively correlated with the pathogenesis of AF [58]. In 2017, Yang et al. reported a higher LAVI among 100 PA patients compared to 100 EH controls [60]. Our previous investigation of left ventricular subclinical systolic dysfunction using strain analysis also showed a higher left atrial diameter and LAVI among PA patients compared to those among matched EH controls, although the difference did not reach statistical significance [61]. Wang et al. recently reported increased left atrial stiffness in 107 PA patients with lower left atrial velocity, strain, and strain rate, and higher left atrial stiffness index compared to 50 EH controls [62].

Left ventricular structure and function

Left ventricular hypertrophy (LVH) with increased left ventricular mass is a key indicator of diastolic dysfunction[38], and diastolic dysfunction is currently considered to be a potential risk factor for the pathogenesis of AF[41]. Numerous previous clinical studies have reported more LVH and increased left ventricular mass index (LVMI) among PA patients compared to EH controls.

In 1996, Rossi et al. reported significantly increased left ventricular wall thickness and LVMI among 34 patients with PA matched to 34 EH controls with a higher percentage of LVH and concentric remodeling [12]. In 2005, Stowasser et al. reported increased left ventricular wall thicknesses and reduced diastolic function using Doppler studies among patients with familial hyperaldosteronism type I [63]. In 2007, Catena et al. reported greater left ventricular mass and more LVH among 54 PA patients compared with 274 EH controls [64]. In 2008, Muiessan et al. investigated left ventricular geometry with more inappropriate left ventricular mass derived from the difference between measured LVMI and predicted LVMI in 125 PA patients compared to 125 EH patients [65]. In 2016, Cesari et al. reported increased left ventricular enlargement and high prevalence of LVH and diastolic dysfunction using Doppler and tissue Doppler studies among 262 PA patients [66]. In our previous study of 30 adrenal adenoma patients, we found a significantly decreased LVMI in patients with LVH after adrenalectomy [67]. We also reported the significant positive predictive ability of 24-hour urinary aldosterone to LVMI and inappropriate LVMI among PA patients, as well as tissue-Doppler studies measuring diastolic dysfunction [68, 69].

Autonomic dysfunction

Autonomic dysfunction has been reported in PA patients with reversible sympathetic overactivity before and after adrenalectomy [70]. Heart rate variability (HRV) has been shown to be a valid tool to evaluate autonomic nerve system [71], and to be a potential predictor of AF in middle-aged individuals [72]. Left atrium dilatation has been correlated with decreased HRV [73]. A recent study further reported an association between decreased HRV and a higher incidence of AF in a large cohort with long-term follow-up, as a presentation of cardiac autonomic dysfunction [74]. In 1995, Veglio et al. reported impaired heart rate and blood pressure variability when responding to tilt in 17 PA patients compared to 11 EH controls[75]. We previously reported comparable conventional HRV parameters but decreased heart rhythm complexity among 20 PA patients compared to 25 EH controls, and partial reversal of heart rhythm complexity impairment after adrenalectomy in PA patients [76]. Impairment of HRV or heart rhythm complexity may contribute AF genesis. However, the relations between HRV and AF in PA patients are still unclear and need further studies.

Treatment of PA and the effect on AF

Correction of hypertension and hypokalemia and targeted treatment for excessive aldosterone

Treatment with antihypertensive agents for elevated blood pressure and potassium supplements has been shown to reduce the

risk of AF in several hypertension trials [77]. PA has been shown to be associated with a much higher cardiovascular risk than age-, sex-, and BP-matched EH patients in a clinical study and meta-analysis [2, 3], and other clinical studies have shown that targeted treatment is beneficial for hypertensive patients [51, 78, 79].

The targeted treatment for PA recommended in current guidelines is unilateral laparoscopic adrenalectomy for patients with documented unilateral PA to cure hyperaldosteronism and hypokalemia and cure or substantially reduce elevated blood pressure. For those with bilateral PA and unilateral PA not receiving surgery, medical treatment with an MRA is suggested to lower both blood pressure and the deleterious effects of aldosterone hypersecretion [1].

Surgical adrenalectomy

With regards to the occurrence of AF in PA, the results of the PAPY study, a large prospective registry of 107 PA patient and 894 EH patients with a median 11.8 years of follow-up reported in 2018 by Rossi et al., demonstrated a trend of a higher risk of NOAF among the PA patients receiving treatment than the EH patients. In addition, the surgically treated PA patients had a similar AF-free survival rate compared to the optimally treated EH patients, while the medically treated PA patients still had a higher risk of AF [80]. Hundemer et al. performed a retrospective chart review study of 396 PA patients, of whom 201 received adrenalectomy, and 40092 EH patients, and found no significant difference in the risk of NOAF between the PA patients treated with surgical adrenalectomy and the patients with EH [81]. In our recent publication using the large nationwide National Health Insurance Research Database (NHIRD) of Taiwan, we found a lower risk of NOAF in 534 PA patients receiving surgical adrenalectomy compared to matched EH patients [82].

Mineralocorticoid receptor antagonists

PA patients receiving MRA treatment in the PAPY study had a higher risk of AF and decreased AF-free survival [80]. In the retrospective study of Hundemer et al. consisting of 396 PA and 40092 EH patients, 195 of the PA patients received MRAs and had different outcomes with regards to NOAF according to post-treatment plasma renin activity level, with a cut-off point of 1 ng/ml/h as a proxy for insufficient or sufficient MR blockade. In addition, the PA patients treated with MRAs with suppressed renin activity and insufficient MR blockade had a higher risk of NOAF than the EH patients, with an adjusted hazard ratio of 2.55. In comparison, the PA patients treated with MRAs with increased renin activity and sufficient MR blockade did not have a statistically significant difference in the risk of NOAF compared to the EH patients [81]. Another larger retrospective study reported by Hundemer et al. with 602 MRA-treated PA patients and 41 853 age-matched EH patients showed a hazard ratio of AF of 1.93 compared with the EH patients, and the PA patients with insufficient MR blockade had a higher risk of cardiovascular events and mortality compared to the PA patients with sufficient blockade [83]. Post-treatment renin activity may reflect the adequacy of MR blockade and further guide the dosage of MRAs to improve cardiovascular outcomes and the risk of NOAF.

These three studies demonstrated a higher risk of NOAF among PA patients receiving MRAs. In our recent publication using the NHIRD, we also found increased risks of NOAF and major adverse cardiovascular and cerebro-cardiovascular events in 1668 PA patients receiving MRAs compared with matched EH patients [82].

Reversal of left ventricular mass/echocardiographic parameters

Rossi et al. found that patients with hyperaldosteronism had increased left ventricular wall thickness and mass and impaired early diastolic left ventricular filling indexes compared with EH patients, and that these effects could be reversed 1 year after adrenalectomy with maintenance therapy after 5 or 10 years of follow-up [84, 85]. In addition, Cetena et al. found that both adrenalectomy and spironolactone in PA patients had a comparable effect on reducing left ventricular mass after a mean follow-up period of 6.4 years [64]. Indra et al. showed that adrenalectomy was more effective in reducing left ventricular mass reduction and left ventricular wall thickening and reversing left ventricular cavity enlargement, while spironolactone only reduced left ventricular cavity size [86]. Our group also previously demonstrated the regression of left ventricular mass in patients receiving adrenalectomy [87]. In addition, the improvement after adrenalectomy was seen in both reversal of left ventricular geometry and also alterations in myocardial texture, as shown by increased cyclic variation of integrated backscatter (CVIBS) and decreased plasma carboxy-terminal propeptide of procollagen type I (PICP) level [88]. We also previously reported that aldosterone-induced left ventricular diastolic dysfunction could be reversed after adrenalectomy [89]. Because of the close relation between left ventricular structure/function and AF genesis, improvement of left ventricular structure/function after PA target treatment may further decrease AF burden.

Future perspectives and other hot topics associated with AF in PA

KCNJ5 somatic mutations, primary aldosteronism, and atrial fibrillation

Several somatic mutations have been found to be highly correlated or causative for PA [34]. Of notice, *KCNJ5* gene mutations, largely seen in aldosterone-producing adrenal adenomas [90, 91], are considered to be the most common somatic mutations in PA [34, 92]. *KCNJ5* mutations have been reported to result in the loss of ion selectivity to cause cell membrane depolarization and increased Ca^{2+} entry in adrenal glomerulosa cells and to increase aldosterone synthesis, and *KCNJ5* mutation-related potassium channelopathy is considered to be an important contributor to the pathogenesis of PA [91]. Among PA patients with somatic *KCNJ5* mutations, higher plasma aldosterone level and LVMI [93], younger age, and more female gender were reported over PA patients without somatic *KCNJ5* mutations [94], with higher rate of cure of hypertension after adrenalectomy [95]. However, the relations between somatic *KCNJ5* mutation and AF are not clear and further studies are warranted.

Subclinical Cushing syndrome, primary aldosteronism, and atrial fibrillation

Subclinical Cushing syndrome has been found to co-exist with certain types of PA [96], and adrenal-cortical tumors have been shown to have great heterogeneity and complexity in clinical, morphological, and molecular presentation [97]. Tang et al. reported 22

patients with aldosterone- and cortisol-coproducing adrenal adenomas among 555 PA patients, and found a higher risk of heart disease including AF compared with 392 adrenal adenoma patients [98]. It is not currently known whether Cushing syndrome is correlated with AF. A previous echocardiographic study showed that patients with Cushing syndrome had a greater reduction in left atrial ejection fraction and increased left ventricular mass and wall thickness compared with EH controls, which were corrected after treatment [99]. In addition, iatrogenic Cushing syndrome with exogenous steroid use has been positively associated with the incidence of AF [100]. Further studies are warranted to investigate the relationships among subclinical Cushing syndrome, PA, and AF.

New treatment targeting aldosterone excess

Newer potential alternatives for surgical adrenalectomy with CT-guided radiofrequency ablation have shown promising results [101], however further long-term outcomes and effects on AF need to be confirmed. The investigational new drug LCI699 has been shown to inhibit aldosterone synthase and to provide a fair short-term effect, however long-term data are lacking [102]. Newer generations of novel non-steroidal MRAs including finerenone (BAY 94–8862) and esaxerenone (CS-3150) have been evaluated in preclinical and clinical trials and have shown the potential to treat PA, however their effects on AF and long-term mortality have not been well studied [103]. In addition, for concurrent MRA treatment with spironolactone and eplerenone, the optimal dosage has not definitively been established. The current guidelines for spironolactone recommend from 12.5 mg per day with slow titration to a maximum dose of daily 100 mg, and for eplerenone 25 mg twice daily with the goals of normalizing serum potassium, reduce blood pressure, and eliminating the vascular, cardiac, and renal effects of aldosterone with a minimum number of drugs and side effects [1]. Further studies to investigate the optimal dosage of MRAs to prevent AF are also needed. Further studies are also need to elucidate whether surgical adrenalectomy can convert pre-existing AF among PA patients. For PA patients with sinus rhythm, the risk factors for developing AF also need to be identified.

Conclusion

PA with excessive aldosterone poses an additional risk of AF as evidenced in clinical trials and basic studies. Further studies are still needed to elucidate the relationship between PA and AF. In-depth investigations are also needed to study the unique pathogenesis of AF in PA patients with a genetic preference or late disease progression and related complications. Further clinical trials are required to evaluate the risk of NOAF with different PA treatments and the long-term outcomes in patients with different subtypes of PA. With a higher level of suspicion and prompt surveys for PA in specific clinical scenarios, more precise therapeutic strategies to improve the management and outcomes of patients with PA can be anticipated.

Appendix [the TAIPAI Study Group]

Membership of the Taiwan Primary Aldosteronism Investigation (TAIPAI) Study Group: Che-Hsiung Wu, MD (Chi-Taz hospital, PI of Committee); Vin-Cent Wu, MD, PhD (NTUH, PI of Committee); Yen-Hung Lin, MD, PhD (NTUH, PI of Committee); Yi-Luwn Ho, MD, PhD (NTUH, PI of Committee); Hung-Wei Chang, MD, PhD (Far Eastern Hospital, PI of Committee); Lian-Yu Lin MD, PhD (NTUH, PI of Committee); Fu-Chang Hu, MS, ScD, (Harvard Statistics, Site Investigator); Kao-Lang Liu, MD (NTUH, PI of Committee); Shuo-Meng Wang, MD (NTUH, PI of Committee); Kuo-How Huang, MD, PhD (NTUH, PI of Committee); Yung-Ming Chen, MD (NTUH, PI of Committee); Chin-Chi Kuo; MD (Yun-Lin, PI of Committee), Chin-Chen Chang, MD (NTUH, PI of Committee); Shih-Cheng Liao, MD, PhD (NTUH, PI of Committee); Ruoh-Fang Yen, MD, PhD (NTUH, PI of Committee); and Kwan-Dun Wu, MD, PhD (NTUH, Director of Coordinating Center).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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