Influence of Different Treatment Strategies on New-Onset Atrial Fibrillation Among Patients With Primary Aldosteronism: A Nationwide Longitudinal Cohort-Based Study

Chien-Ting Pan, MD; Che-Wei Liao, MD; Cheng-Hsuan Tsai, MD; Zheng-Wei Chen, MD; Likwang Chen, PhD; Chi-Sheng Hung, MD, PhD; Yu-Chen Liu, MD; Po-Chih Lin, MD; Chin-Chen Chang, MD, PhD; Yi-Yao Chang, MD; Vin-Cent Wu, MD, PhD; Yen-Hung Lin, MD, PhD; on behalf of the TAIPAI study group*

Background—Primary aldosteronism (PA) is associated with higher atrial fibrillation prevalence and other cardiovascular complications. However, the effect of target treatment to prevent new-onset atrial fibrillation (NOAF) remains unclear. This study investigated incidence of NOAF under different treatment strategies in patients with PA.

Methods and Results—We analyzed longitudinal data for patients with PA without atrial fibrillation history from 1997 to 2009 within the National Health Insurance Research Database in Taiwan. Patients with essential hypertension matched by propensity score were enrolled as controls. The primary outcome measurement was NOAF, and secondary outcome measurements were mortality, major cardiac and cardiac/cerebrovascular events, and a combined end point of NOAF and mortality. We identified 2202 patients with PA (534 adrenalectomy, 1668 mineralocorticoid receptor antagonist [MRA] therapy) and 8808 essential hypertension controls with mean follow-up of 4.4 years. In primary outcome measurement, patients with PA who underwent adrenalectomy had a lower incidence of NOAF (adjusted hazard ratio; 0.28, P=0.011) than controls. In contrast, the patients with PA who received MRA therapy had comparable risk of NOAF (adjusted hazard ratio, 1.20; P=0.224). In secondary outcome measurement, patients with PA who underwent adrenalectomy had a lower rate of mortality and combined end point of NOAF and mortality than controls. Patients with PA who received MRA therapy had a higher risk of mortality, major cardiac and cardiac/cerebrovascular events, and combined NOAF with mortality than the essential hypertension controls.

Conclusions—Compared with patients with essential hypertension, patients with PA who underwent adrenalectomy had a lower incidence of NOAF. However, this finding was not observed in patients with PA who received MRA therapy with a lower dose. Differences between the 2 strategies may reduce with a higher dose of MRA therapy. (***J Am Heart Assoc***. 2020;9:e013699. DOI: 10.1161/JAHA.119.013699.)

Key Words: adrenalectomy • aldosterone • atrial fibrillation • hyperaldosteronism • mineralocorticoid receptor antagonist • spironolactone

P rimary aldosteronism (PA) is defined as excessive autonomous aldosterone production unresponsive to renin regulation, leading to hypertension and electrolyte imbalance, with a prevalence of 4.3% to 9.5% in all patients with hypertension, 13% of patients with stage 3 hypertension, and 17% to 23% of patients with resistant hypertension.[1] Higher rates of long-term mortality and comorbidity have been reported in patients with PA

From the Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan (C.-T.P., Z.-W.C.); Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan (C.-W.L.); Department of Internal Medicine, National Taiwan University Hospital Jin-Shan Branch, New Taipei City, Taiwan (C.-H.T.); Department of Internal Medicine (C.-S.H., P.-C.L., V.-C.W., Y.-H.L.), and Department of Medical Imaging (C.-C.C.), National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (L.C.); Department of Internal Medicine, Far Eastern Poly Clinic, Taipei, Taiwan (Y.-C.L.); Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan (Y.-Y.C.).

*A complete list of the TAIPAI study group members can be found in the appendix at the end of the article.

Correspondence to: Yen-Hung Lin, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, 100, Taiwan. E-mail: austinr34@gmail.com

Received June 20, 2019; accepted January 10, 2020.

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Clinical Perspective

What Is New?

- In this study, we surveyed the incidence of new-onset atrial fibrillation after different treatments in patients with primary aldosteronism by using the Taiwan National Health Insurance Database.
- The result shows that patients with primary aldosteronism undergoing adrenalectomy have a lower incidence of NOAF than patients with essential hypertension.
- However, patients with primary aldosteronism receiving lower-dose mineralocorticoid receptor antagonist therapy have an incidence of new-onset atrial fibrillation comparable with patients with essential hypertension.

What Are the Clinical Implications?

- Cardiovascular complications remain the major clinical consequence in patients with primary aldosteronism.
- Adrenalectomy may alleviate the cardiovascular damage caused by excess aldosterone in patients with primary aldosteronism compared with lower-dose mineralocorticoid receptor antagonist therapy, and differences between the 2 strategies may reduce with the higher dose of mineralocorticoid receptor antagonist therapy.

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compared with patients with essential hypertension (EH).[1–3]

Atrial fibrillation (AF), with prevalence of 3% in adults aged 20 years and greater in elders and patients with chronic illnesses, has been shown to increase the risk of all-cause mortality and major cardiac and cerebrovascular complications.[4] The detection of new-onset atrial fibrillation (NOAF) with prompt stratification and intervention is therefore vital.

Correlation between PA and AF has been identified in previous studies, although the complicated interplay has yet to be completely elucidated.[5] Milliez et al[2] reported a 12.1-fold higher risk of AF in patients with PA compared with EH controls. In addition, a recent meta-analysis with systemic review by Monticone et al[3] demonstrated a 3.52-fold higher risk of AF in patients with PA compared with EH controls. These studies implied that excessive aldosterone in patients with PA may be associated with the development of AF, and that effective treatment of PA may decrease the risk of further occurrences of AF. However, there are limited data regarding the reduction of NOAF after target therapy among patients with PA, and especially studies including large populations. Therefore, the aim of this study is to investigate the long-term risk of NOAF in patients with PA after either surgical or medical treatment using a large population-based database.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Sources

The Taiwan National Health Insurance program is a single-payer, nationwide, and compulsory program that covers prescriptions and intervention procedures from outpatient visits to hospital admissions. It was launched in 1995 and covers over 99% of the population in Taiwan (23.12 million in 2009). Routine surveillance and data audit by the National Health Insurance administration prevent fraud and ensure the reliability of the National Health Insurance Research Database (NHIRD).[6] We analyzed original data for all patients with a diagnosis of PA in the NHIRD from 1997 to 2009 using a retrospective and longitudinal approach.

Study Population Identification and Baseline Characteristics

The process used to select the study subjects is illustrated in Figure 1. We enrolled patients with PA aged >18 years at the time of a first medical record of PA (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 255.1). The use of administrative data to identify patients with PA according to diagnostic codes and mineralocorticoid receptor antagonist (MRA) prescriptions in Taiwan was well validated in our previous report.[6,7] Using this algorithm, the positive predictive value clinical certainty of PA is 0.93 (95% CI, 0.89–0.97), and the negative predictive value clinical certainty of PA is 0.82 (95% CI, 0.74–0.90), respectively.[6] Patients with a diagnosis of AF, mitral valve disease, and hyperthyroidism were also excluded. The patients with PA were divided into 2 groups according to the treatment strategy: (1) those who underwent adrenalectomy and (2) those who did not undergo adrenalectomy before the outcome of interest, NOAF, or end of the study (the MRA group). Adrenalectomy was confirmed according to National Health Insurance data for surgical procedures.

Patients with EH were enrolled as a control group with a sampling ratio of 1:4. The patients with PA and patients with EH were matched by propensity score and CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, and previous stroke/transient ischemic attack–vascular disease) score in each group. The propensity scores were calculated from the risk factors listed in Table 1.
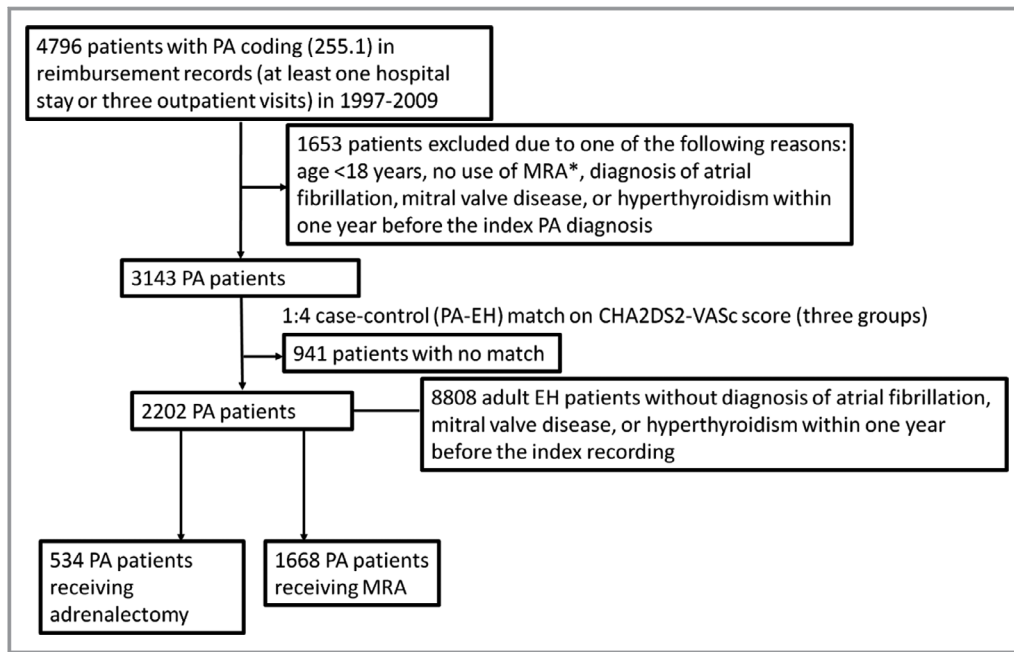
Figure 1. Flow diagram of selecting study subjects. *Our study enrolled only patients who ever used a mineralocorticoid receptor antagonist (belonging to the Anatomical Therapeutic Chemical class C03D) in the 1 year before or the 2 years following the first *International Classification of Diseases*, *Ninth Revision, Clinical Modification* (*ICD-9-CM*) coding of primary aldosteronism, because this additional condition could assure high values for both sensitivity and the positive predictive value according to our validated report. MRA indicates mineralocorticoid receptor antagonist; PA, primary aldosteronism.

Incidence of NOAF, Study End Points, and Other Research Covariates

The primary end point was NOAF, and the diagnosis of NOAF was established on the basis of 1 inpatient or 2 outpatient records of *ICD-9-CM* code 427.31 in the NHIRD. We identified the presence of covariates in both the index hospitalization and clinic visits, and the parameters included age, sex, the year of diagnosis, and various comorbid conditions. Each prediagnosis comorbidity was identified by a record of at least 1 hospital admission or at least 3 outpatient department visits during the 1 year immediately before the index diagnosis as previously validated.[6,7]

Secondary end points were all-cause mortality, major adverse cardiac and cerebrovascular events (MACEs and MACCEs) and combined all-cause mortality with NOAF. MACEs were defined as the incidence of coronary events including nonfatal myocardial infarction, coronary artery bypass graft, and coronary angiography, while MACCEs were defined as a MACE plus any nonfatal stroke including ischemic stroke and hemorrhagic stroke.

Statistical Analysis

Continuous variables are described as mean±SD, and discrete variables are presented as counts or percentages.

A 2-sided *P*<0.05 was considered statistically significant. We used R software, version 2.8.1 (Free Software Foundation, Inc., Vienna, Austria) for data analysis. We used a Cox proportional hazards model with time-varying covariates to evaluate their influence on the risk of NOAF, as adrenalectomy and MRA prescriptions are the main treatments following a diagnosis of PA. Time-varying covariates were assigned a value of 0 before the start of MRA or surgical treatment, and then a value of 1 at the start of each treatment. Additional adjustments in these models included control for the direct effects of age, sex, concomitant medications, and comorbidities (Table 1). Each patient was followed from the index date to NOAF, death, or the end of the study (December 31, 2010), whichever occurred first. We also identified the predictors of NOAF or death with the Fine and Gray model, which extends a Cox proportional hazards model to consider competing risks according to subdistribution hazard ratios (HRs). We constructed a propensity score using a nonparsimonious multivariate logistic regression model in an attempt to make an unbiased estimate of the indicators predicting primary aldosteronism at first diagnosis. The predicted probability derived from the logistic equation was used as the propensity score for each individual at index diagnosis. We matched the patients with PA to patients with EH using a greedy matching algorithm with a caliper width of 0.2 SD of the log odds of the estimated propensity score, and

Table 1. The Demographic, Clinical Characteristics, and Outcomes of Enrollees Among the Study Cohorts

	EH (n=8808)	PA (n=2202)	P Value	SMD
Propensity score	−4.27±1.48	−4.27±1.48	0.992	<0.001
Age	51.75±14.15	51.75±14.15	0.999	<0.001
Sex (male)	3942 (44.75)	1035 (47.00)	0.059	0.045
Comorbidity				
Myocardial infarction	68 (0.77)	16 (0.73)	0.892	−0.005
Coronary artery disease	1130 (12.83)	290 (13.17)	0.670	0.010
Congestive heart failure	223 (2.53)	64 (2.91)	0.331	0.023
Peripheral vascular disease	35 (0.40)	7 (0.32)	0.702	−0.013
Cerebrovascular disease	361 (4.10)	74 (3.36)	0.126	−0.039
Dementia	41 (0.47)	13 (0.59)	0.494	0.017
Chronic obstructive pulmonary disease	478 (5.43)	144 (6.54)	0.044	0.047
Rheumatoid arthritis	53 (0.60)	21 (0.95)	0.080	0.040
Peptic ulcer	634 (7.20)	188 (8.54)	0.037	0.050
Hemiplegia	32 (0.36)	5 (0.23)	0.413	−0.025
Chronic kidney disease	181 (2.05)	59 (2.68)	0.086	0.041
Liver disease	420 (4.77)	128 (5.81)	0.048	0.047
Solid tumor	214 (2.43)	54 (2.45)	0.938	0.001
Diabetes mellitus	1119 (12.70)	278 (12.62)	0.943	−0.002
CHA_2DS_2-VASc	1.7±1.17	1.7±1.17	0.999	0
0	992 (11.26)	248 (11.26)	0.999	<0.001
1–3	7104 (80.65)	1776 (80.65)		<0.001
>4	712 (8.08)	178 (8.08)		<0.001
Medication for hypertension				
α-Blocker	388 (4.41)	129 (5.86)	0.005	0.066
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	3286 (37.31	820 (37.24)	0.961	−0.001
β-blocker	3690 (41.89)	916 (41.60)	0.809	−0.006
Calcium channel blocker	5206 (59.11)	1268 (57.58)	0.200	−0.031
Diuretic	3332 (37.83)	876 (39.78)	0.095	0.040
Other medication				
Aspirin	531 (6.03)	122 (5.54)	0.420	−0.021
Clopidogrel	138 (1.57)	27 (1.23)	0.280	−0.029
Ticlopidine	70 (0.79)	24 (1.09)	0.194	0.031
Dipyridamole	528 (5.99)	159 (7.22)	0.038	0.049
Nitrate	18 (0.20)	6 (0.27)	0.608	0.014
Statin	684 (7.77)	185 (8.40)	0.331	0.023
Outcome				
NOAF	238 (2.70)	59 (2.68)	0.999	−0.001
Ischemic stroke	763 (8.66)	246 (11.17)	<0.001	0.084
Hemorrhagic stroke	199 (2.26)	74 (3.36)	0.004	0.067
MACE	269 (3.05)	96 (4.36)	0.003	0.069
MACCE	585 (6.64)	229 (10.40)	<0.001	0.135

Table 1. Continued

	EH (n=8808)	PA (n=2202)	*P* Value	SMD
All-cause mortality	1199 (13.61)	285 (12.94)	0.422	−0.020
Mortality+NOAF	1347 (15.29)	321 (14.58)	0.425	−0.020

All data are shown as number (%), except mean age and propensity score. Imbalance defined as absolute value >0.05. EH indicates essential hypertension; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; NOAF, new-onset atrial fibrillation; PA, primary aldosteronism; SMD, standardized mean difference.

then with CHA_2DS_2-VASc score classified into 3 groups (0, 1–3, and >4). Specifically, we stratified the patients according to the status of PA at baseline and the time points of receiving adrenalectomy, reaching primary and secondary end points after follow-up.

Ethical Considerations

No informed consent was required because all patient data were anonymized in this study. As the identification numbers of all individuals in the NHIRD were encrypted to protect the privacy of the individuals, this study was exempt from a full ethical review by the Institutional Review Board of National Taiwan University Hospital (201303017RINC).

Results

Patient Characteristics and Demographics

We identified 4796 patients diagnosed with PA from the NHIRD between 1997 and 2009, and 3143 patients were enrolled into the study as the PA group (Figure. 1). 2202 patients with PA (534 of whom underwent adrenalectomy and 1668 of whom received MRA treatment) were matched with 8808 patients with EH at a 1:4 ratio.

The characteristics and demographic data of the patients with PA and controls with EH are listed in Table 1. The mean follow-up times of the PA and EH group are 4.47±5.44 and 4.42±5.45 years.

More chronic obstructive pulmonary disease, peptic ulcer, and liver disease were found in the PA group, while no difference is found regarding diabetes mellitus, chronic kidney disease, coronary artery disease, and cerebrovascular disease. The PA group use significantly more α-blockers than the EH group (5.86% versus 4.41%; *P*=0.005), and there is no significant difference in other antihypertensive medications. Among other medications, dipyridamole is used more often in the PA group.

Outcome Study Between the Patients With PA and Controls With EH

Results and comparison of primary and secondary end points are listed in Tables 1 and 2. Overall, 2.68% and 2.70% of the patients with PA and EH developed NOAF, and incidence rates were both 5.1 and 5.1 per 1000 person-years without significant difference. No significant difference was found in mortality and combined outcome of NOAF and mortality.

The patients with PA had a higher rate of MACEs (4.36% versus 3.05%, *P*=0.003) and MACCEs (10.40% versus 6.64%, *P*<0.001) than the EH controls, including ischemic stroke (11.17% versus 8.66%, *P*<0.001) and hemorrhagic stroke (3.36% versus 2.26%, *P*=0.004). Significantly elevated risk is observed in the patients with PA, with adjusted hazard ratios of 1.40 (95% CI, 1.11–1.77) and 1.57 (95% CI, 1.35–1.83) for MACEs and MACCEs, respectively (both *P*<0.05).

Comparison of Study End Points in PA Patients Who Received Adrenalectomy or Mineralocorticoid Receptor Antagonist Treatment

Patients with PA according to treatment received are divided into 2 groups to compare risks for primary and secondary end points with EH controls, and the results are shown in Table 3. The patients with PA who underwent adrenalectomy had a significantly lower risk of developing NOAF (adjusted HR, 0.28; 95% CI, 0.10–0.74; *P*=0.011), all-cause mortality (adjusted HR, 0.27; 95% CI, 0.17–0.43; *P*<0.001), and combined all-cause long-term with NOAF (adjusted HR, 0.29; 95% CI, 0.19–0.44; *P*<0.001) compared with the EH controls.

There was no significant difference in NOAF between the patients with PA receiving MRA treatment and the EH controls. However, the patients with PA who received MRA had a significantly higher risk for all-cause mortality, NOAF combined with all-cause mortality, MACEs, and MACCEs than the EH controls, with adjusted HRs of 1.15 (95% CI, 1.01–1.31; *P*=0.039), 1.84 (95% CI, 1.57–2.16; *P*<0.001), 1.54 (95% CI, 1.20–1.98; *P*=0.001), and 1.15 (95% CI, 1.01–1.30; *P*=0.034), respectively.

Factors Affecting the Outcome Between Patients With PA Receiving Different Treatments Compared With Controls With EH

We further investigated the consistency of adrenalectomy and MRA treatment among the patients with PA compared with

Table 2. Comparison of Risks From NOAF and Other Cardiovascular Events Between Patients With PA and Their EH Matches, for the Whole PA Cohort

	Events	Incidence Rate (Per 1000 Person-Years)	Person-Years	Events	Incidence Rate (Per 1000 Person-Years)	Person-Years	Crude Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)*	P Value	Subdistribution Hazard Ratio (95% CI)†	P Value
	EH			**PA**			**PA vs EH**					
NOAF	238	5.1	46230.88	59	5.1	11674.41	0.98 (0.74–1.30)	0.891	0.98 (0.74–1.30)	0.884	0.99 (0.74–1.32)	0.950
MACCE	585	12.9	45318.67	229	20.6	11121.79	1.58 (1.36–1.85)	<0.001	1.57 (1.35–1.83)	<0.001		
MACE	269	5.8	46442.62	96	8.2	11649.98	1.42 (1.12–1.79)	0.003	1.40 (1.11–1.77)	0.005		
All-cause mortality	1199	25.5	47056.22	285	24	11858.16	0.94 (0.83–1.07)	0.384	0.95 (0.83–1.08)	0.403		
Mortality+ NOAF	1347	29.1	46230.88	321	27.5	11674.41	0.94 (0.84–1.07)	0.360	0.95 (0.84–1.07)	0.373		

EH indicates essential hypertension; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; NOAF, new-onset atrial fibrillation; PA, primary aldosteronism.
*The multivariable Cox regression model selected covariates from all variables in Table 1 by a stepwise procedure. Our analysis constructed adrenalectomy and steroid and potassium supplement for hypokalemia as time-varying covariates.
†The competing risk regression model included age, sex, and propensity score as covariates.

the controls with EH on the risk of NOAF with a forest plot, shown as Figure 2.

The patients with PA who underwent adrenalectomy and without diabetes mellitus, coronary artery disease, or chronic obstructive pulmonary disease had lower risks of developing NOAF compared with the controls with EH. The use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, or calcium channel blockers was also associated with lower risks of NOAF compared with the EH controls.

Among the patients with PA who received MRA treatment, male patients had a significantly higher risk of NOAF than the controls with EH (HR, 1.65; (95% CI, 1.14–2.40). Patients with PA under MRA control who did not use β-blockers were associated with a significantly higher risk of NOAF (HR, 1.85 (95% CI, 1.25–2.73).

Discussion

In the present study, we found that adrenalectomy reduced the incidence of NOAF, and that MRA treatment did not ameliorate the risk of NOAF among patients with PA compared with controls with EH. We analyzed the incidence of NOAF with a large sample size through a well-validated and trusted PA cohort, providing clear evidence of long-term NOAF in patients with PA after different targeted treatments in comparison with patients with EH.

Excessive aldosterone is recognized as a major contributing factor to AF, and the complex interplay of hypertension, hyperaldosteronism, and AF has been reported.[5] Excessive aldosterone has been shown to promote AF in animal models through the pathogenesis of atrial fibrosis, myocyte hypertrophy, and conduction disturbances.[8] According to electrophysiological and translational studies, aldosterone is reported to cause intracellular calcium overload by means of T-type Ca^{2+} and L-type Ca^{2+} channels among cardiomyocytes and atrial cells further promoting AF and increasing mineralocorticoid receptor expression, again enhancing aldosterone's effects on the heart.[9–12] Upregulation of several proinflammatory genes by aldosterone is reported in previous animal studies.[13,14] One previous study demonstrated an increased expression of mineralocorticoid receptors in AF among human atria and in a mouse cell model with excessive aldosterone to enhance aldosterone-induced atrial ionic remodeling and calcium overload, thereby worsening AF, and that these effects can be attenuated by spironolactone.[9] Spironolactone was also reported to significantly reduce NOAF and recurrent AF in a meta-analysis, in which it was considered to be a part of upstream therapy for the secondary prevention of AF.[15] In addition, left ventricular diastolic dysfunction, which is strongly correlated to AF, has also been

Table 3. Comparison of Risks From NOAF and Other Cardiovascular Events Between Patients With PA and Their EH Matches, for the Whole PA Cohort, by Treatment Type

PA vs EH	Adrenalectomy						MRA					
	Simple Cox Regression		Multivariable Cox Regression*		Competing Risk Regression†		Simple Cox Regression		Multivariable Cox Regression*		Competing Risk Regression†	
	Crude Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value	Subdistribution Hazard Ratio (95% CI)	P Value	Crude Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value	Subdistribution Hazard Ratio (95% CI)	P Value
NOAF	0.28 (0.10–0.75)	0.012	0.28 (0.10–0.74)	0.011	0.29 (0.11–0.77)	0.014	1.20 (0.89–1.61)	0.227	1.20 (0.89–1.61)	0.224	1.19 (0.89–1.60)	0.240
MACCE	0.73 (0.49–1.10)	0.133	0.69 (0.46–1.04)	0.080			1.84 (1.57–2.15)	<0.001	1.84 (1.57–2.16)	<0.001		
MACE	1.08 (0.67–1.75)	0.740	1.01 (0.62–1.63)	0.976			1.53 (1.18–1.96)	0.001	1.54 (1.20–1.98)	0.001		
All-cause mortality	0.27 (0.17–0.42)	<0.001	0.27 (0.17–0.43)	<0.001			1.15 (1.01–1.32)	0.036	1.15 (1.01–1.31)	0.039		
Mortality + NOAF	0.29 (0.19–0.43)	<0.001	0.29 (0.19–0.44)	<0.001			1.15 (1.01–1.30)	0.033	1.15 (1.01–1.30)	0.034		

EH indicates essential hypertension; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; NOAF, new-onset atrial fibrillation; PA, primary aldosteronism.

*The multivariable Cox regression model selected covariates from all variables in Table 1 by a stepwise procedure. Our analysis constructed adrenalectomy, steroid and potassium supplement for hypokalemia as time varying covariates.

†The competing risk regression model included age, sex, and propensity score as covariates.

shown to have a prominent influence on atrial structure and function.[16] Consequently, left ventricular diastolic dysfunction may also play a role in the development of AF in patients with PA. Our previous studies showed that aldosterone increased left ventricular mass, fibrosis, and diastolic dysfunction in clinical studies.[17–21] In addition, the mechanisms may involve increased inflammation and cardiac extracellular matrix turnover.[18,19]

In 2005, Milliez et al[2] reported a 12.1-fold elevated risk of AF among 124 patients with PA compared with 465 controls with EH. The German Conn's Registry also reported a prevalence rate of 7.1% of AF among 553 PA patients.[22] Savard et al[23] reported a significantly higher prevalence of AF with an adjusted odds ratio of 5.0 among 459 patients with PA than controls with EH, and Mulatero et al[24] reported that arrhythmias were significantly more frequent among 270 patients with PA after follow-up with an odds ratio of 2.2 compared with EH patients. Catena et al[25] in 2008 also reported an elevated risk of sustained arrhythmia in patients with PA with an odds ratio of 4.93 over controls with EH. Recently, Monticone et al[3] reported a 3.52-fold higher risk of AF in 3838 patients with PA over controls with EH through a meta-analysis of 31 studies. These data provide evidence of the strong association between aldosterone and AF in addition to the theological relationship in the previously mentioned basic studies.

Data on the incidence of NOAF in patients with PA after targeted treatment are limited. To the best of our knowledge, only 2 recently published studies have discussed NOAF in patients with PA. The first study (PAPY [Primary Aldosteronism Prevalence in Hypertensives]) was a prospective registry of 107 patients with PA and 894 patients with EH.[26] The second study by Hundemer et al[27] was a retrospective study based on chart review, which enrolled 396 patients with PA and 40 092 patients with EH. Our study provides the largest cohort of patients with PA to date, with 2202 patients with PA (534 who underwent adrenalectomy and 1668 who received MRA treatment).

In the PAPY study, the authors reported a trend of a higher risk of NOAF among the patients with PA overall than the patients with EH after a median 11.8 years of follow-up. The higher risk of NOAF was most attributable to the medically treated patients with PA, and the patients with PA who underwent adrenalectomy had a similar incidence of NOAF compared with the patients with EH. Hundemer et al[27] reported similar results to the PAPY study. Both studies showed better outcomes of NOAF in the patients who underwent adrenalectomy over those who received MRA treatment compared with controls with EH. In the study reported by Hundemer et al, after adjustments for other risk factors, the patients who underwent adrenalectomy had a lower but nonsignificant incidence of NOAF than the patients
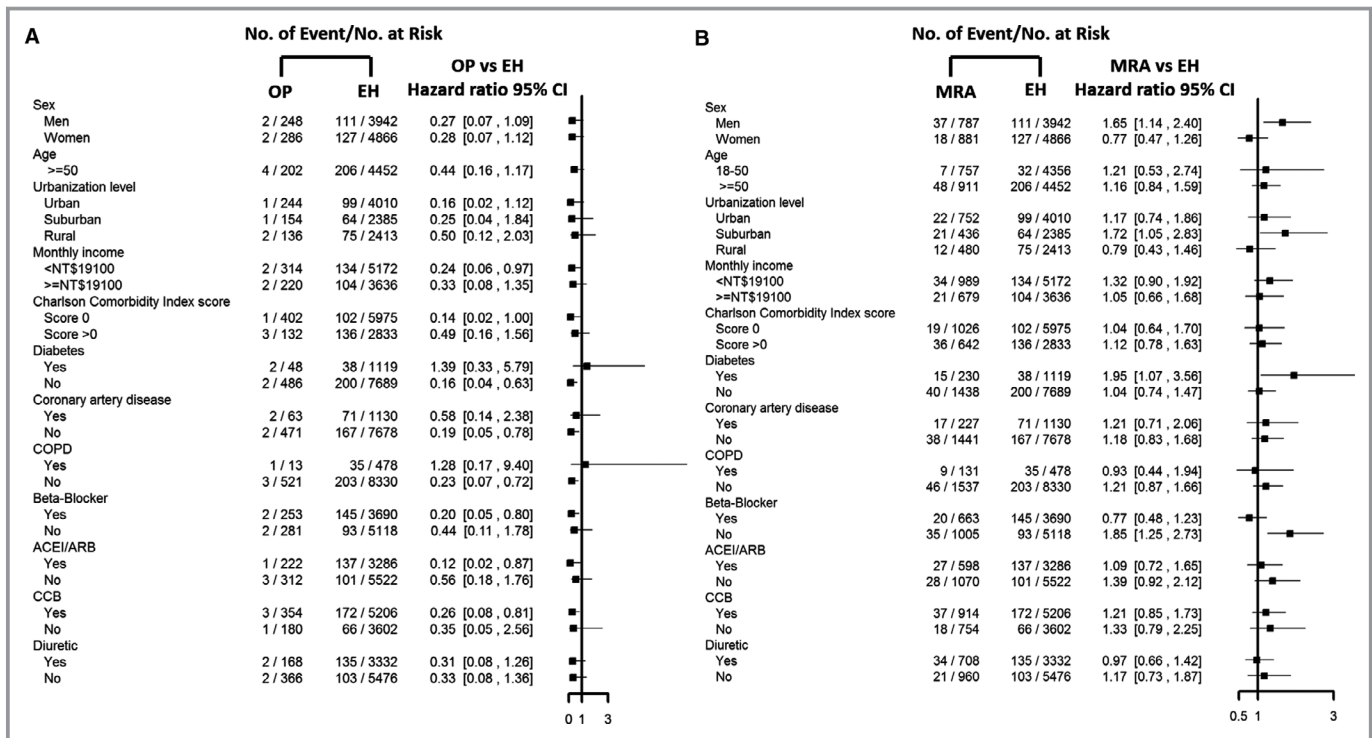
Figure 2. Adjusted hazard ratios for long-term risk of new-onset atrial fibrillation among primary aldosteronism patients based on comparison between primary aldosteronism who underwent adrenalectomy (**A**) and who received MRA and (**B**) essential hypertension groups and subgroup analysis with respect to premorbid risk that further adjusted for age and sex. HR indicates hazard ratio; MRA, mineralocorticoid receptor antagonist; OP, operation indicating adrenalectomy.

with EH, and the patients with MRA therapy with repressed plasma renin activity (PRA) (<1 μg/L per hour) had a significantly higher incidence of NOAF. Moreover, in the patients who received MRA therapy without repressed PRA (≥1 μg/L per hour), the incidence of NOAF was almost the same as the patients with EH. Our findings correspond to these 2 studies and indicate the advantage of adrenalectomy over MRA treatment. In addition, we showed significant advantages in the patients with PA who underwent adrenalectomy than the patients with EH. Furthermore, the incidence of NOAF in the patients with PA who received MRA treatment was not significantly higher than in those with EH. However, the patients with PA who underwent adrenalectomy had a similar risk of MACEs to those with EH, although the patients with PA who received MRA therapy had a significantly higher risk than the patients with EH. It seems that the risk of NOAF among these groups in 3 studies may be different, considering other cardiovascular risk factors. Significant ethnic differences have been reported in the incidence of AF, with a lower incidence of AF reported in North Asian countries than in Western countries,[28] This ethnic difference may explain in part the different outcomes on NOAF between our result and the other 2 studies. In addition, some genetic factors also need to be considered. For example, the ALDH2.2 allele appears to be

most prevalent in Chinese American, Han Chinese, Taiwanese, Japanese, and Korean population,[29] and the dysfunctional ALDH2 allele was reported to be negatively associated with AF among the Japanese population.[30] Current evidence and studies concerning the association between PA and the *ALDH* gene is lacking, and further investigation is warranted.

In Taiwan, only spironolactone is reimbursed for MRA treatment in patients with PA. In this study, the median daily dosage of spironolactone is 50 mg in the first prescription and 75 mg in maximal usage. The dosage of spironolactone use is similar with Hundemer et al.[27] In that study, the mean initial daily dose of spironolactone is 43 mg and maximal total daily dose is 71 mg in patients with a posttreatment group of PRA <1 μg/L per hour; mean initial daily dose of spironolactone is 50 mg, and maximal total daily dose is 84 mg in patients with post-treatment group of PRA ≥1 μg/L per hour. Both studies reflect the usual dosage of spironolactone in daily practice. The optimal dosage of spironolactone is not well established; well-accepted dosage from the guideline is from 12.5 mg/day with slow titration to a maximum dose of daily 100 mg.[1] In our previous study using the same database of NHIRD on long-term outcome among patients with PA receiving target treatment, we found there is a "U"-shape association between clinical outcome and daily dosage of

MRA. The best outcome to alleviate risk of death was found in the group with a mean daily dose of spironolactone between 12.5 and 50 mg.[7] In the study by Hundemer et al,[27,31] they demonstrated that PRA (<1 or ≥1 µg/L per hour) is a good indicator for cardiovascular outcome and NOAF. Interestingly, there was only a small difference of spironolactone dosage between PRA <1 or ≥1 µg/L per hour groups. Probably, the effect of MRA (measured by PRA levels) is a better indicator than MRA dosage for clinical outcome prediction. The use of spironolactone in our study represented "real-world" data about the MRA usage to control patients with PA in Taiwan; underdosage and lack of compliance would be of great influence on the treatment effect of MRA on patients with PA. However, higher-dose MRA treatment is still possible to further decrease NOAF. Catena et al[25] previously reported an alleviation of the additional cardiovascular risk in patients with PA undergoing adrenalectomy or MRA treatment with high-dose spironolactone compared with controls with EH. The clinical outcomes were comparable among patients undergoing adrenalectomy or receiving high-dose spironolactone. In that study, the dosage of spironolactone in patients with PA was from 50 to 300 mg, with a mean dosage of 121 mg/day.[25] This finding also raises the consideration that a higher dosage of spironolactone may have higher clinical efficacy and reduce the differences between adrenalectomy and MRA therapy. However, this issue needs further large prospective randomized trials to figure out.

Patients with PA under MRA control without β-blocker usage were associated with a significantly higher risk of NOAF. β-Blockers have been reported to significantly reduce NOAF in some situations, such as in cardiac surgery.[4] Further studies are needed to elucidate the role of β-blockers in the development of NOAF in patients with PA.

Study Limitations

The main strength of this study is the large national sample size with long-term follow-up in the NHIRD. The reliability of *ICD-9-CM* codes for PA and associated comorbidities, which represents real-world data, was well validated in our large cohort.[6]

However, some limitations still exist. First, healthy survivor bias may have existed during the delay between diagnosis and adrenalectomy, although in survival analysis the date of diagnosis was defined as the index date. Proficiency bias may have occurred if the patients who underwent adrenalectomy received more follow-up medical care than the patients who received MRA cointerventions. Second, this insurance-claimed database had limitations. Clinical data such as blood pressure, serum potassium level, aldosterone level and renin activity, left ventricular mass, and albuminuria are not available. This should be considered in data interpretation

and may limit its clinical applications. Third, some possible residual confounding factors still cannot be excluded despite rigorous matching and adjustments for important variables. Further prospective trials are warranted to confirm the beneficial effect of adrenalectomy on NOAF among patients with PA. Fourth, we do not know the exact percentage of aldosterone-producing adenoma in this study. We can easily identify patients with an aldosterone-producing adenoma who underwent adrenalectomy; however, it is much more difficult in patients with an aldosterone-producing adenoma receiving MRA therapy. In our previous studies, we could identify a group of patients with an aldosterone-producing adenoma receiving MRA therapy by a series of criteria.[32–34] However, many patients with PA receiving MRA therapy still cannot be clearly classified. Fifth, direct comparison of matched patients with similar basic characteristics undergoing adrenalectomy or receiving MRA therapy would provide more straightforward results of the effect of the treatment on NOAF. However, this method is limited by the patients' numbers. Therefore, we used the EH group as a reference group and compare both groups in an indirect way, which was widely used.[2,3,7,23,24,26,27,31–34] Sixth, the small size of subgroups to analyze the effect of comorbidities and medication may cause an insignificant difference. Finally, this study enrolled only subjects who lived in Taiwan and excluded patients with coexisting mitral valve disease and hyperthyroidism. The representativeness of subjects may limit its clinical application in other populations.

Conclusions

Compared with the patients with EH, the patients with PA who underwent adrenalectomy had a lower incidence of NOAF. However, this finding was not observed in the patients with PA who received MRA therapy at a lower dose, who also had elevated risks of major adverse events and mortality. Differences between the 2 strategies may reduce with a higher dose of MRA therapy.

Appendix

Taiwan Primary Aldosteronism Investigation (TAIPAI) Study Group: Vin-Cent Wu, MD, PhD; Yen-Hung Lin, MD, PhD; Che-Hsiung Wu; Yi-Luwn Ho, MD, PhD; Hung-Wei Chang, MD, PhD; Lian-Yu Lin MD, PhD; Fu-Chang Hu, MS, ScD; Kao-Lang Liu, MD; Shuo-Meng Wang, MD; Kuo-How Huang, MD; Yung-Ming Chen, MD; Chin-Chi Kuo; MD, Chin-Chen Chang, MD; Shih-Chieh Chueh, MD, PhD; Ching-Chu Lu, MD; Shih-Cheng Liao, MD; Ruoh-Fang Yen, MD, PhD; and Kwan-Dun Wu, MD, PhD. National Taiwan University Hospital Yun-Lin Branch: Chen-Yu Wang

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