PRIMARY ALDOSTERONISM

Time-Dependent Risk of Atrial Fibrillation in Patients With Primary Aldosteronism After Medical or Surgical Treatment Initiation

Kyoung Jin Kim, Namki Hong, Min Heui Yu, Hokyou Lee, Seunghyun Lee, Jung Soo Lim, Yumie Rhee

ABSTRACT: Increased risk of atrial fibrillation was reported in patients with primary aldosteronism. However, data are limited regarding the time-dependent risk of atrial fibrillation in surgically or medically treated primary aldosteronism. From the National Health Insurance Claim database in Korea (2003–2017), a total of 1418 patients with primary aldosteronism (adrenalectomy [ADX], n=755, mineralocorticoid receptor antagonist n=663) were age- and sex-matched at a 1:5 ratios to patients with essential hypertension (n=7090). Crude incidence of new onset atrial fibrillation was 2.96% in primary aldosteronism and 1.97% in essential hypertension. Because of nonproportional hazard observed in new onset atrial fibrillation, analysis time was split at 3 years. Compared with essential hypertension, risk of new onset atrial fibrillation peaked at 1 year gradually declined but remained elevated up to 3 years in overall treated primary aldosteronism (adjusted hazard ratio [aHR] 3.02; $P<0.001$) as well as in both ADX (aHR, 3.54; $P<0.001$) and mineralocorticoid receptor antagonist groups (aHR 2.27; $P=0.031$), which became comparable to essential hypertension afterward in both groups (ADX aHR, 0.38; $P=0.102$; mineralocorticoid receptor antagonist aHR, 0.60; $P=0.214$). Nonetheless, mineralocorticoid receptor antagonist group was associated with increased risk of nonfatal stroke (aHR, 1.21; $P=0.031$) compared with essential hypertension, whereas ADX was not (aHR, 1.26; $P=0.288$). Our results suggest the risk of new-onset atrial fibrillation remained elevated up to 3 years in treated primary aldosteronism compared with essential hypertension, which declined to comparable risk in essential hypertension thereafter. Monitoring for atrial fibrillation up to 3 years after treatment, particularly ADX, might be warranted.
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Key Words: adrenalectomy ■ atrial fibrillation ■ cardiovascular diseases ■ hypertension ■ hyperaldosteronism ■ stroke

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Primary aldosteronism (PA), characterized by excessive autonomous aldosterone production independent of renin, is the most frequent cause of secondary hypertension.[1] Recent studies have estimated that the prevalence of PA ranges from 5% to 15% in hypertensive patients, with even higher prevalence (17%–23%) in patients with resistant hypertension.[2–5] Aldosterone excess can promote organ damage via the dysregulation of blood volume and electrolyte, as well as through proinflammatory cytokines, oxidative stress, and vascular inflammation.[6–8] Patients with PA were reported to have higher risks of cardiovascular events, including coronary artery disease, heart failure, left ventricular hypertrophy, and stroke compared with those with essential hypertension (EH) independent of blood pressure level.[9–11]

Atrial fibrillation (AF) is the most commonly observed arrhythmia, and has a prevalence of up to 3% in adults. AF is associated with increased risk of thromboembolic events.[12] Notably, the presence of excess aldosterone is associated to profibrotic and proarrhythmogenic effects, which promote AF development.[12,13] PA has been associated with high prevalence of AF up to 7.3%.[14] In the PAPPHY (Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive) Study, PA

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Novelty and Significance

What Is New?

- We identified time-dependent risk associated with new-onset atrial fibrillation in a nationwide Korean cohort of surgically or medically treated primary aldosteronism compared with essential hypertension.

What Is Relevant?

- The new-onset atrial fibrillation risk was elevated for the first 3 years after surgical (ADX) or medical (mineralocorticoid receptor antagonist) treatment, and lessened thereafter.
- Mineralocorticoid receptor antagonist–treated primary aldosteronism had 1.5-fold higher risk for nonfatal stroke than essential hypertension, where risks in ADX and essential hypertension groups did not differ.

Summary

Study findings have primary aldosteronism management implications about post-surgical or medical treatment. Monitoring for new-onset atrial fibrillation is warranted for >3 years, especially within the first year after ADX.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aHR	adjusted hazard ratio
EH	essential hypertension
ICD-10	International Classification of Diseases, Tenth Revision
MRA	mineralocorticoid receptor antagonist
NHIS	National Health Insurance Service
NOAF	new-onset AF
PA	primary aldosteronism
PAPPHY	Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive
PAPY	Primary Aldosteronism Prevalence in Hypertension

was confirmed in 42% of 183 patients who presented with AF with no known structural cause.[15] Based on these findings, recent European Society guidelines emphasized the importance of AF as a sign of PA at presentation.[16] Previous studies reported that surgical adrenalectomy (ADX) was associated with lowered risk of new-onset AF (NOAF) in patients with PA compared with EH, whereas NOAF risk remained elevated in mineralocorticoid receptor antagonist (MRA) treatment group with insufficient MR blockade.[17–19] Given the structural changes because of cardiac remodeling by aldosterone excess and the progressive recovery of cardiac parameters after PA treatment, it is conceivable that risk of NOAF may vary in a time-dependent manner post-ADX or -MRA treatment in patients with PA.[13,20,21] However, data are limited about time-dependent risk of NOAF after ADX or MRA treatment in PA.

In this study, we aimed to investigate whether the risk of NOAF in patients with PA who underwent surgical or medical treatment was elevated compared with patients with EH independent of conventional risk factors, and whether the risk of NOAF in patients with treated PA was time dependent or not.

METHODS

Data Source

We used a nationwide cohort database provided by the National Health Insurance Service (NHIS), which includes 51.5 million inhabitants (≈97% of entire population of South Korea).[22] To facilitate reimbursements, all medical institutions submit health care utilization–related information, which is then stored in the NHIS database. This database contains medical and pharmaceutical claim records, disease diagnosis codes (*International Classification of Diseases, Tenth Revision [ICD-10]*), medical procedure and hospital admission information, prescribed drugs, health examination data such as anthropometric measures, and death records. The data used for this study comprised NHIS claim records between January 1, 2002 and December 31, 2017. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (IRB number: CR318340). Informed consent was waived because data from the NHIS cohort do not involve any personally identifiable information.

Study Subjects

To identify individuals likely to have PA, we used an algorithm composed of diagnosis codes for primary aldosteronism based on *ICD-10* codes and medication/procedure codes, which were validated in multicenter hospital–based cohorts (Methods in the Data Supplement). Among various operational definitions, PA was defined as presence of relevant diagnosis codes along with confirmation tests and treatments, which revealed best performance to detect patients with PA in validation study (sensitivity, 68.1%; positive predictive value, 90.0%; area under the receiver-operating characteristics curve, 0.81). To apply the algorithm to NHIS cohort, we selected patients with PA, who had *ICD-10* diagnostic codes indicating a primary or secondary diagnosis of E26 (hyperaldosteronism), I15.20 (hyperaldosteronism from adrenal adenoma), or I15.21 (hyperaldosteronism from bilateral adrenal hyperplasia) more

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than twice between January of 2003 and December of 2017. Patients aged younger than 18 years and had an *ICD-10* diagnostic code of E26.1 (secondary hyperaldosteronism) at least once were excluded. We also excluded patients who did not undergo a diagnostic procedure (saline infusion test or the captopril challenge test) or any appropriate treatment (adrenalectomy or prescription of MRA for >6 months). To detect new onset cardiovascular events, patients with any previous diagnoses of cardiovascular disease including AF, stroke, myocardial infarction, and heart failure within 1 year before study entry time point were excluded. Patients with PA were subdivided into 2 groups based on the treatment strategy for PA that they received, as follows: (1) those who underwent ADX (ADX group) and (2) those who were prescribed MRA for >6 months without undergoing any ADX during follow-up (MRA group). As a control, patients with EH were defined as *ICD-10* any diagnostic code for I10 at least twice a year with antihypertensive drug fills for >180 days (Table S1 in the Data Supplement).[23] After excluding those with any prior diagnoses of cardiovascular events as listed above among EH group, patients with PA were matched with EH controls (1:5 ratio) based on index year, age group and sex.

Study End Points

The primary outcome was NOAF, ascertained by 1 inpatient or 2 outpatient records of *ICD-10* code I48, which was well validated in several studies based on NHIS cohort.[24] Secondary outcomes assessed were all-cause mortality, cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, and hospitalization because of heart failure (Table S1).[25] Information about deceased individuals were ascertained via death certificate information, which included primary cause of death. Each patient was followed up after the index date (date of claim for ADX or MRA) until the earliest occurrence of any study outcomes, all-cause death, or the end of the observational period (December 31, 2017).

Covariates

Selected comorbidities included this study were obtained from inpatient and outpatient hospital diagnoses (all available primary and secondary diagnoses). Comorbidities (diabetes, dyslipidemia, chronic kidney disease) were defined based on the presence of *ICD-10* diagnostic codes entered for medical claims and prescription medication use (prescribed >30 accumulative days) before the index year (Table S1). Economic status was categorized into 3 groups (lowest 30%, middle 40%, and highest 30%) and were based on the total amount of national health insurance premiums paid by insured individuals.

Statistical Analyses

Baseline characteristics consisting of continuous variables were presented as a mean±SD, and categorical variables were presented as a number (%). Independent *t* test and χ^2 analyses were used to compare clinical characteristics of PA and EH groups, respectively. The cumulative incidences of outcomes were analyzed using Kaplan-Meier estimates, and the log-rank test was used to compare differences among groups. Proportionality of hazards was investigated using time-covariate interactions and plots of Schoenfeld residuals over time. Where hazards were not proportional, data were partitioned into multiple mutually exclusive intervals, and separate Cox models were built for each interval. Cut points were determined using plots of Schoenfeld residuals over time.[26,27] Among primary and secondary outcomes, only the model for NOAF failed to meet the proportional hazard assumption, as confirmed based on the Schonfeld *P* value of ≤0.05. Therefore, we split the study period into 2 periods until the Schonfeld *P* value became higher than 0.05. Proportionality of hazards testing for NOAF was performed within each interval. In addition, a natural cubic spline model was used to visualize time-dependent trends affecting the risk of NOAF.[28] Based on results from Schoenfeld testing and visual inspection of the cubic spline model for risk of NOAF after treatment of PA (Figure S1), we decided to split time interval into 3 years to build time-dependent Cox model. Sensitivity analyses with 1- and 2-year time points were performed to test the robustness of findings. We did not observe any violation in the proportional hazard assumption with regard to secondary clinical outcomes including nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death. This enabled us to apply Cox proportional hazard models without any time-point splitting. We conducted sensitivity analyses to minimize the possibility of reverse causality by excluding individuals who developed AF within 90 days after the index date. We used SAS version 9.3 (SAS Institute, Cary, NC) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) for data analysis. A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Study Population and Baseline Characteristics

A total of 1418 patients with PA were analyzed in this study in comparison with age-, sex-, and index year-matched EH controls (at a 1:5 ratio; n=7090; Figure 1). Mean age (51.3 versus 49.0 years, $P=0.639$) and proportion of women included (53.7% versus 53.6%, $P=0.999$) did not differ between PA and EH groups (Table 1). Index year of study entry was distributed equally among groups (Table S2). Compared with EH, patients with PA were more likely to have chronic kidney disease (9.7 versus 3.3%, $P<0.001$) and use more β blockers (35.1% versus 26.0%), calcium channel blockers (76.3% versus 58.6%), and diuretics (71.2% versus 22.1%, $P<0.001$ for all comparisons). Among subgroups of PA, the MRA group was older (51.3 versus 46.7 years, $P<0.001$), contained a higher proportion of men (50.7% versus 42.5%, $P=0.001$), and had a higher prevalence of comorbidities and antihypertensive medication usage compared with the ADX group.

Time-Dependent Risk of NOAF in Patients With PA After Treatment Initiation

During the median 5 years of follow-up (interquartile range: 2.6–8.7 years), the overall crude incidence of NOAF was 2.96% and 1.97% in PA and EH groups, respectively (unadjusted hazard ratio [HR], 1.33;

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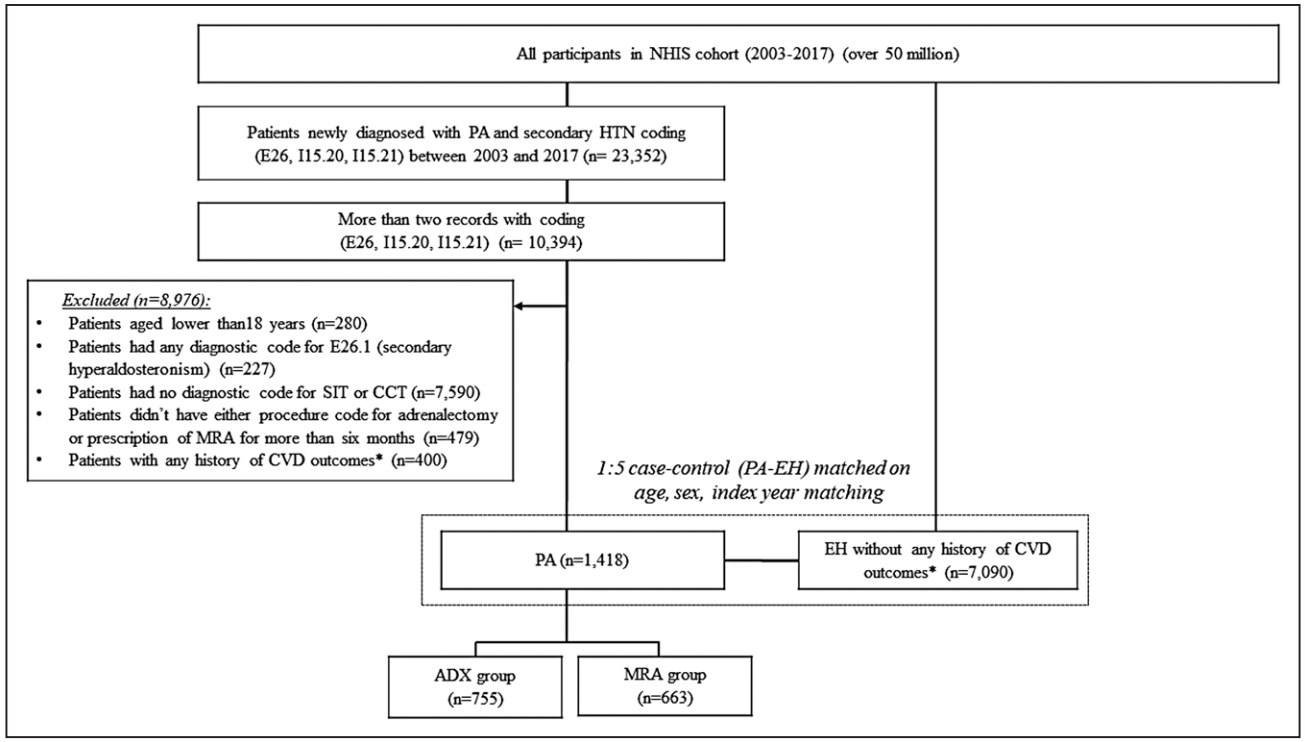

Figure 1. Flow diagram of participant selection.
Selection criteria for the study are described. In this study, we excluded patients with any history of cardiovascular disease including atrial fibrillation, stroke, myocardial infarction, and heart failure before the index year. ADX indicates adrenalectomy; CCT, captopril challenge test; CVD, cardiovascular disease; EH, essential hypertension; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; and SIT, saline infusion test.

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P=0.155; Table 2). When the follow-up duration was limited to 3 years, the risk of NOAF remained higher in PA than EH groups throughout the 3-year period that followed all treatments (adjusted HR, 3.02 [95% CI, 1.76–5.18], *P*<0.001). Thereafter, the risk of NOAF in patients with PA was similar to that of patients with EH (adjusted HR, 0.50 [95% CI, 0.25–1.01], *P*=0.053). The risk of NOAF after initiation of treatment for PA showed gradual decline in natural cubic spline curve within 3 years but remained elevated in both ADX (adjusted HR, 3.54, *P*<0.001) and MRA groups (adjusted HR, 2.27, *P*=0.031; Figure 2), followed by restoration of the NOAF risk to comparable level to that of EH after 3 years (ADX, adjusted HR, 0.38, *P*=0.102; MRA, adjusted HR, 0.60, *P*=0.214; Figure 2). Sensitivity analyses that assessed different time point split (1 and 2 years' post-treatment) revealed similar findings in which a gradual decline of NOAF risk between 1 and 3 years post-treatment was observed (at the 1-, 2-, and 3-year time point; total PA: adjusted HR, 4.67, 3.46, and 3.02; ADX group: adjusted HR, 4.76, 3.75, and 3.54; MRA group: and adjusted HR, 3.17, 2.49, and 2.27, respectively; *P*<0.05 for all comparisons; Table S3). Moreover, further washout for NOAF events which occurred within 90 days after index date to exclude potential reverse causality did not alter the findings observed on total PA and ADX group, whereas the risk of NOAF was statistically attenuated in MRA group within 3 years (adjusted HR, 1.42 [95% CI, 0.54–3.76], *P*=0.483; Table S4). A similar gradual decline of NOAF risk in ADX and MRA groups, which reached comparable level to that of the EH group after about 3 years, was also observed in a natural cubic spline curve after excluding NOAF events that occurred within 90 days of the index date (Figure S1).

Risk of Incident Cardiovascular Events in Patients With PA After Treatment Initiation

During the follow-up period, the risk of incident nonfatal stroke was elevated in patients with PA compared with those with EH (Table 3; crude incidence 4.72% versus 3.46%, respectively; unadjusted HR, 1.39, *P*=0.016). The value remained significant after adjustment for age, sex, income, comorbidities, and medication use (adjusted HR, 1.40, *P*=0.034; Figure S2). Among treatment subgroups, the MRA group was at an increased risk for nonfatal stroke compared with the EH group (adjusted HR, 1.53 [95% CI, 1.04–2.26], *P*=0.031), whereas the ADX group was not (adjusted HR, 1.26 [95% CI, 0.82–1.92], *P*=0.288). The MRA group had increased risks of all-cause mortality (unadjusted HR, 1.98; *P*<0.001) and hospitalization due to heart failure (unadjusted HR, 1.88; *P*=0.001), although the association was not significant after adjustment for covariates in multivariable

Table 1. Baseline Characteristics

	PA			EH*	
	Total (N=1418)	ADX (N=755)	MRA (N=663)	Control (N=7090)	*P* value†
Age, mean (SD)	48.83±11.32	46.71±10.53	51.25±11.72‡	48.99±11.34	0.639
Age group, n (%)					
20–29	45 (3.17)	28 (3.71)	17 (2.56)	225 (3.17)	0.999
30–39	266 (18.76)	173 (22.91)	93 (14.03)	1330 (18.76)	
40–49	432 (30.47)	245 (32.45)	187 (28.21)	2160 (30.47)	
50–59	418 (29.48)	217 (28.74)	201 (30.32)	2090 (29.48)	
60–69	203 (14.32)	87 (11.52)	116 (17.50)	1015 (14.32)	
70–79	49 (3.46)	5 (0.66)	44 (6.64)	245 (3.46)	
≥80	5 (0.35)	0 (0.00)	5 (4.17)	25 (0.35)	
Sex (male)	657 (46.33)	321 (42.52)	336 (50.68)‡	3285 (46.33)	0.999
Social economic status					
Lower 30%	267 (19.35)	152 (20.4)	115 (18.03)	1784 (25.54)	<0.001
Middle 40%	546 (39.57)	295 (39.76)	251 (39.34)	2818 (40.34)	
Highest 30%	567 (41.09)	295 (39.76)	272 (42.63)	2383 (34.12)	
Comorbidity, n (%)					
Diabetes	244 (17.21)	95 (12.58)	149 (22.47)‡	1404 (19.80)	0.005
Dyslipidemia	579 (40.83)	271 (35.89)	308 (46.46)‡	3506 (49.45)	<0.001
Chronic kidney disease	137 (9.66)	59 (7.81)	78 (11.76)‡	236 (3.33)	<0.001
Medication, n (%)					
ARB/ACE inhibitor	695 (49.01)	324 (42.91)	371 (55.96)‡	5497 (77.53)	<0.001
β-blocker	497 (35.05)	224 (29.67)	273 (41.18)‡	1841 (25.97)	<0.001
CCB	1082 (76.30)	543 (71.92)	539 (81.30)‡	4155 (58.60)	<0.001
Diuretics	1010 (71.23)	384 (50.86)	626 (94.42)‡	1566 (22.09)	<0.001
Statins	548 (38.65)	256 (33.91)	292 (44.04)‡	3362 (47.42)	<0.001
Antithrombotics	293 (20.66)	120 (15.89)	173 (26.09)‡	1880 (26.52)	<0.001

Values are presented as frequencies in numbers (percentages) or means (SD). ACE indicates angiotensin-converting enzyme; ADX, adrenalectomy group; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker; EH, essential hypertension; MRA, mineralocorticoid receptor antagonist group; and PA, primary aldosteronism.

*Cases and controls were matched by age, sex, and the index year.

†*P* value for total PA group vs matched EH group.

‡*P*<0.05 vs ADX group.

Cox models (all-cause mortality: adjusted HR, 0.99; *P*=0.965; hospitalization due to heart failure: adjusted HR, 1.27; *P*=0.257).

Risk of Incident Cardiovascular Events in PA and EH From the Time of Hypertension Diagnosis

In Table S5, the risk of incident cardiovascular events from the time of hypertension diagnosis was compared between PA and EH groups, without excluding events before PA treatment initiation. The risk of NOAF (adjusted HR, 1.76; *P*=0.006), nonfatal stroke (adjusted HR, 2.60; *P*<0.001), nonfatal myocardial infarction (adjusted HR, 2.15; *P*<0.001), and hospitalization for heart failure (adjusted HR, 1.80; *P*<0.001) from the time of hypertension diagnosis was higher in patients with PA compared with matched EH, with higher risk in MRA than in ADX group in patients with PA (Table S5).

DISCUSSION

In this study, we observed that individuals treated for PA had a higher risk of NOAF compared with those with EH. Further, time-dependent increases in NOAF risk throughout the first 3 years of following treatment initiation in both ADX and MRA groups were observed compared with the EH group. The risk peaked within the first year after the treatment for PA and gradually declined to a level that was comparable to that of the EH group over a period of 3 years, then was stabilized. Nonetheless, the MRA group had about 1.5-fold higher risk of nonfatal stroke compared with the EH group, which was independent of covariates, whereas the risk of stroke in patients treated with surgical ADX did not differ significantly from that of EH patients during follow-up.

In previous studies, patients with PA were shown to have higher risk of prevalent or incident AF compared with those with EH.[11,14,29] Milliez et al[14] reported

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Table 2. Time-Dependent Changes of Relative Risk for New-Onset Atrial Fibrillation Between Patients With PA and Their EH Matches After Treatment Initiation

PA vs EH	EH		PA		Univariable Cox regression		Multivariable Cox regression*					
							Model 1		Model 2		Model 3	
	Number of events	Cumulative incidence	Number of events	Cumulative incidence	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PA (total, n=1418) vs EH (n=7090)												
Overall	140	1.97	42	2.96	1.33 (0.90–1.97)	0.155	1.59 (1.12–2.26)	0.010	1.49 (1.04–2.13)	0.031	1.33 (0.90–1.97)	0.156
≤3 y	52	0.73	31	2.19	3.26 (2.07–5.11)	<0.001	3.26 (2.07–5.12)	<0.001	2.97 (1.87–4.72)	<0.001	3.02 (1.76–5.18)	<0.001
>3 y	88	1.80	11	1.15	0.63 (0.33–1.21)	0.165	0.61 (0.32–1.18)	0.144	0.58 (0.30–1.13)	0.112	0.50 (0.25–1.01)	0.053
PA (ADX, n=755) vs EH (n=7090)												
Overall	140	1.97	22	2.91	1.54 (0.98–2.41)	0.061	1.83 (1.16–2.88)	0.009	1.75 (1.10–2.77)	0.018	1.60 (0.99–2.58)	0.054
≤3 y	52	0.73	19	2.52	3.75 (2.21–6.36)	<0.001	4.04 (2.36–6.89)	<0.001	3.80 (2.21–6.55)	<0.001	3.54 (1.97–6.37)	<0.001
>3 y	88	1.80	3	0.61	0.36 (0.11–1.14)	0.083	0.42 (0.13–1.33)	0.138	0.40 (0.13–1.29)	0.126	0.38 (0.12–1.22)	0.102
PA (MRA, n=663) vs EH (n=7090)												
Overall	140	1.97	20	3.02	1.51 (0.95–2.42)	0.083	1.38 (0.85–2.24)	0.190	1.27 (0.78–2.07)	0.343	1.08 (0.64–1.85)	0.765
≤3 y	52	0.73	12	1.81	2.70 (1.44–5.08)	<0.001	2.50 (1.32–4.71)	0.005	2.20 (1.15–4.19)	0.017	2.27 (1.08–4.79)	0.031
>3 y	88	1.80	8	1.71	0.92 (0.42–1.99)	0.828	0.77 (0.35–1.66)	0.497	0.72 (0.33–1.57)	0.407	0.60 (0.26–1.35)	0.214

ACE indicates angiotensin-converting enzyme; ADX, adrenalectomy group; ARB, angiotensin II receptor antagonist; EH, essential hypertension; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist group; and PA, primary aldosteronism.

*Model 1: age, sex, income; Model 2: model 1+comorbidities (diabetes, dyslipidemia, and chronic kidney disease); Model 3: model 2+prescribed medication (ARB/ACE inhibitor, β-blocker, CCB, diuretics, statins, and antithrombotics).

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a 12.1-fold higher odds of AF development in patients with PA compared with EH, which corresponded to an overall prevalence of 7.3%. A meta-analysis of 31 studies by Monticone et al[9] also revealed a 3.5-fold higher risk of AF in patients with PA compared with EH during a median follow-up period of 8.8 years. In patients provided with PA treatment, the risk of NOAF was known to differ based on treatment modality used. In the longitudinal follow-up to the PAPY (Primary Aldosteronism Prevalence in Hypertension) Study, patients with PA who were treated with surgical ADX had similar NOAF risk compared with those with optimally treated EH.[17] Similarly, in a retrospective cohort of patients with PA, patients with PA treated with ADX did not have a statistically different risk of NOAF (adjusted HR, 0.75 [95% CI, 0.41–1.36]) when compared with matched EH controls during 10-year follow-up period.[18] In line with these findings, we observed that patients with PA treated with ADX had no statistically different risk of NOAF compared with the EH group throughout long-term follow-up. However, risk of NOAF in the ADX group was time-dependent, residual risk of NOAF persisted for as long as the first 3 years after the initiation of PA treatment, at which point it gradually declined to a level comparable to that of EH. In a large retrospective study involving 2202 patients with PA, which used claim database records from Taiwan, surgical ADX significantly reduced risk of NOAF compared with EH.[19] Further, we determined a similar hazard ratio point estimate of 0.50, which indicate a protective effect against NOAF after 3 years of ADX treatment; however, the value was not statistically significant (95% CI, 0.25–1.01). This could be at least partly attributed to the smaller sample size of our study compared with that which was previously published. Whether longer term follow-up or a larger sample size will reveal low NOAF risk in the ADX group compared with EH after 3 years of follow-up remains unclear.

We observed similar results in MRA group that the risk of NOAF remained elevated up to 3 years in PA group after initiation of MRA treatment when compared with EH, with smaller magnitude of NOAF risk compared with ADX group within the first 3 years. After 3 years, risk of NOAF in MRA group was comparable to that of the EH group. In prior studies, patients with PA that received MRA had increased risk of NOAF, compared with those with EH.[17,19] Of note, the MRA-treated patients with increased renin activity and sufficient MR blockade did not have a statistically significant difference in the NOAF risk compared with patients of the EH group, whereas elevated NOAF risk was observed in MRA-treated patients with suppressed renin activity and insufficient MR blockade during the 10-year follow-up.[18] Given that the minimum criteria for MRA group in our study was MRA treatment for at least 6

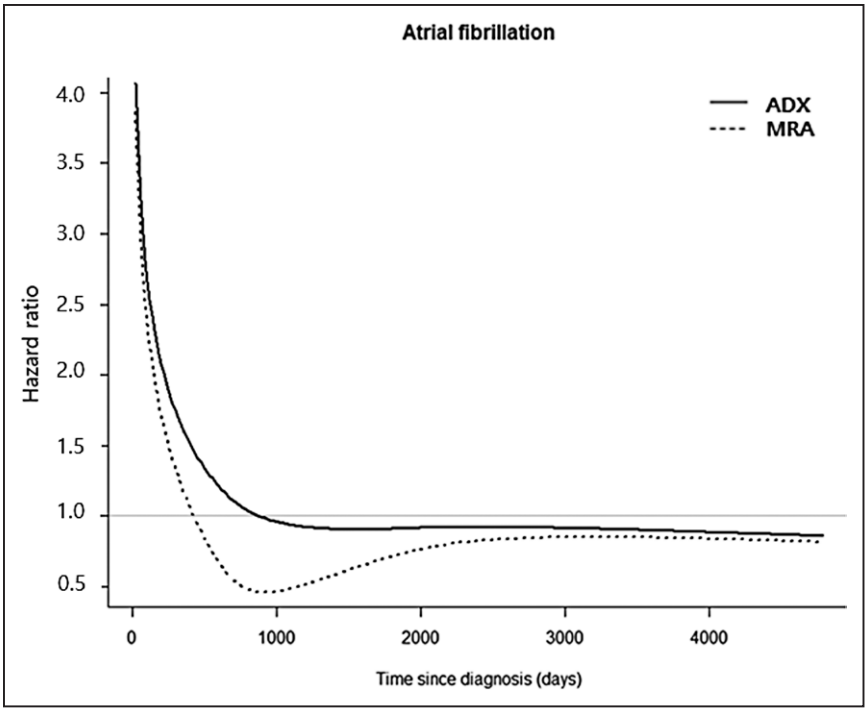

Figure 2. Natural cubic spline curves of the hazard ratio of new onset atrial fibrillation between patients with treated primary aldosteronism in the adrenalectomy (ADX) and mineralocorticoid receptor antagonist (MRA) groups vs matched essential hypertension (EH) group controls.
Time-dependent risk curves of incident NOAF of the 2 groups (ADX and MRA groups) were compared with matched EH controls. Changes in risk over time resulted in gradual risk decline and seemed to be prominent when time points before and after the third-year as a cut point.

months or more based on operational definition, it is conceivable that the MRA-treated patients in our study were patients with relatively high compliance. Considering the relatively short follow-up duration (median=5 years) of our study, a longer observation period might lead to significant differences between MRA and EH, which require further validation.

Although the risk of NOAF was elevated throughout the first 3 years after treatment for PA, the magnitude of residual risk was higher in the ADX group than the MRA group, and a steeper decline of risk in the ADX was observed. When NOAF events occurred within the 90 days after the index date were excluded, residual increased risk within 3 years in MRA group lost statistical significance, whereas the risk in ADX remained significantly higher in this study. Considering the relatively high aldosterone level and elevated prevalence of cardiovascular comorbidities observed in the aldosterone-producing adenoma subtype compared with bilateral adrenal hyperplasia, these findings suggest that the magnitude of short-term residual risk after the initiation of PA treatment might be proportional to the severity of aldosterone excess.[30] Aldosterone excess is known to contribute directly or indirectly to the pathophysiology of AF occurrence.[12,19] Atrial structural remodeling and atrial electrical remodeling are 2 possible direct effects of aldosterone on AF.[12] Cardiac fibrosis in the left ventricle and atrium with increased inflammation promote cardiac structural remodeling, which increases susceptibility to AF.[31] The association between atrial electrical remodeling and AF can be explained by aldosterone-induced atrial fibrosis, intracellular calcium overload, increased mineralocorticoid receptor expression, and enhanced reentry enhancement due to the shortening of action potential.[12] Chronic manifestations such as arterial hypertension and electrolyte imbalance produced by excess aldosterone could be indirectly attributed to the development of AF.[19] As such, echocardiographic studies have shown that blockade of aldosterone excess can restore left ventricular diastolic dysfunction and aldosterone-induced structural remodeling via the recovery of left ventricular hypertrophy.[21] The time needed to improve structural defects induced by aldosterone varied considerably between studies, and ranged from 1 year to 10 years post-treatment, which might reflect variability with respect to disease duration and aldosterone excess severity.[20,32,33] Lin and colleagues reported that vascular stiffness was significantly improved, but remained high compared with EH, after 1 year of-ADX treatment, suggesting the potential for latent recovery of the cardiovascular system even with the complete removal of the source of aldosterone excess.[34] Taken together, our findings suggest a clinical point to which routine monitoring for NOAF may be needed, which extends at least 3-years post-initiation of PA treatment. This is predicted to be particularly important for patients who undergo ADX, but findings presented here require further validation.

In this study, the risk of nonfatal stroke was significantly higher in PA patients in the MRA group compared with EH group, whereas the risk of nonfatal stroke did not differ significantly between ADX and EH groups. Our findings align well with those of previous studies, which demonstrated the increased risk of cerebrovascular accidents in PA patients treated with MRA.[19,35] AF is associated with a 3- to 5-fold higher risk for developing stroke as a well-known predisposing factor.[33] However, in our

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Table 3. Comparison of Risks From Other Cardiovascular Outcomes Between Patients With PA and Their EH Matches After Treatment Initiation

	Number of events	Cumulative incidence	Univariable Cox regression		Multivariable Cox regression*					
					Model 1		Model 2		Model 3	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Nonfatal stroke										
EH (reference)	245	3.46	1.00		1.00		1.00		1.00	
PA (total)	67	4.72	1.39 (1.06–1.82)	0.016	1.48 (1.12–1.95)	0.006	1.47 (1.11–1.95)	0.008	1.40 (1.03–1.90)	0.034
PA (ADX)	26	3.44	1.03 (0.69–1.54)	0.902	1.32 (0.88–1.98)	0.186	1.33 (0.88–2.01)	0.170	1.26 (0.82–1.92)	0.288
PA (MRA)	41	6.18	1.80 (1.29–2.50)	<0.001	1.61 (1.14–2.27)	0.006	1.58 (1.11–2.23)	0.010	1.53 (1.04–2.26)	0.031
Nonfatal myocardial infarction										
EH (reference)	194	2.74	1.00		1.00		1.00		1.00	
PA (total)	36	2.54	0.93 (0.65–1.33)	0.701	0.92 (0.64–1.32)	0.658	0.90 (0.63–1.31)	0.589	0.80 (0.54–1.20)	0.285
PA (ADX)	15	2.26	0.74 (0.44–1.25)	0.262	0.86 (0.51–1.46)	0.571	0.88 (0.52–1.49)	0.623	0.75 (0.44–1.30)	0.306
PA (MRA)	21	2.78	1.15 (0.73–1.80)	0.553	0.98 (0.61–1.56)	0.916	0.93 (0.58–1.48)	0.746	0.86 (0.51–1.43)	0.549
Hospitalization for heart failure										
EH (reference)	198	2.79	1.00		1.00		1.00		1.00	
PA (total)	52	3.67	1.05 (0.74–1.48)	0.804	1.42 (1.04–1.95)	0.028	1.25 (0.90–1.72)	0.179	1.05 (0.74–1.48)	0.804
PA (ADX)	17	2.25	0.83 (0.50–1.36)	0.451	0.99 (0.61–1.64)	0.987	0.92 (0.56–1.52)	0.744	0.80 (0.48–1.33)	0.385
PA (MRA)	35	5.28	1.88 (1.32–2.70)	0.001	1.82 (1.26–2.65)	0.002	1.54 (1.05–2.25)	0.028	1.27 (0.84–1.92)	0.257
Cardiovascular deaths										
EH (reference)	33	0.47	1.00		1.00		1.00		1.00	
PA (total)	7	0.49	1.07 (0.47–2.41)	0.878	1.23 (0.53–2.83)	0.627	1.06 (0.45–2.49)	0.897	0.94 (0.38–2.30)	0.890
PA (ADX)	1	0.13	0.29 (0.04–2.14)	0.227	0.54 (0.07–4.02)	0.548	0.47 (0.06–3.51)	0.458	0.44 (0.06–3.39)	0.433
PA (MRA)	6	0.90	1.89 (0.80–4.53)	0.148	1.57 (0.64–3.84)	0.325	1.34 (0.54–3.34)	0.529	1.17 (0.45–3.06)	0.754
All-cause mortality										
EH (reference)	188	2.65	1.00		1.00		1.00		1.00	
PA (total)	45	3.17	1.22 (0.88–1.68)	0.241	1.34 (0.96–1.87)	0.090	1.08 (0.76–1.54)	0.654	0.84 (0.58–1.21)	0.341
PA (ADX)	10	1.32	0.52 (0.27–0.98)	0.042	0.79 (0.42–1.50)	0.473	0.66 (0.34–1.26)	0.207	0.57 (0.29–1.09)	0.089
PA (MRA)	35	5.28	1.98 (1.38–2.84)	<0.001	1.69 (1.16–2.46)	0.006	1.35 (0.91–1.99)	0.132	0.99 (0.66–1.49)	0.956

ACE indicates angiotensin-converting enzyme; ADX, adrenalectomy group; ARB, angiotensin II receptor antagonist; EH, essential hypertension; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist group; and PA, primary aldosteronism.

*Model 1: age, sex, income; Model 2: model 1+baseline comorbidities (diabetes, dyslipidemia, and chronic kidney disease); Model 3: model 2+prescribed medication (ARB/ACE inhibitor, β-blocker, CCB, diuretics, statins, antithrombotics).

data, nonfatal stroke risk was significantly increased in the MRA group versus the EH group, despite the fact that NOAF risk was alleviated after 3 years when reviewing data with a median follow-up period of 5 years. This finding indicates that the elevation of nonfatal stroke risk may not be fully explained by AF alone in MRA group. Aldosterone excess is known to directly induce cerebral ischemia via increased oxidative stress, vessel wall fibrosis, and excessive dilatation of the cerebral vessels.[4] Similar to cardiac remodeling observed in the pathogenesis of AF, aldosterone is responsible for increased arterial wall stiffness.[36] In line with these findings, excess risk of other various cardiovascular events and mortality was also observed in patients who were treated with MRA versus EH patients, independent of blood pressure control.[35] Our findings and those of prior studies suggest that current MRA treatments in patients with PA may not be sufficient to prevent cardiovascular accidents including nonfatal stroke. As a result, further investigation to facilitate the development of a strategy to optimize MRA therapy in patients with PA is needed.

In this study, we analyzed the residual risk of cardiovascular events after initiation of medical or surgical treatment in patients with PA, which showed no significant difference between PA and EH in all events except nonfatal stroke. However, when we extended the analysis with the comparison of cardiovascular risk from the time of hypertension diagnosis, patients with PA had significantly higher risk of NOAF, nonfatal stroke, nonfatal myocardial infarction, and hospitalization for heart failure compared with EH, in line with prior meta-analysis of median 8.8 years follow-up from the diagnosis of hypertension.[9] These findings indicate that the cardiovascular risk measured in this study was not the peak but the residual risk after treatment initiation for PA, which need to be distinguished from overall risk from the time of diagnosis of hypertension considering that PA is often diagnosed late.

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This study has several limitations. It was based on secondary analyses of claim database, which lacked information about individual level clinical characteristics such as blood pressure, serum potassium level, aldosterone level, renin activity, and echocardiography data as well as potential diagnoses error and medication compliance rate.[37] Due to the retrospective, observational study design, residual confounding cannot be ruled out, although we tried to adjust covariates including comorbidities and medication use as well as possible. Although we detected individuals who were likely to have PA using an operational definition, due to inherent structural limitation of the claim database, we used validated definition based on a multicenter hospital-based cohort, which showed good performance and a high positive predictive value. To detect new-onset cardiovascular outcomes using the claim database, we inevitably excluded individuals with any cardiovascular diagnoses throughout the year that preceded the index date, which might lead to selection bias since individuals with relatively milder diseases that lacked cardiovascular events were preferentially selected. Therefore, our findings may not be generalizable to patients with PA generally, or to ethnicities other than Koreans. However, despite potential selection bias for milder diseases, we observed significant, time-dependent risk of NOAF in patients treated for PA, which has not been demonstrated previously.

PERSPECTIVES

This study revealed that the risk of NOAF remained elevated up to the first 3 years after treatment in patients with PA by both ADX and MRA. NOAF risk peaked in the first year after treatment and gradually declined. However, risk still elevated throughout the first 3-year period after treatment and reached levels comparable to that of the EH group after 3 years. The magnitude of the increased risk was higher in the ADX than MRA group, and a steeper decline was observed after the surgical treatment. Nevertheless, MRA group had increased risk of nonfatal stroke compared with the EH group, while the ADX group did not. Our findings indicate that NOAF monitoring for at least 3-years after PA treatment, particularly for those that undergo ADX, may be warranted.

ARTICLE INFORMATION

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Disclosures

None

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