Prevalence of Cardiovascular Disease and Its Risk Factors in Primary Aldosteronism

A Multicenter Study in Japan

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See Editorial Commentary, pp 413–414

Abstract—There have been several clinical studies examining the factors associated with cardiovascular disease (CVD) in patients with primary aldosteronism (PA); however, their results have left it unclear whether CVD is affected by the plasma aldosterone concentration or hypokalemia. We assessed the PA database established by the multicenter JPAS (Japan Primary Aldosteronism Study) and compared the prevalence of CVD among patients with PA with that among age-, sex-, and blood pressure-matched essential hypertension patients and participants with hypertension in a general population cohort. We also performed binary logistic regression analysis to determine which parameters significantly increased the odds ratio for CVD. Of the 2582 patients with PA studied, the prevalence of CVD, including stroke (cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage), ischemic heart disease (myocardial infarction or angina pectoris), and heart failure, was 9.4% (stroke, 7.4%; ischemic heart disease, 2.1%; and heart failure, 0.6%). The prevalence of CVD, especially stroke, was higher among the patients with PA than those with essential hypertension/hypertension. Hypokalemia (K^+ ≤3.5 mEq/L) and the unilateral subtype significantly increased adjusted odds ratios for CVD. Although aldosterone levels were not linearly related to the adjusted odds ratio for CVD, patients with plasma

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*A list of all participants in the Nagahama Study is given in the Appendix.

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aldosterone concentrations ≥125 pg/mL had significantly higher adjusted odds ratios for CVD than those with plasma aldosterone concentrations <125 pg/mL. Thus, patients with PA seem to be at a higher risk of developing CVD than patients with essential hypertension. Moreover, patients with PA presenting with hypokalemia, the unilateral subtype, or plasma aldosterone concentration ≥125 pg/mL are at a greater risk of CVD and have a greater need for PA-specific treatments than others. (***Hypertension*. 2018;71:530-537. DOI: 10.1161/HYPERTENSIONAHA.117.10263.)** ● **Online Data Supplement**

Key Words: aldosterone ■ cardiovascular diseases ■ hyperaldosteronism ■ myocardial ischemia ■ stroke

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Primary aldosteronism (PA) is characterized by high plasma aldosterone levels and low renin hypertension, with varying degrees of hypokalemia and metabolic alkalosis.[1–3] The hypertension associated with PA is a common form of secondary hypertension and accounts for 5% to 10% of patients with hypertension.[1,4,5]

Aldosterone is now known to be associated with a variety of cardiovascular complications. In clinical retrospective case–control studies, the prevalences of coronary artery disease (5.7% versus 2.8%), myocardial infarction (MI; 4.0%–4.4% versus 0.6%–1.7%), heart failure (4.1% versus 1.2%), arrhythmias (4.8% versus 2.2%), atrial fibrillation (3.9%–7.3% versus 0.6%–1.1%), and stroke (7.4%–12.9% versus 3.4%–3.5%) are all higher in patients with PA than in patients with essential hypertension (EHT) after adjusting age, sex, and blood pressure.[6–8] In a German retrospective case–control study, cardiovascular disease (CVD) was the main cause of death in the cohorts and was more frequent in PA than in EHT.[9] In addition, Monticone et al[10] reported that patients with PA display a higher rate of CVD at diagnosis than non-PA hypertensives (15.2% versus 6%; $P<0.001$). The reason for the higher incidence of cardiovascular complications in patients with PA is thought to be that aldosterone causes organ damage, irrespective of blood pressure.

In animal studies, rats fed a high-salt diet and chronically administered aldosterone experienced stroke and renal injury, and treatment with a mineralocorticoid blocker ameliorated those effects, irrespective of blood pressure.[3,11,12] Similarly, rats fed a high-salt diet together with chronic aldosterone administration exhibited cardiomegaly and coronary inflammatory lesions, and those effects too were eliminated by treatment with a mineralocorticoid blocker, regardless of blood pressure.[13–15] It thus seems that high aldosterone, itself, elevates CVD risk. In several clinical studies, however, the prevalence of CVD was distributed nearly equally across the spectrum of plasma aldosterone or potassium levels,[5,7,9] although another study reported that hypokalemic patients with PA had an elevated rate of CVD.[6] Patients with an aldosterone-producing adenoma tended to have lower plasma K^+ levels and higher plasma aldosterone concentrations (PACs) than patients with idiopathic hyperaldosteronism, but it was unclear whether or not the unilateral subtype was associated with development of CVD.[6,7,16] Thus, although aldosterone causes organ damage in animal models, and patients with PA have a higher risk of CVD irrespective of blood pressure, the specific factors associated with CVD in patients with PA remain unclear. Therefore, our objective in the present study was to clarify the prevalence of CVD in patients with PA and to determine the factors associated with that CVD. This was the largest multicenter study in the world addressing the prevalence of CVD in patients with PA whose subtype diagnoses were confirmed through adrenal venous sampling (AVS).

Methods

Study Population

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

This study was conducted as a part of the JPAS (Japan Primary Aldosteronism Study) and was a retrospective cross-sectional analysis. The nationwide PA registry in Japan was established at 29 centers, including 15 university hospitals and 14 city hospitals. Patients with PA who were diagnosed and underwent AVS between January 2006 and October 2016 were enrolled. Patients eligible for JPAS were men and women aged 20 to 90 years. Patients whom the investigators deemed unsuitable were excluded. The clinical characteristics, biochemical findings, results of confirmatory testing, imaging findings, AVS results, treatment, surgical findings, and related follow-up data were electronically collected using the web registry system. System construction, data security, and maintenance of the registered data were outsourced to EPS Corporation (Tokyo, Japan).

The study was conducted using a data set valid at May 2017. Patients with available data on clinical characteristics, biochemistry, and successful adrenocorticotropic hormone–stimulated AVS were included. The diagnosis of PA was made in accordance with guidelines from the Japan Endocrine Society and the Japan Society of Hypertension.[17,18] PA was diagnosed based on positive case detection of a ratio of PAC (measured in pg/mL) to plasma renin activity (measured in ng/mL per hour) >200 or PAC to active renin concentration (measured in pg/mL) >40 and at least 1 positive result from a confirmatory test, including the captopril-challenge test, the saline-infusion test, the furosemide-upright test, or the oral salt-loading test. Antihypertensive medications were usually changed to calcium channel blockers or α-adrenergic blockers, as appropriate, until the final diagnosis was made. Hypokalemia was considered to be present if K^+ was ≤3.5 mEq/L or when a patient was taking a potassium supplement. Oral potassium was supplemented if hypokalemia was present. The subtype diagnosis of PA was determined based on an AVS with adrenocorticotropic hormone (cosyntropin) stimulation, the procedures for which have been described.[19] Adrenal vein cannulation was defined as successful if the selectivity index was >5.[20] The selectivity index was defined as the ratio of the cortisol concentration in the adrenal vein to that in the inferior vena cava. Unilateral subtype diagnosis of PA was defined as a lateralization index >4. The lateralization index was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side. In the subtype diagnosis of PA, patients with suspected autonomous cortisol secretion defined as serum cortisol levels >3 μg/dL after 1 mg dexamethasone were excluded.[21]

Measurements

We investigated the prevalence of CVD and arrhythmias. CVD included stroke, ischemic heart disease (IHD), and heart failure

that required hospitalization for treatment. Stroke included cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. IHD included MI and angina pectoris. Arrhythmias included atrial fibrillation and ventricular arrhythmias. Cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage were confirmed by neurologists. MI and angina pectoris were confirmed by cardiologists.

We also assessed the prevalence of low estimated glomerular filtration rate (eGFR) defined as eGFR <60 mL/min per 1.73 m^2, proteinuria (+, 2+, or 3+ protein in urinalyses), diabetes mellitus (DM), dyslipidemia, obesity (body mass index ≥25 kg/m^2), and hypokalemia. Glomerular filtration rate was measured using an abbreviated equation, which took into consideration serum creatinine (Cre), age, and sex for easy computation: eGFR ($mL \times min^{-1} \times 1.73\ m^{-2}$)=$186 \times (Cre)^{-1.094} \times (age)^{-0.287} \times$(0.742 if women). The diagnostic criteria for DM followed those of the Japan Diabetes Guidelines.[22] The diagnostic criteria for dyslipidemia followed those of the Japan Atherosclerosis Society Guidelines.[23]

We collected data on age, sex, family history of hypertension, duration of hypertension, smoking habits, drinking habits, body mass index, systolic blood pressure, diastolic blood pressure (DBP), blood tests (Na^+, K^+, Cre, eGFR, PAC, plasma renin activity, aldosterone-to-renin ratio [ARR], serum cortisol levels, fasting blood sugar, HbA1c [NGSP, National Glycohemoglobin Standardization Program], total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), left ventricular hypertrophy (ECG left ventricular hypertrophy [LVH]: defined as a Sokolow–Lyon index >35 mm), subtype diagnosis based on AVS, cardiothoracic ratio (CTR), and ejection fraction (measured by Simpson or Teichholz method).

The prevalence of CVD in patients with PA was compared with that in patients with EHT in 2 cohorts: patients with EHT at the outpatient clinic of the Kyoto Medical Center and participants with hypertension in the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study).

Among the 274 patients with EHT treated at the clinic of Kyoto Medical Center between January 2006 and December 2013, 236 were subjected for comparison after age (±1 year), sex, and systolic blood pressure (±3 mm Hg) matching. The Nagahama Study cohort was recruited between 2008 and 2010 from the general population living in Nagahama City. Nagahama City residents aged 30 to 74 years at recruitment and without serious health problems were recruited from the local community via mass communications, such as magazines and newspapers. Of the 9764 participants, 1923 were diagnosed with hypertension by a physician. Among those diagnosed with hypertension, 1263 were subjected for comparison with patients with PA after age, sex, and systolic blood pressure matching, as was done with the Kyoto Medical Center cohort. In the Nagahama Study, stroke and IHD were confirmed by questionnaire to patients.

Detailed description of the blood pressure measurements, assay methods, statistical analysis, and ethics is available in the online-only Data Supplement.

Results

Prevalence of CVD in Patients With PA

The prevalence of CVD was 9.4%. The prevalence of stroke was 7.4%, which included cerebral hemorrhage (2.7%), cerebral infarction (4.6%), and subarachnoid hemorrhage (0.5%). Ten patients (0.4%) experienced both cerebral hemorrhage and cerebral infarction, and 3 patients (0.1%) experienced both cerebral hemorrhage and subarachnoid hemorrhage. The prevalence of IHD was 2.1%, which included MI (0.9%) and angina pectoris (1.3%). The prevalence of heart failure was 0.6%. The prevalence of low eGFR was 17.1%. The prevalence of proteinuria was 12.0%. The prevalences of other complications are shown in Table 1. The clinical and biochemical parameters are shown in Table S1 in the online-only Data Supplement.

Comparison Between Patients With PA and EHT/Hypertension in Japan

We compared the prevalence of CVD in our PA study with the prevalence among age-, sex-, and blood pressure-matched patients with EHT at the Kyoto Medical Center (Table 2). The prevalences of CVD, stroke, or IHD, stroke, IHD, and atrial fibrillation were all significantly higher among patients with PA than those with EHT. Body mass index and the percentage of proteinuria were also significantly higher in patients with PA than those with EHT.

The prevalences of stroke or IHD and stroke among patients with PA were also significantly higher than those among patients with hypertension in the Nagahama Study. However, the prevalence of IHD did not differ between patients with PA and hypertension. Body mass index and the prevalences of proteinuria, DM, and dyslipidemia were significantly higher in patients with PA than those with hypertension.

Factors Associated With CVD in Patients With PA

We next determined which factors were associated with the prevalence of CVD in patients with PA (Table 3). In a univariate analysis, we found that old age, being men, DBP, duration of hypertension, smoking, drinking, history of DM, dyslipidemia, ECG-LVH and proteinuria, low eGFR, hypokalemia, high PAC level, high CTR, and unilateral subtype were all factors significantly associated with CVD. If these variables were correlated with each other, we would not be able to correctly calculate the odds ratio (OR) because of the multicollinearity. We, therefore, checked correlations among these parameters using Pearson correlation test or Spearman rank correlation test. Age, DBP, duration of hypertension, drinking habits, smoker, history of DM, history of dyslipidemia, proteinuria, ECG-LVH, and CTR were all independent of other parameters. K^+, PAC, hypokalemia, and lateralization were correlated with each other. Sex, Cre, and eGFR were also correlated with each other. However, sex and Cre are well-known risk factors for CVD,[24–26] and eGFR was calculated based on age, sex, and Cre. We, therefore, selected age, sex, DBP, duration of hypertension, drinking habits, smoker, Cre, history of DM, history of dyslipidemia, proteinuria, ECG-LVH, and CTR as known CVD risk factors in our logistic regression analysis.

We performed logistic regression analysis to determine whether K^+, PAC, hypokalemia, and lateralization were significantly related to the odds of developing CVD. We selected 2 kinds of parameters: PA-associated factors, such as K^+, PAC, hypokalemia, and lateralization, and known CVD risk factors, such as age, sex, DBP, duration of hypertension, smoking habits, drinking habits, Cre, history of DM, history of dyslipidemia, proteinuria, ECG-LVH, and CTR. Because K^+, PAC, hypokalemia, and lateralization were correlated with each other, we analyzed these parameters individually adjusting for known CVD risk factors (Table 4). We found that hypokalemia (OR, 1.832; 95% confidence interval [CI], 1.219–2.753) and lateralization (OR, 1.931; 95% CI, 1.155–3.229) significantly increase the odds of developing CVD after adjusting for known CVD risk factors. On the contrary, the PAC (OR, 1.000; 95% CI, 0.999–1.001) did not itself linearly affect the odds of developing CVD. The K^+ level (OR,

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Table 1. Prevalences of CVD in Japan and Comparison With the Prevalence of CVD in Other Countries

	JPAS Study (Japan)	Born-Frontsberg et al[5] (Germany)	Mulatero et al[6] (Italy)	Milliez et al[7] (France)	Savard et al[8] (France)
Backgrounds and Events	n=2582	n=553	n=270	n=124	n=459
Age, y	53.2±11.3	61±13	44±8.5	52±10	51.1±10.2
Sex, men, %	47.1	57	59.6	67	67
Systolic BP, mm Hg	141.4±18.2	158±29	155±21	176±23	151±24.4
DBP, mm Hg	86.5±12.8	94±16	96±12	107±14	87.7±13.1
DM, %	16.9	…	4.1	…	17
CVD, %	9.4	16.3	14.1	…	…
Stroke, %	7.4	…	7.4	12.9	…
Ischemic heart disease, %	2.1	…	2.6	…	5.7
Myocardial infarction, %	0.9	…	…	4.0	4.4
Heart failure, %	0.6	…	0.7	…	4.1
Arrhythmias, %	4.0	…	4.8	…	…
Atrial fibrillation, %	2.8	7.1	…	7.3	3.9

CVD in our study includes cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, myocardial infarction, angina pectoris, and heart failure. CVD in the study reported by Born-Frontsberg et al[5] includes myocardial infarction, angina pectoris, chronic cardiac insufficiency, and coronary angioplasty. CVD in the study reported by Mulatero et al[6] includes myocardial infarction, unstable angina, stroke, transient ischemic attack, heart failure, and arrhythmias. Arrhythmias include atrial fibrillation and ventricular arrhythmias. BP indicates blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; and JPAS, Japan Primary Aldosteronism Study.

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0.735; 95% CI, 0.503–1.073) also did not linearly affect the odds of developing CVD. We, therefore, generated a receiver operating characteristic curve to determine the PAC with the greatest sensitivity and specificity for predicting CVD. Using the maximum Youden index to calculate the optimal cutoff point on the receiver operating characteristic curve, we determined the optimal threshold PAC to be 125 pg/mL. We then divided the patients with PA into 2 groups: those with a PAC <125 pg/mL and those with a PAC ≥125 pg/mL; the former accounted for 24.6% of the patients and the latter, 75.4%. In binary variables, the prevalence of CVD was significantly higher in patients with a PAC ≥125 pg/mL than in those with a PAC <125 pg/mL, adjusting for known CVD risk factors. High PAC levels increased the odds of developing CVD after adjusting for known CVD risk factors (OR, 1.938; 95% CI, 1.096–3.428).

Discussion

We determined the prevalence of CVD and the risk factors associated with CVD among 2582 patients with PA in Japan. This is the largest clinical study in the world addressing the prevalence of CVD in patients with PA and the risk factors associated with it.

The prevalence of CVD was compared between Japan and 3 countries in Europe (Table 1).[5–8] Although the prevalences of CVD and stroke were comparable, the prevalences of IHD, heart failure, and atrial fibrillation were lower in Japan than in other countries. The lower prevalence of IHD and other heart diseases may be attributable to the lower total cholesterol and low-density lipoprotein cholesterol levels in Japan than in other countries.[27–32] In addition, the similar prevalence of stroke in Japan and other counties may be related to the similar levels of salt intake in these countries.[33,34] Furthermore, blood pressure levels in our study were lower than those in the other studies, and the proportion of women was higher in our study than in the other studies. These differences in background may have affected the prevalence of CVD in the different countries.

We compared the prevalence of CVD in our PA study with that in 2 cohorts of patients with EHT/hypertension. Previous clinical studies indicated that patients with PA were at higher risk of developing CVD than those with EHT.[6–8,35] Our results also suggested patients with PA were at significantly greater risk of CVD than patients with EHT and hypertension in a general population. Nevertheless, the prevalence of IHD among patients with hypertension in the Nagahama Study did not differ from the prevalence among patients with PA in the JPAS study. This may be because IHD was assessed using a questionnaire in the Nagahama Study and was not always diagnosed by a cardiologist.

Factors Related to the Higher Prevalence of CVD in Patients With PA

To investigate factors related to the higher prevalence of CVD in patients with PA, we performed binary logistic regression analysis to determine which parameters significantly increased the OR for CVD. Hypokalemia and unilateral subtype were associated with CVD development after adjusting for known CVD risk factors. However, PAC did not itself significantly increase the adjusted OR for CVD.

In experimental studies, hyperaldosteronism is known to be a risk factor that does substantial damage to cardiovascular organs.[3,11–15] In clinical reports, including the present study, however, PACs are not linearly related to the adjusted OR for

Table 2. Comparison of Patients With PA (JPAS Study) and EHT (Kyoto Medical Center) and Participants With Hypertension in a General Population (Nagahama Study) Matched for Age, Sex, and SBP

Parameter	JPAS Study (PA) n=236	Kyoto Medical Center (EHT) n=236	*P* Value	JPAS Study (PA) n=1263	Nagahama Study (Hypertension) n=1263	*P* Value
Age, y	58.7±11.7	58.8±11.8	0.959	60.2±8.4	60.4±8.4	0.479
Sex, men, %	47.5	47.5	1.000	43.1	43.1	1.000
SBP, mm Hg	144.7±17.3	144.7±17.3	0.998	140.1±15.6	139.6±15.6	0.437
DBP, mm Hg	87.4±12.5	87.1±12.1	0.809	84.9±12.2	86.6±9.9	<0.001*
Duration of hypertension, y	4 (1–13)	5 (1–12)	0.489	…	…	…
BMI, kg/m^2	25.1±3.7	23.8±3.5	<0.001*	24.4±3.7	23.9±3.4	0.003*
Serum K$^+$, mEq/L	3.8±0.5	4.1±0.4	<0.001*	…	…	…
Creatinine, mg/dL	0.81±0.5	0.78±0.3	0.473	0.77±0.41	0.76±0.36	0.791
eGFR, mL/min per 1.73 m^2	71.1±18.6	71.9±17.1	0.592	71.2±16.9	70.1±14.7	0.065
Low eGFR, %	23.3	22.6	0.866	23.3	21.1	0.185
Proteinuria, %	14.7	5.5	<0.001*	13.7	4.8	<0.001*
DM, %	22.0	14.0	0.108	20.7	13.2	<0.001*
Dyslipidemia, %	33.5	30.4	0.474	33.1	25.2	<0.001*
CVD, %	11.0	3.4	0.001*	…	…	…
Stroke and IHD, %	11.0	3.4	0.001*	11.0	4.4	<0.001*
Stroke, %	7.2	2.5	0.019*	8.4	1.6	<0.001*
IHD, %	3.8	0.8	0.033*	3.0	2.9	0.907
Heart failure, %	0.8	0.4	0.562	…	…	…
Atrial fibrillation, %	4.2	0.8	0.021*	…	…	…

The parameters were evaluated using univariate analyses. Stroke includes cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage. Ischemic heart disease includes myocardial infarction and angina pectoris. DM was defined as a known history of DM (fasting plasma glucose levels ≥126 mg/dL and HbA1c ≥6.5%) or current intake of antidiabetic therapy. Dyslipidemia was defined as a known history of dyslipidemia (TG levels ≥150 mg/dL, LDL levels ≥140 mg/dL, and HDL levels <40 mg/dL) or current intake of antidyslipidemic therapy. BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHT, essential hypertension; HDL, high-density lipoprotein cholesterol; HT, hypertension; IHD, ischemic heart disease; JPAS, Japan Primary Aldosteronism Study; LDL, low-density lipoprotein cholesterol; PA, primary aldosteronism; SBP, systolic blood pressure; and TG, triglyceride.

*Significant differences (*P*<0.05).

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CVD.[5,9] We, therefore, divided patients with PA into 2 groups: a high PAC group and a low PAC group, after determining a PAC cutoff value of 125 pg/mL using the maximum Youden index calculated from the receiver operating characteristic curve for predicting CVD. The CVD risk was significantly higher in patients with a PAC ≥125 pg/mL than in those with a PAC <125 pg/mL. This may indicate the existence of a threshold PAC, above which the likelihood of developing CVD is increased. In general, when we use only ARR to screen for PA, there are several false positives because of low renin. Using a threshold PAC along with ARRs would be advantageous. We suggest that a PAC cutoff of 125 pg/mL would be useful for screening to detect patients at a higher risk of developing CVD. On the contrary, patients with PACs <125 pg/mL have a relatively low risk for CVD, even if they satisfied the screening threshold for PA based on ARR. The need for further examination in these cases may not be urgent. However, because the PAC can vary with posture, time of day, and sodium intake, a PAC cutoff of 125 pg/mL can be used for rough screening in combination with ARR, but it is not generally applicable to all situations. In addition, a PAC cutoff value of 125 pg/mL could be used to predict CVD risk in patients with PA in whom renin is suppressed and aldosterone is autonomously secreted. This cutoff value would not be applicable to non-PA patients.

Regarding hypokalemia and lateralization, it was controversial whether or not they were associated with CVD.[5–8] In the present study, hypokalemia significantly increased the OR for CVD after adjusting for known CVD risk factors. Among community-living individuals, those with low serum K$^+$ concentrations were reportedly at higher risk of CVD than those with normal serum K$^+$ concentrations.[36] Among patients with EHT, K$^+$ levels outside the normal range were reportedly associated with increased mortality risk, and in particular, the prevalence of stroke was higher among patients with low serum K$^+$ levels.[37] Our results are consistent with those reports. K$^+$ is, therefore, thought to be important for preventing stroke, regardless of the PAC.

We also found that after adjusting for known CVD risk factors, patients with the unilateral subtype and suspected of having an aldosterone-producing adenoma experienced

Table 3. Clinical and Biochemical Parameters in CVD-Positive and CVD-Negative PA Patients

Parameter	CVD-Positive PA Patients n=243	CVD-Negative PA Patients n=2339	*P* Value
Age, y	58.6±10.5	52.7±11.2	<0.001*
Sex, men, %	63.2	45.4	<0.001*
BMI, kg/m^2	25.3±4.3	24.8±4.1	0.079
BMI >25, %	47.1	43.1	0.332
Family history of hypertension, %	61.3	61.9	0.786
Current or past drinking, %	45.4	54.8	0.013*
Current or past smoking, %	44.8	34.5	0.003*
Low eGFR, %	35.8	15.6	<0.001*
Proteinuria, %	25.8	10.5	<0.001*
DM, %	29.3	15.6	<0.001*
Dyslipidemia, %	43.8	25.3	<0.001*
Duration of hypertension, y	13 (5–20)	5 (2–11)	<0.001*
Systolic blood pressure, mm Hg	142.1±19.9	141.3±18.0	0.511
Diastolic blood pressure, mm Hg	84.5±12.4	86.7±12.8	0.008*
Na^+, mEq/L	142.2±2.6	141.9±2.3	0.064
K^+, mEq/L	3.6±0.6	3.7±0.5	0.008*
Hypokalemia	54.3	37.4	<0.001*
Creatinine, mg/dL	0.92±0.59	0.73±0.32	<0.001*
eGFR, mL/min per 1.73 m^2	66.0±20.1	77.3±18.6	<0.001*
HbA1c (NGSP), %	6.0±1.2	5.8±0.9	0.008*
FBS, mg/dL	111±37	104±26	<0.001*
TC, mg/dL	183±35	193±33	<0.001*
TG, mg/dL	126±73	123±74	0.574
LDL, mg/dL	107±31	114±29	0.001*
HDL, mg/dL	53±16	56±16	0.007*
ECG-LVH, %	35.5	27.0	0.002*
CTR, %	49.5±5.6	47.6±4.8	<0.001*
EF, %	68.2±8.8	68.5±7.7	0.631
Cortisol, pg/mL	10.2 (8.0–13.9)	10.7 (8.1–14.1)	0.596
ARR, pg/mL per ng/mL per h	700 (330–1250)	534 (321–1100)	0.047*
PAC, pg/mL	203 (139–338)	175 (123–276)	<0.001*
PRA, ng/mL per h	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.500
Lateralization, %	48.5	32.1	<0.001*

The parameters were evaluated using univariate analyses. ARR indicates aldosterone-to-renin ratio; BMI, body mass index; CTR, cardiothoracic ratio; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NGSP, National Glycohemoglobin Standardization Program; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA plasma renin activity; TC, total cholesterol; and TG, triglyceride.

*Significant differences (P<0.05).

Table 4. ORs and 95% CIs After Separately Adjusting for Known Cardiovascular Disease Risk Factors

Parameter	OR	95% CI	*P* Value
Serum potassium	0.735	0.503–1.073	0.111
Serum potassium ≤3.5 mEq/L	1.832	1.219–2.753	0.004*
Unilateral subtype	1.931	1.155–3.229	0.012*
PAC, pg/mL	1.000	0.999–1.001	0.423
PAC ≥125 pg/mL	1.938	1.096–3.428	0.023*

Known cardiovascular disease risk factors include age, sex, diastolic blood pressure, duration of hypertension, smoking habits, drinking habits, creatinine, history of diabetes mellitus, history of dyslipidemia, proteinuria, left ventricular hypertrophy, and cardiothoracic ratio. CI indicates confidence interval; OR, odds ratio; and PAC, plasma aldosterone concentration.

*Significant differences (P<0.05).

more CVD than patients with the bilateral subtype and suspected of having idiopathic hyperaldosteronism. Compared with patients with the bilateral subtype, those with the unilateral subtype tended to have lower serum K^+ and a higher PAC. The risk of CVD would be higher in patients with the unilateral subtype because of the hypokalemia and hyperaldosteronism.

It has been reported that the prevalence of metabolic disorders related to metabolic syndrome is high among patients with PA.[38,39] Consistent with those reports, our data also show a high prevalence of DM. Arlt et al[40] recently reported that glucocorticoid cosecretion is linked to the metabolic phenotype in patients with PA. Although our data do not show a difference in basal cortisol secretion between CVD-positive and negative PA, an approach such as 24-hour urine steroid metabolome analysis could be used to more precisely evaluate the effect of glucocorticoid cosecretion on CVD in PA.

We would expect the severity of PA to be a key determinant of the degree of CVD risk. Our results suggest PA severity is not determined by the PAC itself but by dysregulation of electrolyte homeostasis (hypokalemia), the presence of the unilateral subtype, and a high PAC (≥125 pg/mL). Patients with PA exhibiting dysregulated electrolyte homeostasis, the unilateral subtype, or a high PAC should be treated as a priority to prevent CVD.

Limitations

Our study has several limitations. This is a retrospective cross-sectional study. To clarify the incidence of CVD in patients with PA, we will need to perform a prospective study. However, it would be ethically difficult to prospectively follow patients with PA without specific treatment, such as surgical resection or administration of a mineralocorticoid receptor antagonist.

Our results indicate that there is a threshold PAC, above which CVD risk is increased. However, because PAC assays are not standardized around the world, whether the PAC cutoff level of 125 pg/mL is appropriate in countries other than Japan must be confirmed through additional studies.

In the JPAS study, data were collected only from patients with PA. Therefore, for comparison with patients with PA, we collected data from patients with EHT at the Kyoto Medical Center and from patients with hypertension in the Nagahama

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Study. Because the former were data from a single center and the latter were data from a community-based cohort study, there will be several differences in the patient's background, making it important to interpret the results carefully.

Perspectives

This large cohort study demonstrated that the prevalence of CVD, especially stroke, was higher in patients with PA than in age- and sex-matched patients with EHT and hypertension in a general population. It was also demonstrated that dysregulated electrolyte homeostasis (K^+ ≤3.5 mEq/L) and the unilateral subtype are positively associated with CVD in patients with PA. The PAC was not itself associated with CVD, although a high PAC (≥125 pg/mL) was positively associated with CVD. Our results suggest that PA patients with hypokalemia, the unilateral subtype, or a PAC ≥125 pg/mL have a greater need for PA-specific treatments because of their higher risk of CVD. In addition, because patients with the unilateral subtype have a higher risk of CVD, early subtype diagnosis is also important.

Appendix

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Disclosures

None.

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Novelty and Significance

What Is New?

- This was the largest multicenter study in the world. Investigated were 2582 patients with primary aldosteronism (PA) who had received adrenal venous sampling.
- The presence of hypokalemia correlated with the prevalence of cardiovascular disease (CVD).
- Plasma aldosterone concentrations (PACs) were not linearly related to the adjusted odds ratio for CVD but had a threshold (PAC ≥125 pg/mL) for developing of CVD. A PAC cutoff of 125 pg/mL would be a useful criterion for screening to detect patients at high risk of developing CVD.
- From 2 previous major studies, it was unclear whether or not the unilateral subtype was associated with development of CVD. We clarified that the unilateral subtype has a higher risk of CVD than with bilateral subtype.

What Is Relevant?

- Patients with PA are at a higher risk of CVD than patients with essential hypertension. In particular, PA patients with hypokalemia, the unilateral subtype, or a PAC higher than the upper limit of normal, are at higher risk of developing CVD, and, therefore, have a greater need for PA-specific treatments.

Summary

We investigated the prevalence of CVD and the factors associated with CVD in 2582 patients with PA. The prevalence of CVD among patients with PA was higher than that in age-, sex-, and blood pressure-matched essential hypertension and hypertensive patients in a general population. The presence of hypokalemia, the unilateral subtype, or a PAC ≥125 pg/mL were factors relating to a higher risk of CVD in patients with PA. Consequently, these patients have a greater need for PA-specific treatments. Because patients with the unilateral subtype have a higher risk of CVD, early subtype diagnosis is also important.

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ONLINE SUPPLEMENT

Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: A multicenter study in Japan

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SUPPLEMENTAL METHODS

BP measurements

In JPAS study and the Kyoto Medical Center Cohort, office BP measurement in the sitting position was obtained from medical records at the time of diagnosis. In the Nagahama Study, BP were measured twice after 5 min rest in the sitting position, with HEM-9000AI; Omron Healthcare, Kyoto, Japan, and the mean value was used in the analysis.

Assay methods

PACs were measured using commercially available radioimmunoassays (SPAC-S Aldosterone kits, Fuji Rebio, Co., Ltd, Tokyo, Japan) at all centers. The reference range for PACs with patients in a supine position was 30-159 pg/ml. PRA was measured using a radioimmunoassay or enzyme immunoassay (EIA). The reference range for PRA with patients in a supine position was 0.3-2.9 ng/ml/h (PRA-FR RIA kits, Fuji Rebio, Co., Ltd, Tokyo, Japan) at 16 centers, 0.2-2.3 ng/ml/h (PRA EIA kits, Yamasa, Co., Ltd, Choshi, Japan) at 8 centers, and 0.2-2.7 ng/ml/h (PRA RIA kits, Yamasa, Co., Ltd, Choshi, 122 Japan) at 4 centers. Plasma active renin concentrations (ARCs) were measured by immunoradiometric assay (Renin IRMA-FR, Fuji Rebio, Co., Ltd, Tokyo, Japan) in one center. The reference range for ARCs with patients in a supine position was 2.5-21.4 pg/ml.

Statistical analysis

Stata/SE ver. 14 software developed by LightStone® was used for statistical analyses. All data were expressed as the mean ± SD for normally distributed variables and as the median (25th to 75th percentile) for variables not normally distributed. Sex, obesity, family history of hypertension, smoking, drinking, history of DM, history of dyslipidemia, hypokalemia, proteinuria, ECG-LVH and lateralization were considered as binary variables. For comparison in our study, data of PA patients from JPAS study and data of EHT/HT patients from the Kyoto Medical Center and the Nagahama Study were randomly matched 1:1 with respect to age, sex and SBP. Student's *t* test or the Mann-Whitney *U* test was used for quantitative variables. Pearson's χ^2 test was used for qualitative parameters. Values of $P < 0.05$ were considered to indicate significant differences. Pearson's correlation coefficients or Spearman's rank correlation coefficients for parameters associated with CVD in the univariate analysis were deemed statistically significant when the correlation coefficient $r > 0.4$ and $P < 0.05$. In principle, we selected one parameter in cases where two or more parameters showed significant correlation with each other. The risk of CVD was expressed as an odds ratio (OR) ± 95% confidence interval (CI). In the logistic regression analysis, we included variables that were significantly associated with CVD in the univariate analysis and were not significantly correlated with each other. For reliable analysis, we required at least 10 events for the primary outcome measure per variable.

Ethics

The study was conducted according to Declaration of Helsinki Guidelines and the guidelines for clinical studies published by the Ministry of Health and Labor, Japan and was approved by the ethics committee of the National Hospital Organization Kyoto Medical Center as the project leader center and by the institutional ethics committees of the participating centers. This observational study was registered as UMIN ID 18756. The data from the JPAS study and from EHT patients at the Kyoto Medical Center were studied

retrospectively. These studies were performed using an opt-out methodology. The opt out option was presented on the website and as a notice in a prominent place at each center. The Nagahama study procedures were approved by the ethics committee of the Kyoto University Graduate School of Medicine and by the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.

SUPLEMENTAL TABLE

Table S1. Clinical and biochemical parameters for all PA participants in the JPAS study

Parameter	Participants in JPAS study (n = 2582)
Age, year	53.2 ± 11.3
Sex, male, %	47.1
BMI, kg/m^2	24.8 ± 4.2
BMI >25, %	43.5
Family history of hypertension, %	61.9
Current or past drinking, %	53.9
Current or past smoking, %	35.5
Low eGFR, %	17.1
Proteinuria, %	12.0
Diabetes mellitus, %	16.9
Dyslipidemia, %	27.0
Duration of hypertension, year	5 (2 - 13)
Systolic blood pressure, mm Hg	141.4 ± 18.2
Diastolic blood pressure, mm Hg	86.5 ± 12.8
Na^+, mEq/l	141.9 ± 2.3
K^+, mEq/l	3.7 ± 0.5
Hypokalemia, %	39.0
Creatinine, mg/dl	0.75 ± 0.36
EGFR, ml/min/1.73m^2	76.3 ± 19.0
HbA1c(NGSP), %	5.8 ± 0.9
FBS, mg/dl	105 ± 27
TC, mg/dl	192 ± 34
TG, mg/dl	123 ± 74
LDL, mg/dl	113 ± 30
HDL, mg/dl	56 ± 16
ECG-LVH, %	28.8
CTR, %	47.8 ± 4.9
EF, %	68.5 ± 7.9
Cortisol, pg/ml	10.7 (8.0-14.1)
ARR, pg/ml per ng/ml/h	544 (323 - 1128)
PAC, pg/ml	177 (125 - 281)
PRA, ng/ml/h	0.3 (0.2 - 0.5)
Lateralization index	1.8 (1.3 – 5.6)
Lateralization, %	33.6

ARR indicates the aldosterone to renin ratio; BMI, body mass index; CTR, cardio thoracic ratio; ECG, electrocardiogram; EF, ejection fraction; EGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol: LDL, low-density lipoprotein cholesterol: LVH, left ventricular hypertrophy; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA plasma renin activity; TC, total cholesterol; TG, triglyceride.