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Evidence for an Increased Rate of Cardiovascular Events in Patients With Primary Aldosteronism

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OBJECTIVES The aim of this report was to show that the rate of cardiovascular events is increased in patients with either subtype of primary aldosteronism (PA).

BACKGROUND Primary aldosteronism involves hypertension (HTN), hypokalemia, and low plasma renin. The two major PA subtypes are unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia.

METHODS During a three-year period, the diagnosis of PA was made in 124 of 5,500 patients referred for comprehensive evaluation and management. Adenomas were diagnosed in 65 patients and idiopathic hyperaldosteronism in 59 patients. During the same period, clinical characteristics and cardiovascular events of this group were compared with those of 465 patients with essential hypertension (EHT) randomly matched for age, gender, and systolic and diastolic blood pressure.

RESULTS A history of stroke was found in 12.9% of patients with PA and 3.4% of patients with EHT (odds ratio [OR] = 4.2; 95% confidence interval [CI] 2.0 to 8.6]). Non-fatal myocardial infarction was diagnosed in 4.0% of patients with PA and in 0.6% of patients with EHT (OR = 6.5; 95% CI 1.5 to 27.4). A history of atrial fibrillation was diagnosed in 7.3% of patients with PA and 0.6% of patients with EHT (OR = 12.1; 95% CI 3.2 to 45.2). The occurrence of cardiovascular complications was comparable in both subtypes of PA.

CONCLUSIONS Patients presenting with PA experienced more cardiovascular events than did EHT patients independent of blood pressure. The presence of PA should be detected, not only to determine the cause of HTN, but also to prevent such complications. (J Am Coll Cardiol 2005;45: 1243–8) © 2005 by the American College of Cardiology Foundation

Primary aldosteronism (PA), resulting from an adrenocortical adenoma, is a potentially curable form of hypertension (HTN). The two major subtypes of PA are unilateral aldosterone-producing adenoma (APA), or Conn's adenoma, and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) (1). Prevalence estimates for PA vary from 0.5% to 2% of the hypertensive population (2,3), but recent

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studies have reported increased values (4). Initially, HTN associated with PA was considered mild and readily controlled as well as rarely complicated (5). However, several authors reported series or case reports of PA with severe to malignant HTN, or with marked target organ damage affecting the heart, the carotid artery, or the kidney (6–8). Other studies noted an increased prevalence of cerebrovascular diseases (9–11) in PA. Rossi et al. (12) reported that in patients with PA, the excess aldosterone could be associated with a pressure-independent remodeling of the left ventricle. Surprisingly, despite this cardiac remodeling, few cardiac complications (myocardial infarction [MI], arrhythmias) have been noted in association with PA. Two case reports described association of atrial fibrillation (AF) (13) and ventricular fibrillation (14) with PA. Most recently, Nishimura et al. (11) found only one patient in their study of PA with associated coronary artery disease.

The aim of this investigation was to conduct a case-control study to test the hypothesis that the rate of cardiovascular complications is increased in a large group of patients with either subtype (APA or bilateral adrenal hyperplasia) of PA.

METHODS

Overall patient population and PA diagnostic workup. From January 1997 to December 1999, approximately 5,500 hypertensive patients were referred to the Department of Hypertension of Broussais Hospital (Paris, France). This department was composed of three units: one was devoted to consultation and the two others specialized in either hormonal or hemodynamic evaluations. In the three units, the same comprehensive evaluation and management was performed, using the same investigation algorithm and the same computerized program databank, ARTEMIS (15). This database has been used since 1975 and was initially designed to replace the traditional handwritten medical

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Abbreviations and Acronyms

AF = atrial fibrillation
APA = aldosterone-producing adenoma
ARR = aldosterone to renin ratio
BP = blood pressure
CI = confidence interval
CT = computed tomographic
ECG = electrocardiogram/electrocardiographic
EHT = essential hypertension
HTN = hypertension
LVH = left ventricular hypertrophy
MI = myocardial infarction
OR = odds ratio
PA = primary aldosteronism

record. An expert system has been integrated to the data management system in order to provide additional information (complementary patient interrogation, biological or radiologic investigations, and so on). Answer rates to 12 mandatory questions regarding history and examination at first visit were >95% in 19,601 records (15). All patients in the study underwent a standardized protocol to measure blood pressure (BP) and biological and hormonal parameters. Standard BP tests were performed using mercury sphygmomanometer in the supine position after 10 min rest. One physician performed three consecutive measurements and the average of the last two measurements was then recorded. Semiautomatic noninvasive measurements of BP were performed by the Dinamap 1846SX device (Critikon Inc., Tampa, Florida). Ten automatic measurements were recorded on a printer before the standard measurement. The average of the last five measurements was considered as the value of BP obtained with this device.

Medications were withdrawn approximately two weeks before the evaluation (for spironolactone, at least six weeks) (16). In the presence of severe or symptomatic hypertension, the workup was made under antihypertensive medications known as poorly affecting measurements of plasma renin and aldosterone (16). In the case of suspected PA (i.e., low plasma renin concentration, high rates of plasma and urinary aldosterone, and elevated plasma aldosterone to plasma renin ratio [ARR]), patients underwent: 1) a suppression test that consisted of the measurement of plasma renin and aldosterone levels before and after the oral administration of 1 mg/kg weight of the converting enzyme inhibitor captopril (17), and 2) a computed tomographic (CT) scanning of the adrenal glands (3-mm slices) (16). In 15 subjects with equivocal CT findings, adrenal venous sampling was performed to evaluate whether one or both adrenal glands were producing aldosterone (18).

Study population. During this period, the diagnosis of PA was made in 124 patients. Adenomas (n = 65) were diagnosed when an adrenal tumor was observed by CT scan, together with evidence of functional autonomy or lateralization of adrenal aldosterone secretion. In patients with a family history of hypertension, genetic tests were performed to exclude inherited forms of hyperaldosteronism (mainly glucocorticoid-suppressible hyperaldosteronim) (19). An adenoma was confirmed surgically in 58 patients, but 7 other patients did not accept surgery and were treated by the aldosterone antagonist spironolactone, alone or associated with various other antihypertensive drugs. Idiopathic hyperaldosteronism was diagnosed in 59 patients whose CT scans showed unilateral or bilateral adrenal hyperplasia without any significant adenoma. These patients were treated with antihypertensive medication, mainly based on spironolactone (20). During the follow-up of this group (mean follow-up 13.6 ± 0.4 months), no change in diagnosis was reported and no patient experienced any cardiovascular complication. At the end of the follow-up, systolic BP was 137 ± 13 mm Hg and diastolic BP was 84 ± 9 mm Hg.

During the same period, the diagnosis of essential hypertension was made using the same diagnostic work-up in approximately 4,000 patients. For each case of PA, the software (15) randomly extracted from the database patients with essential hypertension matched for age (±5 years), gender, and systolic and diastolic BP (±2 mm Hg), on the theoretical basis of one case for four controls.

Finally, the clinical characteristics and cardiovascular events of the group of patients with PA were compared with those of 465 matched patients who underwent the same initial clinical and biological evaluation that lead to the diagnosis of essential hypertension (EHT). Criteria for ruling out secondary forms of hypertension involved constant measurements of plasma renin and aldosterone and duplex ultrasound of the renal arteries.

The medical records of the participants were reviewed independently by two investigators (P.M. and J.J.M.), who assessed whether any of the following major clinical events had occurred: MI, stroke, cardiac arrhythmias (originating from either atrium or ventricle), as described elsewhere (21). Arrhythmias were counted as such when episodes of resented palpitations were documented by either conventional 12-lead surface electrocardiogram (ECG) or 24-h ECG recording (Holter). Criteria for left ventricular hypertrophy (LVH) either by ECG or echocardiography have been reported elsewhere (22). Silent myocardial ischemia noted on classical ECGs, stable or transient angina pectoris, atypical chest pain, intermittent symptoms possibly related to transient ischemic attacks were excluded from the statistical evaluation. All these parameters were collected at entry and stored in the database before any diagnosis of PA. The events were finally confirmed at the end of the diagnostic workup by a committee composed of three physicians independent of the department and blinded for the diagnosis.

Statistical analysis. Selection of the controls was computerized on a large database, ARTEMIS (15), and was automatically and randomly performed in respect to our criteria (age, gender, and BP) up to four subjects, if existing in the database. This "blinded" procedure limited potential selection bias but resulted in the absence of knowing which controls were allocated to which case, that is to say, that only non-paired procedures could be used for data analysis.

All results are expressed as a mean values ± SD. Univariate analysis allowed screening of potential predictors of PA. The Student *t* test was used for a quantitative variable and chi-square or Fisher exact test for qualitative or semiquantitative variables. The risk of cardiovascular complications was expressed in terms of odds ratio (OR) ±95% confidence interval (CI). In multiparametric logistic regression analysis, considering a history of MI, stroke, or AF as response variables, we included in the model factors significantly ($p < 0.05$) associated in univariate analysis with those three parameters. No parameter was forced in the model. Age, systolic BP, diastolic BP, plasma glucose, potassium, and total cholesterol were expressed as quantitative variables, whereas gender, smoking, PA, and EHT were expressed as dummy variables. Because the study was begun in 1997, low-density lipoprotein and high-density lipoprotein cholesterol, glycated hemoglobin, or other biological parameters were excluded from the study because they were not systematically determined in each individual. Analyses were performed with SPSS software version 11.0 (SPSS Inc., Chicago, Illinois) under Windows XP (Microsoft, Redmond, Washington). All the Student *t* tests were general normal non-paired tests with a 0.05 significance level.

RESULTS

Clinical characteristics of the population. Clinical and biological data of the PA patients and their EHT controls are summarized in Tables 1 and 2. By definition, cases and controls were similar in age (52 ± 10 years), gender (67% vs. 63% male, respectively), systolic BP (176 ± 23 mm Hg vs. 174 ± 20 mm Hg, respectively) and diastolic BP (107 ± 14 mm Hg vs. 106 ± 14 mm Hg, respectively). Of the remaining parameters, plasma total cholesterol was significantly higher in the EHT group (5.9 ± 1.1 mmol/l vs. 5.4 ± 0.9 mmol/l in the PA group; $p < 0.0004$). Past or current smoking habits and serum glucose did not differ.

As expected, patients with PA had lower serum potassium than controls (3.5 ± 0.3 mmol/l vs. 4.4 ± 0.3 mmol/l, respectively; $p < 0.0001$), whereas serum creatinine was comparable (92 ± 24 μmol/l vs. 87 ± 36 μmol/l respectively, p = NS). Similarly, urinary potassium, plasma aldosterone, aldosterone/renin ratio, and urinary aldosterone were significantly higher in the PA group than in the EHT controls (Table 2).

Rate of cardiovascular events. A history of stroke was reported in 16 patients with PA and in 16 patients with EHT (12.9% vs. 3.4%; OR = 4.2; 95% CI 2.0 to 8.6). The etiology was clearly ischemic in 11 of the PA group and in 9 patients with EH (Table 3). Univariate analysis indicated that the group of patients with a history of stroke was older ($p < 0.0005$) and had a higher systolic BP ($p < 0.02$) and serum creatinine ($p < 0.005$). In addition, the prevalence of diabetes, hypercholesterolemia, and ECG left ventricular hypertrophy was higher in patients with a history of stroke when compared with subjects free from cerebrovascular events ($p < 0.0005$, $p < 0.0005$, and $p < 0.002$, respectively). Multivariate analysis indicated that parameters independently associated with a history of stroke were age ($p = 0.004$), Sokolow-Lyon index ($p = 0.003$), and the presence of PA ($p = 0.0003$).

Table 1. Clinical Characteristics and Risk Factors Parameters of Primary Aldosteronism Patients and Controls

	Primary Aldosteronism (n = 124)	Essential Hypertension (n = 465)	p Value
Age (yrs)	52 ± 10	52 ± 10	NS
Men/women (%)	67/33	63/37	NS
SBP (mm Hg)	176 ± 23	174 ± 20	NS
DBP (mm Hg)	107 ± 14	106 ± 14	NS
Heart rate (beats/min)	72 ± 8	72 ± 10	NS
Current or past smokers (%)	42	44	NS
Serum glucose (mmol/l)	6.0 ± 1.3	5.9 ± 1.9	NS
Total cholesterol (mmol/l)	5.4 ± 0.9	5.9 ± 1.1	0.0004

Values expressed as mean ± SD.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

A history of non-fatal MI was diagnosed in five patients with PA and in three patients with EHT (4.0% vs. 0.6%; OR = 6.5; 95% CI 1.5 to 27.4). Patients with a history of MI were significantly older ($p < 0.01$) and were more likely to have PA ($p < 0.005$). These two parameters were still independently associated with a history of MI in multivariate analysis ($p = 0.008$ and $p = 0.005$, respectively).

A history of AF was diagnosed in 10 patients with PA and in 3 patients with EHT (7.3% versus 0.6%; OR = 12.1; 95% CI 3.2 to 45.2). In multivariate analysis, including parameters significantly associated with the presence of AF, are three remaining factors: age ($p < 0.005$), duration of hypertension ($p < 0.01$), and the presence of PA ($p < 0.001$). All of these factors are independently associated with a history of AF.

Electrocardiographic as well as echocardiographic LVH was significantly more frequent in the PA group than in the EHT group (32% vs. 14% [$p < 0.001$] for ECG LVH, respectively, and 34% vs. 24% [$p < 0.01$] for echocardiography, respectively).

Comparison between subtypes of PA. Of the 124 patients with PA, 65 had adenomas and 59 had bilateral adrenal hyperplasia. The two subgroups were similar in age, BP, cardiovascular risk factors, serum potassium, and prevalence of cardiovascular events (data not shown). However, APA had a more pronounced hormonal profile of hyperaldosteronism than hyperplasia, with a higher serum aldosterone (360 ± 193 pg/ml vs. 259 ± 137 pg/ml, respectively; $p = 0.01$) and a higher aldosterone/renin ratio (114 ± 103 vs. 72 ± 67, respectively; $p = 0.01$).

Fifty-eight patients (out of 65 with adenomas) underwent surgery. Although almost all patients had improved control of BP after surgery, long-term (mean follow-up 13.6 ± 0.4 months) cure rate (BP <140/90 mm Hg without drug) with unilateral adrenalectomy for APA was 43% in this study (25 of 58). Seventeen patients were normalized (BP <140/90

Table 2. Biological Characteristics of Primary Aldosteronism Patients and Controls

	Primary Aldosteronism (n = 124)	Essential Hypertension (n = 465)	p Value
Serum potassium (mmol/l)	3.5 ± 0.3	4.4 ± 0.3	0.0001
Serum creatinine (μmol/l)	92 ± 24	87 ± 36	NS
Urinary potassium (mmol/24 h)	80 ± 37	63 ± 25	0.0003
Active plasma renin (pg/ml)	4.7 ± 2.6	17.5 ± 15.3	0.0001
Plasma aldosterone (pg/ml)	374 ± 174	116 ± 60	0.0001
Aldosterone/renin ratio	94 ± 90	11 ± 10	0.0001
Urinary aldosterone (μg/24 h)	34 ± 17	16 ± 6	0.01

Values expressed as mean ± SD.

mm Hg under drug treatment) and 16 patients were uncontrolled at the end of the follow-up (mean BP 153 ± 2/91 ± 2 mm Hg). All patients were normokaliemic after surgery.

DISCUSSION

This study has shown that patients presenting with PA from either aldosterone-producing adenoma or bilateral adrenal hyperplasia subtype have a significantly higher rate of cardiovascular events than the matched EHT patients. To our knowledge, this investigation is the first to indicate that both subtypes of PA are substantially and equally complicated, particularly owing to an unusual rate of cardiovascular complications including arrhythmia.

Rate of cardiovascular events in patients with PA. In the past, experimental models of hypertension have shown that excess aldosterone induces severe injury in the heart, brain, and kidneys independent of BP level and that pharmacological antagonists of aldosterone or adrenalectomy markedly reduced myocardial injury, cerebral hemorrhage, and renal vascular disease (see review in Rocha and Stier [23]). In clinical studies (5,9–11), no comparable results have been reported, either because bilateral adrenal hyperplasia was excluded from the analysis (6,9,11) or the investigation did not include a control population (10,11). In the work by Takeda et al. (9), which constituted the largest case-control study of PA, EHT controls were matched for age and gender, but not for BP level. Thus, the role of high BP on the mechanism of cardiovascular complications could not be excluded.

In our institution, we performed a specific workup to spot patients having secondary forms of hypertension. Hence, all patients were diagnosed with the same hormonal and radio imaging protocols (CT scanning and in case of doubt, adrenal venous sampling) (15). As a consequence, between January 1997 and December 1999, all of the 5,500 patients were studied consecutively and homogeneously, and the 124 PA cases were diagnosed and cured by the same physicians during this period. The BP measurements were made using the same methodology in the different units of the department. The selection of the subjects as well as the statistical evaluation was performed from the same database in order to minimize any selection bias. Although no 24-h ambulatory BP measurements were constantly performed, it appears that relatively severe hypertension was found in all patients with systolic BP of 176 ± 23 mm Hg and diastolic BP of 107 ± 14 mm Hg and a predominance of younger males (52 ± 10 years; 67%). These findings agree with previous reports that emphasized such elevated BP (2,3,6). Interestingly, no predominance of one subtype of PA was found (65 APA vs. 59 hyperplasia). Hence, bilateral adrenal hyperplasia should not be considered as a minor form of PA.

Our group was aware of the risk of inflating the diagnosis of PA by considering only the ARR level (24). We constantly required an elevated plasma aldosterone level before considering the ARR as abnormal. Applying this strict protocol together with rigorous conditions for measurements of plasma renin and aldosterone may explain the small proportion of normokalemic PA patients in this cohort (3 of 124) by contrast with others (25).

In the present study, both patients with documented APA and idiopathic aldosteronism were considered for comparing the rate of cardiovascular events to matched EHT patients. Furthermore, it appeared relevant to note

Table 3. Rate of Cardiovascular Events and Cardiac Structure in Primary Aldosteronism Patients and Controls

	Primary Aldosteronism (n = 124)	Essential Hypertension (n = 465)	Odds Ratio (95% CI)	p Value
Stroke (%)	12.9	3.4	4.2 (2.0–8.6)	<0.001
Myocardial infarction (%)	4.0	0.6	6.5 (1.5–27.4)	<0.005*
Atrial fibrillation (%)	7.3	0.6	12.1 (3.2–45.2)	<0.0001*
Echocardiographic LVH (%)	34	24	1.6 (1.1–2.5)	<0.01
Electrocardiographic LVH (%)	32	14	2.9 (1.8–4.6)	<0.001

*Fisher exact test.
CI = confidence interval; LVH = left ventricular hypertrophy.

whether or not this rate differed between both subtypes of PA. We found higher percentage of strokes (either hemorrhagic or infarction) in our PA population than in controls (12.9 % vs. 3.4%; $p < 0.001$), confirming all previous studies (10,11). However, we observed an unusual rate of cardiac complications in PA patients. Myocardial infarction was significantly more frequent in PA group than in controls (4.0% vs. 0.6%; $p < 0.005$). Similarly, an impressive rate of AF was found in patients with PA (7.3% vs. 0.6% in PA and EHT patients, respectively; $p < 0.0001$). This frequency of cardiac and arrhythmic events had never been previously reported. To our knowledge, only two case reports noted association of cardiac arrhythmias and PA (AF [13] and ventricular fibrillation [14]). Regarding the incidence of MI, Takeda et al. (9) found identical rates of MI in PA and EHT populations.

Relative contribution of BP and hyperaldosteronism to cardiovascular complications and limitations of the study. In this investigation, both patients with documented APA and idiopathic aldosteronism were matched to EHT for gender, age, and most importantly, BP. Hence, within the limitations of the methodology of this case-control study, the rate of cardiovascular events has been studied independently from BP level, suggesting that aldosterone alone has a specific role in the occurrence of cardiovascular complications. The results of multiple regression analysis confirm this possibility and, furthermore, do not suggest that hypokalemia played a crucial role in the pathophysiology of such complications.

Hypertensive heart disease associated with LVH is known to be associated with an increase of plasma aldosterone and an increase of cardiac collagen volume fraction and fibrosis, as derived from experimental and clinical works (26,27). Aldosterone excess and LVH are known to independently increase fibrosis within the heart (28–30). The underlying mechanisms are incompletely understood; recently, the role of endothelin pathway had been highlighted (31). In our study, PA patients had, independent of BP, a higher rate of LVH than the EHT controls. Thus it seems logical to suggest that aldosterone and/or cardiac fibrosis might play a role on the occurrence of LVH and possible resulting cardiac complications (28,29). Minor or no (32) evidence of left ventricular dysfunction has been reported in PA.

Regarding arrhythmias, experimental models of congestive heart failure have shown that cardiac fibrosis might be at the origin of these alterations. Cardiac fibrosis often predominate in the left atrium and may be mediated more by the renin-angiotensin pathway than by mechanical stretch (33–35). Recently, the Randomized ALdactone Evaluation Study (RALES) demonstrated that in patients with congestive heart failure, adjunction of spironolactone to usual medical therapy significantly reduced both cardiac mortality and sudden cardiac death, which is known to be partly due to arrhythmic disorders (36,37). Thus, the weight of evidence suggests that excess aldosterone might be a risk factor for arrhythmic disorders occurring either via LVH or via cardiac fibrosis or a combination of both (38,39). In the particular case of AF, an increased incidence of reentry mechanisms has been also reported (38–40). In practice, such clinical pictures raise the issue of differentiating strokes occurring in PA patients with and without AF, the latter potentially caused by aldosterone-induced local microangiopathy. These diagnoses are difficult to perform in clinical practice, also because the role of aldosterone-induced hemorrhagic mechanisms cannot be excluded in PA patients (40,41).

Although LVH and myocardial fibrosis would explain the increase in AF, it may be more difficult to explain the increase in MI and stroke on this basis. However, it has been shown that aldosterone may be associated with endothelial dysfunction independent of BP and to produce microvascular inflammation in the brain but also the myocardium (23). On the other hand, recent studies have noticed that chronic excess aldosterone experimentally produces an increase of aortic stiffness, independent of BP. The increased stiffness is reversed under administration of the specific alosterone antagonist eplerenone (42). Both in subjects with hypertension (43) and in subjects with congestive heart failure (44), a positive, significant, and independent association has been reported between high plasma aldosterone and high arterial stiffness. Increased arterial stiffness, an important feature of hyperaldosteronism, is known to be a strong and independent predictor of MI (21).

Finally, the interpretation of the interactions among hyperaldosteronism, BP, and cardiovascular complications should be done cautiously because this case-control study is retrospective with potential selection bias. Furthermore, because of the design of our study with computerized and random selection of the controls, only non-paired procedures were used for data analysis. Time-dependent relationship should be important to evaluate in order to establish cause to effect links between PA and the occurrence of cardiovascular events. Nevertheless, for ethical reasons, such a prospective study should be difficult to conduct.

In conclusion, the present study has shown that patients presenting PA experienced more cardiovascular events than did EHT controls, independent of BP. Cardiovascular complications (including arrhythmic) are significantly increased in both subtypes of PA. Consequently, PA should be more carefully detected in order to avoid such complications.

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