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

Paul Milliez, MD,* Xavier Girerd, MD, PtD,† Pierre-François Plouin, MD,‡ Jacques Blacher, MD, PtD,§ Michel E. Safar, MD,§ Jean-Jacques Mourad, MD, PtD∥

Paris and Bobigny, France

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 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...
Cardiovascular Events and Primary Aldosteronism

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

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 hyperaldosteronism) (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 resected 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 semi-quantitative 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 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 EHT (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).

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, there 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>
<thead>
<tr>
<th>Table 1. Clinical Characteristics and Risk Factors Parameters of Primary Aldosteronism Patients and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Aldosteronism</strong> (n = 124)</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Men/women (%)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Current or past smokers (%)</td>
</tr>
<tr>
<td>Serum glucose (mmol/l)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. DBP = diastolic blood pressure; SBP = systolic blood pressure.
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 normokalemic 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 events than the matched EHT patients. To date, aldosterone-producing adenoma or bilateral adrenal hyperplasia should not be considered as a minor form of PA.

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.

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 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.

| 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 (1.9–4.6) | <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 be associated with an increase of 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).

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.

Reprint requests and correspondence: Dr. Michel Safar, Centre de Diagnostic, Hôtel-Dieu, 1, Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France. E-mail: michel.safar@htd.aphp.fr.

REFERENCES
