Cardiovascular Outcomes in Patients With Primary Aldosteronism After Treatment

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Background: Experimental and human studies demonstrate that long-term exposure to elevated aldosterone levels results in cardiac and vascular damage.

Methods: We investigated long-term cardiovascular outcomes in patients with primary aldosteronism after surgical or medical treatment. Fifty-four patients with or without evidence of adrenal adenomas were prospectively followed up for a mean of 7.4 years after treatment with adrenalectomy or spironolactone. Patients with primary aldosteronism were compared with patients with essential hypertension and were treated to reach a blood pressure of less than 140/90 mm Hg. The main outcome measure was a combined cardiovascular end point comprising myocardial infarction, stroke, any type of revascularization procedure, and sustained arrhythmias.

Results: At baseline, the prevalence of cardiovascular events was greater in primary aldosteronism (35%) than in essential hypertension (11%) (odds ratio, 4.61; 95% confidence interval, 2.38-8.95; P < .001), with odds ratios of 4.93, 4.36, and 2.80 for sustained arrhythmias, cerebrovascular events, and coronary heart disease, respectively. Blood pressure during follow-up was comparable in the primary aldosteronism and essential hypertension groups. Ten patients in the primary aldosteronism group and 19 in the essential hypertension group reached the primary end point (P = .85). Cox analysis indicated that older age and longer duration of hypertension were factors independently associated with the cardiovascular end point. Cardiovascular outcome was comparable in patients with aldosteronism treated with adrenalectomy vs aldosterone antagonists (P = .71).

Conclusion: Primary aldosteronism is associated with a cardiovascular complication rate out of proportion to blood pressure levels that benefits substantially from surgical and medical treatment in the long term.

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Primary aldosteronism is an endocrine disorder associated with hypertension, hypokalemia, and suppressed plasma renin levels in which inappropriate aldosterone secretion is caused by an adrenal adenoma or bilateral adrenal hyperplasia. Recent evidence indicates a greater frequency of this disorder in hypertensive patients than the previously accepted prevalence of approximately 1%. Such increased prevalence may result from more effective identification of this disease. Because initial descriptions of patients with primary aldosteronism reported a low incidence of cardiovascular events, this form of hypertension has traditionally been considered relatively benign. More recent views, however, suggest that long-term exposure to elevated aldosterone levels might result in substantial cardiovascular damage independent of blood pressure. Animal studies demonstrate that exposure to excess levels of aldosterone, under appropriate dietary salt conditions, induces myocardial fibrosis, and evidence of aldosterone-related cardiac damage has been obtained from clinical trials conducted in patients with heart failure treated with mineralocorticoid receptor antagonists, with a significant decrease in the mortality rate. Although many surrogate cardiovascular end points as well as evidence of an increased rate of cardiovascular events have been reported in cross-sectional investigations conducted in patients with primary aldosteronism, longitudinal evidence is limited to 1 retrospective case-control study. The present study investigates long-term cardiovascular outcomes in patients with tumoral or idiopathic disease who were followed up after either adrenalectomy or treatment with spironolactone.

Methods

Study Population

We conducted a prospective study in 54 consecutive patients who received a diagnosis of primary aldosteronism between January 1, 1994, and December 31, 2001. Recruitment of...
patients, criteria used for diagnosis, and methods of follow-up have been described in a previous publication. Patients were referred to the hypertension clinic of the University of Udine for evaluation of their hypertensive state. Blood pressure was measured using a mercury sphygmomanometer, and hypertension was diagnosed according to current guidelines. All patients seen at the clinic were screened with extensive testing to define the cause of hypertension. Antihypertensive drugs were discontinued a minimum of 2 weeks before diagnostic assessment. No patient was taking aldosterone antagonists before the study.

Primary aldosteronism was screened for by the demonstration of an increased plasma aldosterone to active renin ratio (≥20) in the presence of a plasma aldosterone level greater than 150 pg/mL (15 ng/dL) (to convert to picomoles per liter, multiply by 27.74), and the diagnosis was confirmed by the lack of aldosterone suppression (values of ≥50 pg/mL [≥5 ng/dL]) after an intravenous saline load (2 L of 0.9% saline infused during 4 hours). This test is highly effective in the distinction of primary aldosteronism from low-renin essential hypertension. Measurements were performed in combination with a normal sodium diet, and 24-hour urinary sodium excretion was assessed in all the patients. Renal artery stenosis was excluded in all the patients by means of angiographic computed tomography (CT) and, in patients with measurable active renin concentrations (>2.5 pg/mL [to convert to picomoles per liter, multiply by 0.0237]), renal angiography. A plasma potassium concentration of 3.5 mEq/L or less (to convert to millimoles per liter, multiply by 1.0) was corrected by means of oral supplementation before assessment of the aldosterone to renin ratio and the saline suppression test. Differentiation between an adrenal adenoma and idiopathic aldosteronism was obtained using high-resolution CT followed by selective adrenal vein sampling (n=14) or adrenal scintigraphy (n=47) performed using iodocholesterol 131 with dexm ethasone suppression. In all the patients who underwent adrenalectomy, an adenoma was confirmed by histologic examination and by a significant decrease in aldosterone concentrations. Patients were treated with unilateral adrenalectomy or spironolactone (30-300 mg/d; mean, 121 mg/d), and in all the patients, treatment was followed by either normalization of or a significant reduction (a decrease >20% or use of fewer antihypertensive drugs) in blood pressure. At baseline, patients with primary aldosteronism were compared with 323 patients with essential hypertension recruited by frequency matching after specification of the inclusion criteria to avoid age, sex, body mass index (calculated as weight divided by height in meters squared), and estimated duration of hypertension as potential confounders. In these patients, secondary causes of hypertension were excluded after drug washout.4,11 Informed consent was obtained from all patients, and the protocol was approved by the institutional review board of the University of Udine.

Cardiovascular status was assessed in patients with primary aldosteronism and essential hypertension via a thorough medical record review and was confirmed at the end of the diagnostic workup. The workup included history, physical examination, electrocardiography (ECG), echocardiography, and ultrasound examination of the abdominal aorta and the carotid, iliac, and femoral arteries. Additional assessments, including exercise stress testing, myocardial perfusion scanning, coronary arteriography, 24-hour ECG recording, and brain CT or magnetic resonance imaging, were performed when appropriate. All medical records were reviewed independently by 2 investigators (C.C. and L.A.S.) masked to the diagnosis of hypertension to assess previous occurrences of the following clinical events: myocardial infarction or reversible myocardial ischemia (angina pectoris or silent ischemia), stroke or transient ischemic attacks, sustained arrhythmias, and leg pain on exertion (claudication). All the retrospective diagnoses were confirmed by documentation of previous ECG changes, 24-hour ECG recording, significant elevation of the serum creatinine kinase MB fraction or troponin level, CT or magnetic resonance imaging of the brain, vascular ultrasonography, or arteriography of the lower limbs.

FOLLOW-UP AND CARDIOVASCULAR OUTCOMES

All 54 patients with primary aldosteronism and 108 patients with essential hypertension (obtained from the 323 individuals included in the baseline comparison) were prospectively followed up. After inclusion of each new patient with primary aldosteronism, 2 consecutive matched patients were selected for the longitudinal study. Twenty-four of 29 patients with adrenal adenomas underwent adrenalectomy; of the remaining 5 patients, 2 had bilateral adenomas and 3 refused surgery and were treated with spironolactone. Treatment with spironolactone was started at a dosage of 100 mg/d and was titrated to reach the target blood pressure. Clinical assessment and laboratory tests were performed 1, 3, and 6 months after enrollment and every 12 months thereafter. Dynamic 24-hour ECG recording was reassessed at 6 months and at 3, 6, 9, and 12 years to detect asymptomatic arrhythmic events and ST-segment changes. At each visit, antihypertensive drug therapy was adjusted according to the physician’s judgment to achieve a blood pressure less than 140/90 mm Hg. Use of all antihypertensive agents was permitted. The cardiovascular status was reassessed at all periodic visits, with a mean follow-up of 7.4 years. A composite cardiovascular end point comprising myocardial infarction, stroke, any type of revascularization procedure, and sustained arrhythmias was designated as the primary outcome.

STATISTICAL ANALYSIS

Continuous data are expressed as mean (SD) unless otherwise indicated. Variables with a skewed distribution were analyzed after logarithmic transformation. Characteristics of the study participants were compared among groups using analysis of covariance. Categorical variables were compared using the χ2 test. In a multivariate logistic regression analysis, we included the variables significantly associated with a history of cardiovascular events in univariate analysis. Data from the date of inclusion through the end of follow-up for all 54 patients with primary aldosteronism and 108 with essential hypertension were included in the analysis of cardiovascular outcomes. Actuarial analysis was applied to assess cardiovascular outcomes, and the log-rank test was used to compare the distributions of time with the cardiovascular end point. The Cox proportional hazards model was fitted to the data with all the significant risk factors to provide information on the hazard ratios (HRs). All tests for significance and resulting P values were 2-sided, with a level of significance of P<.05.

RESULTS

BASELINE CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS

Adrenal adenomas were demonstrated in 29 of 54 patients (54%) with primary aldosteronism, whereas the remaining 25 patients (46%) had idiopathic aldosteronism. Patients with primary aldosteronism and essential hypertension (n=323) had comparable blood pressure,
estimated duration of hypertension, plasma glucose levels, plasma lipid levels, smoking frequency, and alcohol intake (Table 1). As expected, patients with primary aldosteronism had higher plasma aldosterone levels and lower plasma potassium and renin levels than patients with essential hypertension.

A history of cardiovascular events was reported in 34 patients (11%) with essential hypertension and in 19 (35%) with primary aldosteronism, respectively (all nonsignificant). On univariate analysis, the factors associated with occurrence of the primary end point (HR, 0.93; 95% CI, 0.42-2.02; P = .85) (Figure). Myocardial infarction, stroke, revascularization procedures, and sustained arrhythmias occurred in 1 (2%), 2 (4%), 3 (6%), and 4 (7%) of the patients with primary aldosteronism and in 2 (2%), 3 (3%), 5 (5%), and 9 (8%) of the patients with essential hypertension, respectively (all nonsignificant). On univariate analysis, the factors associated with occurrence of the primary end point in the primary aldosteronism and essential hypertension groups were age (27% of patients aged

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Essential Hypertension (n=323)</th>
<th>Adrenal Adenoma (n=29)</th>
<th>Idiopathic Aldosteronism (n=25)</th>
<th>All Patients (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52 (9)</td>
<td>54 (12)</td>
<td>52 (13)</td>
<td>53 (12)</td>
</tr>
<tr>
<td>Sex, F/M, No.</td>
<td>103/220</td>
<td>8/21</td>
<td>8/17</td>
<td>16/38</td>
</tr>
<tr>
<td>BMI</td>
<td>28.1 (3.1)</td>
<td>28.7 (3.8)</td>
<td>28.4 (3.7)</td>
<td>28.6 (3.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>166 (18)</td>
<td>167 (14)</td>
<td>166 (19)</td>
<td>167 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>103 (8)</td>
<td>103 (8)</td>
<td>103 (9)</td>
<td>103 (9)</td>
</tr>
<tr>
<td>Estimated duration of hypertension, y</td>
<td>10 (6)</td>
<td>10 (7)</td>
<td>9 (7)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Current smoking, No. (%)</td>
<td>81 (25)</td>
<td>7 (24)</td>
<td>8 (32)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>32 (8)</td>
<td>33 (6)</td>
<td>36 (10)</td>
<td>34 (9)</td>
</tr>
<tr>
<td><strong>Laboratory variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose, mg/dL</td>
<td>90 (14)</td>
<td>86 (16)</td>
<td>86 (16)</td>
<td>88 (16)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>208 (43)</td>
<td>201 (41)</td>
<td>195 (43)</td>
<td>198 (42)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49 (14)</td>
<td>51 (16)</td>
<td>48 (15)</td>
<td>49 (16)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>131 (80)</td>
<td>104 (60)</td>
<td>114 (65)</td>
<td>109 (62)</td>
</tr>
<tr>
<td>Plasma sodium, mEq/L</td>
<td>140 (3)</td>
<td>141 (2)</td>
<td>141 (3)</td>
<td>141 (2)</td>
</tr>
<tr>
<td>Plasma potassium, mEq/L</td>
<td>4.2 (0.4)</td>
<td>3.2 (0.4)</td>
<td>3.3 (0.5)</td>
<td>3.2 (0.4)</td>
</tr>
<tr>
<td>Plasma aldosterone, pg/mL [ng/dL]</td>
<td>154 (99) [15.4 (9.9)]</td>
<td>260 (181) [28.0 (18.1)]</td>
<td>230 (206) [23.0 (20.6)]</td>
<td>246 (191) [24.6 (19.1)]</td>
</tr>
<tr>
<td>Plasma active renin, pg/mL</td>
<td>9.4 (10.9)</td>
<td>4.7 (5.7)</td>
<td>5.0 (7.5)</td>
<td>4.8 (6.4)</td>
</tr>
<tr>
<td>Plasma aldosterone to active renin ratio</td>
<td>16.6 (1.9)</td>
<td>56.2 (3.8)</td>
<td>45.6 (3.1)</td>
<td>52.3 (3.5)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein.

a Blood pressure was measured after appropriate washout of antihypertensive drugs.
b Plasma potassium levels were lower in the primary aldosteronism group than in the essential hypertension group (P < .001).
c Plasma active renin levels were lower in patients with primary aldosteronism than in patients with essential hypertension (P < .001).
d Values were measured before correction with oral supplementation.

### TREATMENT AND FOLLOW-UP

Twenty-four patients with primary aldosteronism underwent adrenalectomy, and 30 (3 with adrenal adenoma and 25 with idiopathic aldosteronism) were treated with a spironolactone-based regimen. The mean duration of follow-up was 7.4 years. No patient discontinued the study, and adherence at the yearly visits was 93% in the primary aldosteronism group and 89% in the essential hypertension group. Of 21 men treated with spironolactone, 4 (19%) had clinically relevant gynecomastia that responded well to a reduction in dosage. In the primary aldosteronism group and 89% in the essential hypertension group. Of 21 men treated with spironolactone, 4 (19%) had clinically relevant gynecomastia that responded well to a reduction in dosage. In the primary aldosteronism group and 89% in the essential hypertension group. Of 21 men treated with spironolactone, 4 (19%) had clinically relevant gynecomastia that responded well to a reduction in dosage. In the primary aldosteronism group and 89% in the essential hypertension group. Of 21 men treated with spironolactone, 4 (19%) had clinically relevant gynecomastia that responded well to a reduction in dosage. In the primary aldosteronism group and 89% in the essential hypertension group. Of 21 men treated with spironolactone, 4 (19%) had clinically relevant gynecomastia that responded well to a reduction in dosage. In the primary aldosteronism group and 89% in the essential hypertension group.
Primary aldosteronism is a simple clinical model to assess possible detrimental effects of elevated aldosterone levels on the cardiovascular system because, in this condition, its effects are isolated from those of the renin-angiotensin axis. Although left ventricular hypertrophy, impaired diastolic function, abnormalities of blood vessels, and endothelial dysfunction have been reported in patients with this endocrine disorder, clinical evidence supporting an association between primary aldosteronism and cardiovascular events is limited to cross-sectional studies that have yielded variable results.

This study examined the prevalence of cardiovascular events in patients with tumoral and idiopathic aldosteronism and the long-term incidence of cardiovascular outcomes after treatment. The results demonstrate that cardiovascular complications are more prevalent in patients with primary aldosteronism than in patients with essential hypertension and comparable cardiovascular risk profiles. This difference in the rate of cardiovascular events is reversed by removing the effects of excess aldosterone with either adrenalectomy or treatment with aldosterone antagonists.

Primary aldosteronism and essential hypertension (OR, 4.36; 95% CI, 1.49-12.80; P = .007) were associated with a better cardiovascular outcome. A proportional hazards model was fitted with the significant risk factors as categorical variables showing that age older than 52 years (OR, 2.80; 95% CI, 1.30-6.06; P = .004), whereas no significant associations were found with sex, body mass index, plasma lipid levels, diagnosis of primary aldosteronism, or specific drug types taken during follow-up. Potentially relevant factors were included in a multivariate model to predict determinants of outcome. Stepwise logistic regression analysis showed that younger age (as a continuous variable, P = .01) and shorter duration of hypertension (as a continuous variable, P = .02) were associated with a better cardiovascular outcome. A proportional hazards model was fitted with the significant risk factors as categorical variables showing that age older than 52 years (HR, 1.61; 95% CI, 1.17-2.28; P = .01) and a history of hypertension lasting more than 10 years (HR, 1.52; 95% CI, 1.11-2.15; P = .03) were significant adverse factors. Actuarial analysis of patients treated with adrenalectomy vs aldosterone antagonists did not reveal significant differences in the occurrence of the combined cardiovascular end point (HR, 1.26; 95% CI, 0.36-4.44; P = .71) (Figure).

### Table 2. Prevalence of Cardiovascular Events in the Study Population

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Essential Hypertension (n=323)</th>
<th>Adrenal Adenoma (n=29)</th>
<th>Idiopathic (n=25)</th>
<th>All Patients (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction or reversible ischemia</td>
<td>27 (8)</td>
<td>6 (21)</td>
<td>5 (20)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>9 (3)</td>
<td>3 (10)</td>
<td>3 (12)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Sustained arrhythmias</td>
<td>11 (3)</td>
<td>5 (17)</td>
<td>3 (12)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>8 (2)</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>16</td>
<td>12</td>
<td>28</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated.
*The prevalence of myocardial infarction or reversible ischemia (angina pectoris and silent ischemia) was higher in patients with primary aldosteronism than in patients with essential hypertension (odds ratio [OR], 2.80; 95% confidence interval [CI], 1.30-6.06; P = .007).
*The prevalence of stroke or transient ischemic attack was higher in patients with primary aldosteronism than in patients with essential hypertension (OR, 4.36; 95% CI, 1.49-12.80; P = .004).
*The prevalence of sustained arrhythmias was higher in patients with primary aldosteronism than in patients with essential hypertension (OR, 4.93; 95% CI, 1.89-12.91; P < .001).
*The prevalence of peripheral arterial disease was not significantly different in the primary aldosteronism and essential hypertension groups (P = .21).
tions increase arterial stiffness and induce endothelial dysfunction, effects that might be related to the increased rates of sustained arrhythmias and coronary heart disease, respectively. Also, the prevalence of cardiovascular complications was comparable in patients with tumoral or idiopathic disease, showing that those with both subtypes are at increased risk. These findings support the contention that elevated aldosterone levels contribute to cardiovascular damage independent of blood pressure.

To our knowledge, this is the first prospective study to examine the long-term cardiovascular outcomes of patients with primary aldosteronism after treatment. Our long-term follow-up establishes that in this condition, the incidence of cardiovascular events does not differ from that of essential hypertension when the effects of excess aldosterone are permanently removed. Stepwise logistic regression and multivariate Cox analyses indicate that younger age and shorter duration of hypertension are independent predictors of better cardiovascular outcome, underscoring the importance of a timely correction of this disorder. Furthermore, the Kaplan-Meier curves did not differ in patients with primary aldosteronism treated with adrenalectomy or spironolactone, showing that these treatments have comparable effects in this context.

The findings of the present study are in keeping with the results of the Randomized Aldactone Evaluation Study and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. These trials were prompted by the experimental demonstration of aldosterone-induced myocardial fibrosis and clinical evidence of abnormal myocardial texture and diastolic dysfunction in patients with primary aldosteronism. Consistently, mineralocorticoid receptor blockade has been shown to improve variables of diastolic function in hypertensive patients with diastolic heart failure. Therefore, it seems reasonable to suggest that elevated aldosterone levels induce cardiac fibrosis that, in turn, could explain the increased rates of sustained arrhythmias and possible myocardial ischemia. On the other hand, clinical studies indicate that excess aldosterone concentrations increase arterial stiffness and induce endothelial dysfunction, effects that might be related to the increased rate of coronary and cerebrovascular disease.

A limitation of this study could be the use of a variety of antihypertensive medications during follow-up, which might have affected the cardiovascular outcomes. A greater percentage of patients with essential hypertension received these drugs compared with patients with primary aldosteronism. This difference, however, should have determined better outcomes in the essential hypertension group, but this was not the case. Moreover, separate analysis of patients who were and were not taking specific types of drugs did not show a different rate of cardiovascular events.

The prevention of cardiovascular complications is a mandatory goal in patients with high blood pressure. Primary aldosteronism was once considered a rare disease, but recent evidence suggests that it might be the most common curable cause of hypertension. Therefore, despite a consensus not being reached yet, it might be worth considering broad screening by use of the aldosterone to renin ratio in every patient with high blood pressure. This study demonstrates that primary aldosteronism is associated with a prevalence of cardiovascular complications out of proportion to blood pressure that benefits substantially from treatment in the long term. In this view, adrenalectomy and aldosterone antagonists seem to be of considerable therapeutic value to the extent that, with adequate blood pressure control, they limit the progression of cardiovascular disease. These findings underline the importance of appropriate timing in the identification of this endocrine disorder to effectively prevent cardiovascular complications.

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