Long-term Renal Outcomes in Patients With Primary Aldosteronism

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Context Experimental animal studies indicate that exposure to increased aldosterone levels might result in renal damage, but the clinical evidence supporting this role of aldosterone is preliminary.

Objective To determine the long-term outcome of renal function in patients with primary aldosteronism after surgical or medical treatment.

Design, Setting, and Participants Prospective study conducted at an Italian university medical center among a consecutive sample of 50 patients who were diagnosed as having primary aldosteronism between January 1994 and December 2001 and who were followed up for a mean of 6.4 years after treatment with adrenalectomy or spironolactone. Patients with primary aldosteronism were compared with 100 patients with essential hypertension, matched for severity and duration of hypertension. All patients were treated with antihypertensive drugs to reach a target blood pressure of less than 140/90 mm Hg.

Main Outcome Measures Primary outcome measures were rates of change of glomerular filtration rate and albuminuria during follow-up. Detection of new-onset microalbuminuria and restoration of normal albumin excretion during follow-up were considered as secondary outcomes.

Results At baseline, glomerular filtration rate and albuminuria were higher in patients with primary aldosteronism than those with essential hypertension. The mean blood pressure during the study was 136/81 mm Hg in the primary aldosteronism group and 137/81 mm Hg in the essential hypertension group. Glomerular filtration rate and albuminuria declined during the initial 6-month period in both groups, with a change that was significantly greater ($P<.001$ for both variables) in patients with primary aldosteronism. Subsequent rate of decline of glomerular filtration was comparable in the 2 groups, whereas albuminuria did not progress in the remainder of the follow-up. Restoration of normal albumin excretion from microalbuminuria was significantly more frequent in primary aldosteronism than in essential hypertension ($P=.02$).

Conclusion In the majority of patients in this study, primary aldosteronism was characterized by partially reversible renal dysfunction in which elevated albuminuria is a marker of a dynamic rather than structural renal defect.

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PRIMARY ALDOSTERONISM IS A form of endocrine hypertension characterized by high blood pressure, hypokalemia, suppressed plasma renin activity, and inappropriate aldosterone secretion. Recent studies have reported a greater frequency of primary aldosteronism among patients with hypertension than the previously accepted prevalence of approximately 1%.[1,2] Such increased frequency may be the result of more effective identification of this condition due to widespread use of the aldosterone-renin ratio as a screening test.[3] Although primary aldosteronism is considered correctable with either removal of an adrenal adenoma or administration of mineralocorticoid receptor antagonists, in many cases, hypertension may persist after treatment.[4]

Primary aldosteronism has long been considered a relatively benign form of hypertension associated with low incidence of organ complications.[5] This has been generally ascribed to the suppression of the renin-angiotensin axis that occurs as a result of an aldosterone-generated volume expansion.[6] Recent experimental studies, however, suggest that long-term exposure to increased aldosterone levels might result in cardiovascular[7] and renal[8,9] structural damage, independent of the blood pressure level. Cardiovascular surrogate end points, including endothelial dysfunction, structural changes in resistance vessels, left ventricular hypertrophy, and impaired diastolic function, have been demonstrated in patients with primary aldosteronism,[10] and indirect evidence of aldosterone-related damage has been obtained from clinical trials conducted in patients with heart failure who were treated with mineralocorticoid receptor antagonists, with significant decrease in the mortality rate.[11,12] The clinical evidence of a role of aldosterone as a potential contributor to renal dysfunction is weaker than that which has emerged for

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the cardiovascular system and has been summarized in thorough reviews.[9,13,14] Studies performed in patients with diabetic nephropathy[15-17] and chronic kidney disease[18,19] suggest a beneficial effect of aldosterone antagonists on urinary protein excretion, and a recent study has demonstrated increased albuminuria in patients with primary aldosteronism compared with patients with essential hypertension.[20] This study was designed to test the hypothesis that the excess renal damage found in primary aldosteronism is mainly related to a functional and reversible hemodynamic adaptation of the kidney and that treatment of primary aldosteronism can improve renal dysfunction, reflecting correction of this functional abnormality. We investigated the short-term and long-term outcomes of renal function in patients with primary aldosteronism who were followed up after either surgical or medical treatment.

METHODS

Study Population

We conducted a prospective study in consecutive patients who received a diagnosis of primary aldosteronism between January 1994 and December 2001. Patients were referred to the hypertension clinic of the University of Udine, Udine, Italy, for evaluation of their hypertensive state. Blood pressure was measured by a mercury sphygmomanometer after each patient had been supine for at least 15 minutes. The average of 3 readings obtained in 5 minutes was recorded. Hypertension was diagnosed according to established guidelines when systolic blood pressure was 140 mm Hg or more and/or diastolic blood pressure was 90 mm Hg or more at least twice on 3 different visits. All patients seen at the clinic are screened with exhaustive testing to determine the cause of hypertension.[21] Predefined exclusion criteria were age younger than 25 years or older than 70 years, diabetes mellitus, impaired glucose tolerance (as established by an oral glucose test), renal failure with creatinine clearance of less than 30 mL/min (0.5 mL/s) per 1.73 m^2 of body surface area, proteinuria greater than 1.0 g/d, congestive heart failure, and presence of concomitant diseases that could affect renal function. Patients treated with antihypertensive drugs were withdrawn from treatment a minimum of 2 weeks before diagnostic assessment. β-Blockers, lipophilic calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers were withdrawn for 3 weeks.[22]

Primary aldosteronism was screened by the demonstration of an increased plasma aldosterone–active renin ratio (≥20)[23] in the presence of a plasma aldosterone concentration of more than 150 pg/mL, and the diagnosis was confirmed by the lack of aldosterone suppression following an intravenous saline load (2 L of 0.9% saline infused over 4 hours).[2] The suppression test result was considered positive when plasma aldosterone concentration was higher than 50 pg/mL after saline infusion. Plasma potassium concentrations of 3.5 mmoL/L or less were corrected by oral supplementation before assessment of the plasma aldosterone–active renin ratio and saline suppression test.[2]

Differentiation between adrenal adenoma and idiopathic aldosteronism was obtained by high-resolution computed tomography scan followed by selective adrenal vein sampling with measurements of both aldosterone and cortisol to ensure the adequacy of the cannulation (n=12) and/or adrenal scintigraphy with iodocholesterol performed under dexamethasone suppression (n=44). In all patients who underwent adrenalectomy, adenoma was confirmed histologically. Patients were treated by unilateral adrenalectomy or spironolactone (50-300 mg/d; mean, 123 mg/d) and treatment was followed by normalization (<140/90 mm Hg without the aid of antihypertensive agents except spironolactone [42%]) or significant reduction of blood pressure (decrease by more than 20% and/or fewer antihypertensive agents taken [58%]).

Patients with primary aldosteronism were compared with patients with essential hypertension who were recruited at our clinic using the same criteria as for patients with primary aldosteronism. After inclusion of each new case of primary aldosteronism, 2 consecutive patients with essential hypertension who were of the same sex and comparable age, body mass index, and estimated duration of hypertension were selected. In these patients, secondary causes of hypertension were excluded by thorough examination after appropriate drug washout.[21]

One hundred normotensive healthy individuals served as controls at baseline evaluation. These controls were selected from the general population of the same geographic area as the patients with hypertension by convenience sampling and individual matching, after specification of inclusion criteria to avoid age and sex as potential confounding variables. Normotensive controls were not taking any regular medications and did not have any concomitant disease. All participants in the comparison groups were admitted to our inpatient clinical unit to obtain 24-hour measurements, and the measurements were made under the same circumstances as for patients with primary aldosteronism. At baseline, all participants were allowed to maintain their usual diet. Written informed consent was obtained from all patients, and the protocol was approved by the ethical committee of the University of Udine.

Renal Function Studies

Both at baseline and during follow-up, patients were admitted to the inpatient clinical unit, where duplicate 24-hour urine samples were obtained for determination of creatinine clearance and urinary protein excretion and the average of measurements with less than 10% interassay variation were recorded. Creatinine clearance was normalized for body surface area (mL/min per 1.73 m^2). Creatinine concentration was measured by a modification of the Jaffe reaction,[24] urinary protein excretion by nephelometry,[25] and urinary albumin excretion, plasma active renin, and plasma aldosterone by radioimmunoassay.[26] Throughout this article, glomerular filtration rate and albuminuria are

defined, respectively, as the mean of 2 separate measurements of creatinine clearance and urinary albumin excretion (expressed as the log-transformed urine albumin to creatinine [UA:UCr] ratio).

Follow-up and Renal Outcomes

Patients with primary aldosteronism and essential hypertension, but not normotensive controls, were prospectively followed up. Clinical assessment and laboratory tests, including serum creatinine and potassium measurements, were done at 1, 3, and 6 months after enrollment and every 12 months thereafter. At each visit, antihypertensive therapy was adjusted according to the physician's judgment to reach a target value of less than 140/90 mm Hg. Nonpharmacologic therapy consisted of recommendations for exercise, weight loss, and reduction of dietary sodium and alcohol. For pharmacologic treatment, use of all classes of antihypertensive agents was permitted. Glomerular filtration rate and albuminuria were reassessed at 6 months and at 3, 6, and 9 years.

The analysis consisted of the evaluation of the rate of change in glomerular filtration rate and albuminuria from baseline. Changes were determined separately during the initial 6 months and during subsequent follow-up because previous studies indicated that treatment of primary aldosteronism may have acute effects that might differ from their long-term effects.[20,27] Short-term and long-term changes of glomerular filtration rate and albuminuria were designated as the primary outcomes. Detection of microalbuminuria (urinary albumin excretion of 30-299 mg/d) in patients who had normal albumin excretion at baseline and restoration of normal albumin excretion (urinary albumin excretion of <30 mg/d) in patients who had microalbuminuria at baseline were considered as the secondary outcomes.

Statistical Analysis

In this report, continuous data are expressed as mean (SD) unless otherwise indicated. Variables with skewed distribution were analyzed after logarithmic transformation. Characteristics of the study participants were compared among groups by analysis of covariance after adjustment for age, sex, and body mass index. Baseline *P* values are reported either for overall comparisons among all groups or for pairwise comparisons with the Bonferroni correction. Categorical variables were compared using the χ^2 test. Data from the date of inclusion through the end of follow-up for all 50 patients with primary aldosteronism and 100 with essential hypertension were included in the analysis of renal outcomes. For the analysis of the progression of renal disease, the changes of glomerular filtration rate and albuminuria were compared by means of a mixed-effects model.[28] The relations between variables measured at baseline and changes in the glomerular filtration rate or albuminuria were analyzed by linear regression, with adjustment for age and sex. All tests for significance and resulting *P* values were 2-sided, with a level of significance of .05. Analyses were performed with GB-Stat version 6.5 software (Dynamic Microsystems Inc, Silver Spring, Md).

RESULTS

Enrollment and Patient Characteristics

Between January 1994 and December 2001, we screened 1277 hypertensive patients, and among 156 (12.2%) who had an increased plasma aldosterone–active renin ratio, 54 (4.2%) were diagnosed as having primary aldosteronism. Four patients were excluded because of detection of diabetes, impaired glucose tolerance, or congestive heart failure. In 27 patients adrenal adenoma was demonstrated, whereas the remaining 23 had idiopathic aldosteronism. One hundred patients with essential hypertension and 100 normotensive participants were selected for comparison. The baseline characteristics of participants were well balanced among the study groups (TABLE 1). The adjusted glomerular filtration rate was significantly higher in patients with primary aldosteronism than those with essential hypertension (*P*=.001) and normotensive controls (*P*=.02). Also, daily urinary albumin excretion was higher in the primary aldosteronism group than in the essential hypertension group (*P*=.04), but this difference was eliminated when the UA:UCr ratio was considered (*P*=.56), suggesting that renal hyperfiltration is a major determinant of increased urinary albumin loss in primary aldosteronism.

The prevalence of microalbuminuria and overt proteinuria (≥300 mg/d) was 42% and 6%, respectively, in primary aldosteronism vs 45% (*P*=.86) and 8% (*P*=.92) in essential hypertension. The relatively high prevalence of albuminuria in these patients could be due to the long-standing duration of their hypertensive disease. No significant differences were observed between patients with tumoral and idiopathic forms (Table 1), but when patients with primary aldosteronism were subdivided according to median plasma aldosterone level (225 pg/mL), patients with higher aldosterone levels had a significantly higher glomerular filtration rate (mean, 113 [SD, 35] mL/min per 1.73 m^2) and urinary albumin excretion (median, 23 mg/d; interquartile range, 18-43 mg/d) than patients with lower aldosterone levels (respectively, mean, 95 [27] mL/min per 1.73 m^2; *P*=.04 and median, 15 mg/d; interquartile range, 7-33 mg/d; *P*=.03).

Treatment and Blood Pressure

The average duration of follow-up was 6.4 years (range, 3-11 years) with 100%, 56%, and 32% of patients completing the 3-, 6-, and 9-year evaluations, respectively. 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. Twenty-two of 27 patients with adrenal adenoma underwent adrenalectomy; among the remaining 5 patients, 2 had bilateral adenoma and 3 refused surgery and were treated with spironolactone. Antihypertensive medications used during the study are shown in

TABLE 2. In both groups, the trough blood pressure declined significantly in the first year of study and remained stable thereafter, with mean values of 136/81 mm Hg in the primary aldosteronism group and 137/81 mm Hg in the essential hypertension group (FIGURE 1). Absolute rates of increase in serum creatinine concentration did not differ between the groups. Body mass index (defined as weight in kilograms divided by height in meters squared) did not change significantly during the study, both in the primary aldosteronism group (mean [SD] at baseline, 28.7 [3.8]; at 6 months, 28.4 [3.4]; at 3 years, 28.6 [3.3]; at 6 years, 28.6 [3.2]; and at 9 years, 28.8 [3.4]) and in the essential hypertension group (mean [SD] at baseline, 28.6 [2.7]; at 6 months, 28.4 [3.0]; at 3 years, 28.5 [2.9]; at 6 years, 28.7 [3.1]; and at 9 years, 28.8 [3.0]). Mean (SD) markers of volume change such as body weight (from 79.9 [10.5] kg to 78.9 [9.4] kg]), packed cell volume (from 44% [3%] to 45 [3%]), and serum albumin (from 41 [2] to 41 [2] g/dL) did

Table 1. Baseline Characteristics of the Study Population*

Characteristics	Normotensive Control Group (n = 100)	Essential Hypertension Group (n = 100)	Primary Aldosteronism Group		
			All Patients (n = 50)	Adrenal Adenoma (n = 27)	Idiopathic (n = 23)
Age, y	51 (12)	52 (9)	53 (12)	54 (12)	52 (12)
Male, No. (%)	72 (72)	72 (72)	36 (72)	20 (74)	16 (70)
Clinical characteristics					
Body mass index†	26.0 (3.3)	28.6 (2.7)	28.7 (3.8)	28.9 (3.9)	28.4 (3.6)
Heart rate, beats/min	68 (4)	71 (3)	70 (4)	69 (4)	71 (3)
Blood pressure, mm Hg‡					
Systolic	128 (10)	167 (19)	166 (17)	166 (15)	166 (19)
Diastolic	78 (8)	102 (9)	103 (9)	103 (8)	102 (10)
Estimated duration of hypertension, y	. . .	10 (5)	10 (6)	10 (7)	9 (6)
Medical history, No. (%)					
Angina pectoris	. . .	15 (15)	6 (12)	4 (15)	2 (9)
Myocardial infarction	. . .	7 (7)	3 (6)	1 (4)	2 (7)
Stroke or transient ischemic attack	. . .	4 (4)	3 (6)	2 (7)	1 (4)
Peripheral arterial disease	. . .	4 (4)	1 (2)	1 (4)	0
Lipid disorder	19 (19)	24 (24)	11 (22)	6 (22)	5 (22)
Current smoking	12 (12)	28 (28)	15 (30)	7 (26)	8 (35)
Laboratory variables					
Packed cell volume, %	43 (2)	44 (3)	44 (3)	45 (2)	44 (2)
Serum albumin, g/dL	41 (2)	40 (2)	41 (2)	41 (1)	40 (2)
Plasma glucose, mmol/L	4.8 (0.8)	5.0 (0.8)	4.9 (0.9)	4.8 (0.9)	4.8 (0.9)
Plasma sodium, mmol/L	140 (2)	142 (3)	141 (2)	141 (2)	140 (3)
Plasma potassium, mmol/L§	4.3 (0.3)	4.2 (0.4)	3.2 (0.4)‖	3.2 (0.3)‖	3.3 (0.5)‖
Urinary sodium excretion, mmol/24 h	121 (56)	110 (41)	106 (52)	102 (39)	111 (64)
Urinary potassium excretion, mmol/24 h	48 (24)	44 (19)	50 (18)	50 (17)	49 (18)
Serum creatinine, µmol/L	83 (24)	96 (31)	91 (19)	92 (19)	90 (21)
Creatinine clearance, mL/min per 1.73 m^2¶	94 (16)	90 (24)	104 (32)	102 (30)	106 (35)
Urinary protein excretion, median (IQR), mg/24 h	. . .	116 (82-167)	117 (84-169)	115 (95-161)	121 (74-182)
Urinary albumin excretion, median (IQR), mg/24 h#	3 (1-10)	17 (6-30)	21 (9-36)	20 (7-38)	23 (11-35)
Urinary albumin/creatinine ratio, median (IQR)	0.009 (0.001-0.023)	0.043 (0.016-0.081)	0.045 (0.021-0.084)	0.045 (0.017-0.088)	0.046 (0.019-0.071)
Plasma active renin, pg/mL**	9.1 (11.6)	9.2 (11.3)	4.8 (6.6)	4.6 (5.7)	5.1 (7.8)
Plasma aldosterone, pg/mL††	134 (81)	167 (97)	243 (195)	257 (175)	232 (213)

Abbreviations: IQR, interquartile range. Ellipses indicate data not applicable.
SI conversions: To convert glucose to mg/dL, divide by 0.0555; to convert creatinine to mg/dL, divide by 88.4; to convert creatinine clearance to mL/s, multiply by 0.0167.
*Data are expressed as mean (SD) unless otherwise indicated. Characteristics of the study participants were compared among groups by analysis of covariance after adjustment for age, sex, and body mass index.
†Body mass index was defined as weight in kilograms divided by height in meters squared.
‡Blood pressure was measured after appropriate washout of antihypertensive drugs as described in the text.
§Plasma potassium levels were lower in the primary aldosteronism group than in the essential hypertension group ($P<.001$) or in normotensive controls ($P<.001$).
‖Values are those that were measured before correction with oral supplementation.
¶Creatinine clearance was higher in the primary aldosteronism group than in the essential hypertension group ($P = .001$) or in normotensive controls ($P = .02$).
#Daily urinary albumin excretion was higher in the primary aldosteronism group than in the essential hypertension group ($P = .04$).
**Plasma active renin was lower in the primary aldosteronism group than in the essential hypertension group ($P = .04$).
††Plasma aldosterone was higher in the primary aldosteronism group than in the essential hypertension group ($P<.001$) or in normotensive controls ($P<.001$).

not change significantly during the first 6 months of follow-up in patients with primary aldosteronism.

Renal Outcomes

During the initial 6-month period, the mean glomerular filtration rate decreased in patients with primary aldosteronism (–13.6 mL/min per 1.73 m^2; $P<.001$) and those with essential hypertension (–2.1 mL/min per 1.73 m^2; $P=.27$; $P<.001$ vs primary aldosteronism) (FIGURE 2). In primary aldosteronism, this change occurred in patients with adrenal adenoma who underwent adrenalectomy (from a mean [SD] of 102 [27] to 89 [31] mL/min per 1.73 m^2; $P=.003$) and in patients with adrenal adenoma (from a mean [SD] of 103 [15] to 90 [18] mL/min per 1.73 m^2; $P=.03$) and idiopathic aldosteronism (from a mean [SD] of 106 [33] to 92 [29] mL/min per 1.73 m^2; $P=.006$) who were treated with spironolactone. Subsequent declines in glomerular filtration rate in patients with primary aldosteronism (–1.15 [95% confidence interval {CI}, –0.74 to –1.56] mL/min per 1.73 m^2 per year) and those with essential hypertension (–1.06 [95% CI, –0.70 to –1.41] mL/min per 1.73 m^2 per year) were comparable ($P=.49$). The overall change from baseline to the end of follow-up was greater in primary aldosteronism (–2.18 [95% CI, –1.45 to –2.94] mL/min per 1.73 m^2 per year) than in essential hypertension (–1.09 [95% CI, –0.86 to –1.40] mL/min per 1.73 m^2 per year; $P=.03$).

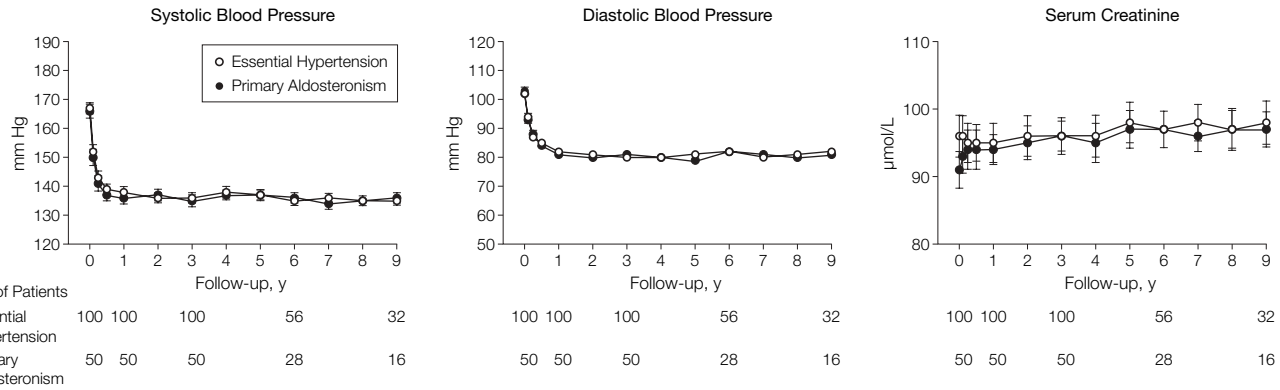
During the first 6 months of follow-up, the median level of UA:UCr ratio declined by 34% (95% CI, 29%-40%) in primary aldosteronism and by 20% (95% CI, 15%-26%) in essential hypertension ($P<.001$) (Figure 2 and TABLE 3). The difference persisted throughout the study, with changes from baseline at the 3-, 6-, and 9-year evaluations that were –38%, –36%, and –36%, respectively, among patients with primary aldosteronism and

Table 2. Use of Medications in Patients With Primary Aldosteronism or Essential Hypertension at Baseline and at End of Follow-up*

	Essential Hypertension Group		Primary Aldosteronism Group	
Medications	Baseline	End of Study	Baseline	End of Study
Antihypertensive agents				
Diuretics	45 (45)	55 (54)	28 (56)	4 (8)
β-Blockers	43 (43)	51 (51)	26 (52)	7 (14)
Calcium channel blockers	46 (46)	61 (61)	26 (52)	13 (26)
Angiotensin-converting enzyme inhibitors	40 (40)	57 (56)	19 (38)	11 (22)
Angiotensin receptor blockers	11 (11)	19 (19)	9 (18)	5 (10)
α-Blockers	3 (3)	4 (4)	10 (20)	0
Aldosterone antagonists	0	0	0	28 (56)
Other antihypertensive agents	0	0	6 (12)	0
Total antihypertensive agents	188	247	124	68
Statins	21 (21)	31 (31)	10 (20)	14 (28)
Antiplatelet agents	19 (19)	24 (24)	9 (18)	11 (22)

*Data are expressed as No. (%). Medication use was defined as receipt of the specific drug for more than 50% of follow-up visits. Data were available for all participants in both the essential hypertension and primary aldosteronism groups. At baseline, 8% of patients with primary aldosteronism were taking no antihypertensive drug, 8% were receiving monotherapy, and the remaining 84% had multiple-drug treatment, with a mean of 2.86 antihypertensive drugs per patient. Among patients with essential hypertension, 9% were taking no antihypertensive drug, 12% were receiving monotherapy, and 79% had multiple-drug treatment, with a mean of 2.23 drugs per patient. At the end of follow-up, 18% of patients with primary aldosteronism were taking no drugs, 36% were receiving monotherapy, and the remaining 46% had multiple-drug treatment, with a mean of 2.19 drugs per patient. Among patients with essential hypertension, 6% were receiving monotherapy and 94% had multiple-drug treatment, with a mean of 2.56 drugs per patient. No patients among those treated with spironolactone had hyperkalemia. The incidence of gynecomastia in the group of 20 men treated with spironolactone was 20%.

Figure 1. Mean Systolic and Diastolic Blood Pressure and Serum Creatinine Values at Baseline and During Follow-up in Patients With Primary Aldosteronism and Essential Hypertension



Trough blood pressure was measured immediately before administration of medication. Both systolic and diastolic blood pressure levels declined significantly in the first year of the study (both $P<.001$) and remained stable and comparable (systolic blood pressure, $P=.63$; diastolic blood pressure, $P=.57$) in the 2 groups thereafter, with average blood pressure values of 136/81 mm Hg in the primary aldosteronism group and 137/81 mm Hg in the essential hypertension group. Absolute rates of increase in serum creatinine concentration did not differ between the primary aldosteronism group (0.39 [95% confidence interval, 0.23-0.56] μmol/L per year) and essential hypertension group (0.34 [95% confidence interval, 0.22-0.45] μmol/L per year; $P=.39$). To convert creatinine to mg/dL, divide by 88.4.

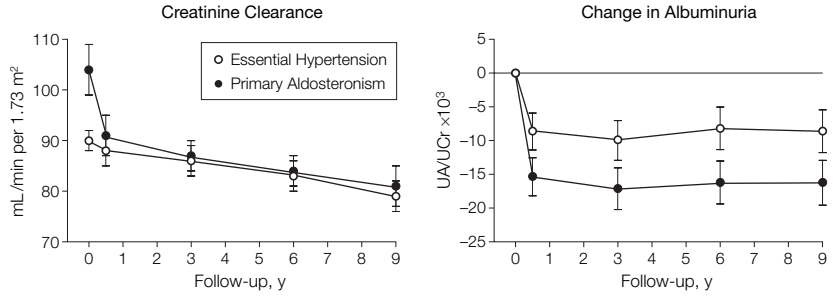
–23%, –19%, and –20%, respectively, among patients with essential hypertension. Mean UA:UCr ratio decline did not differ between the groups during the long-term phase ($P=.56$), but the overall effect was significantly greater in primary aldosteronism than in essential hypertension ($P=.04$). Microalbuminuria developed in 12% of 26 patients with primary aldosteronism who had normal albumin excretion at baseline and 15% of 47 patients with essential hypertension ($P=.97$). Restoration of normal albumin excretion after microalbuminuria was significantly more frequent in primary aldosteronism (43%) than in essential hypertension (13%; $P=.02$). In both groups, restoration of normal albumin excretion occurred mainly during the initial 3-year period (Table 3).

In patients with primary aldosteronism but not essential hypertension, baseline glomerular filtration rate was a predictor of both glomerular filtration and albuminuria decline during follow-up. During the first 6 months, glomerular filtration rate decreased in patients with primary aldosteronism and baseline glomerular filtration rates both above (–19.5 mL/min per 1.73 m^2; $P<.001$) and below (–6.7 mL/min per 1.73 m^2; $P=.01$) the median (105 mL/min per 1.73 m^2), with a change that was significantly greater ($P<.001$) in the former group (FIGURE 3). Subsequent decline was comparable in patients with higher and lower baseline glomerular filtration rates. During the initial 6 months, the median UA:UCr ratio decreased by 41% (95% CI, 35%-46%) in patients with primary aldosteronism with higher baseline glomerular filtration rates and by 28% (95% CI, 21%-34%) in patients with lower baseline glomerular filtration rates ($P=.01$). Subsequent changes were not significant in both groups. Analysis of renal outcomes in patients with tumoral or idiopathic adrenal disease did not reveal any significant differences (data not shown).

COMMENT

Our study demonstrates that improved blood pressure control generates an overall renal benefit in primary aldosteronism that is superior to that observed in essential hypertension and results from the early response of renal function to treatment. Both patients with adrenal adenoma and those with idiopathic aldosteronism had glomerular hyperfiltration and elevated urinary albumin excretion that were rapidly reversed after removal of the effects of excess aldosterone by adrenalectomy or spironolactone. Reversible glomerular hyperfiltration also was reported in studies that were conducted in patients with aldosterone-

Figure 2. Creatinine Clearance at Baseline and During Follow-up and Change From Baseline of Urinary Albumin Excretion in Patients With Primary Aldosteronism and Essential Hypertension



No. of Patients										
Essential Hypertension	100	100	100	56	32	100	100	100	56	32
Primary Aldosteronism	50	50	50	28	16	50	50	50	28	16

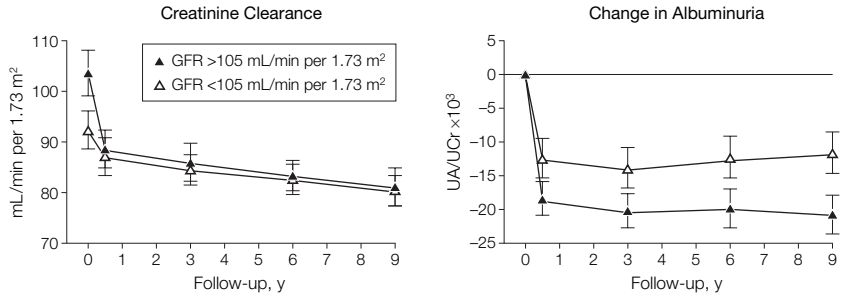
Duplicate 24-hour urine collections were obtained for determination of creatinine clearance and urinary albumin excretion, and the mean was considered. Creatinine clearance was normalized to body surface area. Albuminuria was expressed as the log-transformed urine albumin to urine creatinine (UA/UCr) ratio. The mean follow-up time was 6.4 years. Decrease of creatinine clearance during the initial 6-month period was significantly greater ($P<.001$) in patients with primary aldosteronism (13.6 mL/min per 1.73 m^2) than in those with essential hypertension (2.1 mL/min per 1.73 m^2). Subsequent decline of creatinine clearance was comparable in the 2 groups ($P=.49$). Decrease of albuminuria during the initial 6-month period was significantly greater ($P<.001$) in patients with primary aldosteronism (34%) than essential hypertension (20%). The difference between the groups persisted in the remainder of the follow-up period with only minor further changes. To convert creatinine clearance to mL/s, multiply by 0.0167. Error bars indicate SE for creatinine clearance and 95% confidence interval for albuminuria.

Table 3. Distribution of Patients According to Nephropathy Status and Urinary Albumin Excretion During the Study

	Baseline	6 Months	3 Years	6 Years	9 Years
Primary aldosteronism					
No. of patients	50	50	50	28	16
Proteinuria, No. (%)	3 (6)	3 (6)	3 (6)	2 (7)	1 (6)
Microalbuminuria, No. (%)	21 (42)	17 (34)	15 (30)	10 (36)	6 (38)
Normal albumin excretion, No. (%)*	26 (52)	30 (60)	32 (64)	16 (57)	9 (56)
Urinary albumin excretion, median (IQR), mg/24 h	21 (9-36)	13 (6-27)†	12 (6-26)	12 (7-25)	13 (8-28)
Essential hypertension					
No. of patients	100	100	100	56	32
Proteinuria, No. (%)	8 (8)	8 (8)	8 (8)	5 (9)	2 (6)
Microalbuminuria, No. (%)	45 (45)	42 (42)	41 (41)	24 (43)	15 (47)
Normal albumin excretion, No. (%)*	47 (47)	50 (50)	51 (51)	27 (48)	15 (47)
Urinary albumin excretion, median (IQR), mg/24 h	17 (6-30)	13 (4-26)‡	13 (6-24)	14 (6-25)	14 (6-25)

Abbreviation: IQR, interquartile range.
*The lower limits of the albumin excretion rate for microalbuminuria and proteinuria were 30 and 300 mg/d, respectively.
†$P<.001$ vs baseline.
‡$P<.01$ vs baseline.

Figure 3. Creatinine Clearance at Baseline and During Follow-up and Change From Baseline of Urinary Albumin Excretion in Patients With Primary Aldosteronism and Creatinine Clearance Above or Below the Median Group Value



No. of Patients										
GFR <105 mL/min per 1.73 m²	25	25	25	14	8	25	25	25	14	8
GFR >105 mL/min per 1.73 m²	25	25	25	14	8	25	25	25	14	8

Duplicate 24-hour urine collections were obtained for determination of creatinine clearance and urinary albumin excretion, and the mean was considered. Creatinine clearance was normalized to body surface area. Albuminuria was expressed as the log-transformed urine albumin to urine creatinine (UA/UCr) ratio. The mean follow-up time was 6.4 years. The decrease of creatinine clearance during the initial 6-month period was significantly greater ($P<.001$) in patients with high (19.5 mL/min per 1.73 m^2) than low (6.7 mL/min per 1.73 m^2) baseline creatinine clearance. Subsequent decline of creatinine clearance was comparable in the 2 groups ($P=.77$). The decrease of albuminuria during the initial 6-month period was significantly greater ($P=.01$) in patients with high (41%) than low (28%) baseline creatinine clearance. The difference between the groups persisted in the remainder of the follow-up period with only minor further changes. GFR indicates glomerular filtration rate. To convert creatinine clearance to mL/s, multiply by 0.0167. Error bars indicate SE for creatinine clearance and 95% confidence interval for albuminuria.

secreting adrenal adenoma after adrenalectomy.[20,27] This functional response to treatment occurs within the first few months and is due to a hemodynamic effect that could have many explanations, including decreased systemic blood pressure, decreased extracellular fluid volume, recovery of renin activity, postoperative aldosterone suppression, and removal of direct vasomotor effects of aldosterone on intrarenal vessels.[29,30] In addition, this is the first study that investigates long-term renal outcomes in primary aldosteronism and establishes that in this condition, the long-term progression of renal dysfunction does not differ from essential hypertension. In both hypertension groups, sustained decline of glomerular filtration during follow-up was slightly higher than the rate of decline that has been attributed to aging in patients without kidney disease,[31] and this could be possibly ascribed to the tight control of blood pressure values obtained during the study.

A relationship between elevated plasma levels of aldosterone and renal deterioration was reported in patients with advanced renal failure,[32,33] suggesting that aldosterone might contribute to progressive loss of renal function. This possibility has received recent support from the results of small clinical trials in which mineralocorticoid receptor antagonists reduced proteinuria in patients with diabetes[15-17] and chronic kidney disease due to various renal conditions.[18,19] Past evaluations of renal function in primary aldosteronism are limited to a few cross-sectional studies and a longitudinal study with short follow-up. In cross-sectional evaluations, prevalence of overt proteinuria varied from 8%[34] to 24%[35] with a disparity that might be explained by different duration and severity of hypertension. In the only published longitudinal study, Ribstein et al[20] reported a decrease in urinary albumin excretion after adrenalectomy in 25 patients who were followed up for 6 months. In agreement with our findings, the initial decrease in albuminuria was steeper in primary aldosteronism than in essential hypertension and was associated with significant decline in glomerular filtration rate. In the long term, we have observed no further changes in albuminuria, indicating persistent benefit of either surgical or medical treatment.

Moreover, our 9-year follow-up of patients with primary aldosteronism with well-documented microalbuminuria before treatment demonstrates that in this condition, microalbuminuria is more likely to subside to normal levels after treatment than to progress to overt proteinuria. Restoration of normal albumin excretion was more common in primary aldosteronism than in essential hypertension, and this benefit appeared to be independent of systemic blood pressure. This frequency of regression suggests a model of renal dysfunction of primary aldosteronism in which elevated urinary albumin excretion is, at least in part, a marker of dynamic rather than structural renal defect. However, long-term persistence of albuminuria in a substantial proportion of patients suggests coexistence of irreversible structural damage, presumably due to long-standing hypertension prior to treatment; a study of patients with primary aldosteronism and hypertension of shorter duration would be very helpful in this context. Therefore, the present observation should not lead physicians to overlook the relevance of high blood pressure per se in the induction of arteriolosclerotic renal damage in these patients.[36]

Our study is limited because of the use of certain medications that might have influenced renal outcomes. For instance, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers could slow progression of albuminuria,[37,38] and a greater percentage of patients with essential hypertension received these drugs compared with patients with primary aldosteronism. This difference, however, should have been associated with better renal outcome in the essential hypertension group, but this was not the case. Also,

statins have antialbuminuric effects,[39] but the frequency of their use was comparable in the primary aldosteronism and essential hypertension groups. In this study, separate analysis of patients who were and were not taking these types of medications did not show a different rate of decline of glomerular filtration or progression of albuminuria (data not shown).

Preventing or delaying development of renal insufficiency and proteinuria is a mandatory goal of treatment in patients with hypertension. Primary aldosteronism was once considered a rare disease, but recent work suggests that it might be the most common curable cause of hypertension, worth screening for in every patient with hypertension. This study presents evidence that primary aldosteronism is associated with functional renal abnormalities out of proportion to blood pressure levels that benefit substantially from treatment in both the short and long terms. In this view, both adrenalectomy and mineralocorticoid receptor blockade appear to be of considerable therapeutic value inasmuch as they rapidly reverse glomerular hyperfiltration, decrease albuminuria, and, under adequate blood pressure control, permit only minor progressive loss of renal function.

In summary, in patients with primary aldosteronism, renal dysfunction is strictly related to the functional adaptation of the kidney to the effect of aldosterone excess and is substantially reversible with treatment. These findings underline the importance of appropriate timing in the identification of this endocrine disorder to effectively prevent late renal complications.

Author Contributions: Dr Sechi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Sechi and Catena contributed equally to this work.
Study concept and design: Sechi, Catena.
Acquisition of data: Sechi, Novello, Lapenna, Baroselli, Nadalini, Colussi, Catena.
Analysis and interpretation of data: Sechi, Novello, Lapenna, Baroselli, Nadalini, Colussi, Catena.
Drafting of the manuscript: Sechi, Catena.
Critical revision of the manuscript for important intellectual content: Sechi, Novello, Lapenna, Baroselli, Nadalini, Colussi, Catena.
Statistical analysis: Sechi, Catena.
Obtained funding: Sechi, Novello, Colussi, Catena.
Administrative, technical, or material support: Sechi, Novello, Lapenna, Baroselli, Nadalini, Colussi, Catena.
Study supervision: Sechi, Novello, Lapenna, Baroselli, Nadalini, Colussi, Catena.
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Role of the Sponsors: The research sponsors had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

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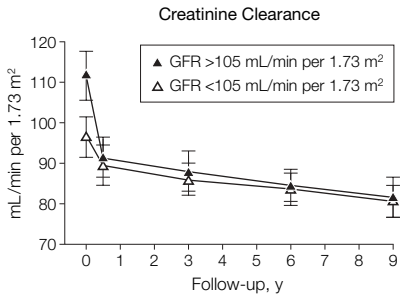
CORRECTIONS

Incorrect Formula: In the Special Communication entitled "Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement" published in the March 8, 2006, issue of *JAMA* (2006;295:1152-1160), a formula for a 2-sided confidence interval (CI) used to assess noninferiority of a new treatment compared with a standard one with regard to an outcome was incorrect. On page 1158 in the subsection titled "Elaboration" that reads "the upper bound of the 2-sided $(1-\alpha/2)\times 100\%$ CI for the treatment effect has to be below the margin Δ to declare that noninferiority has been shown . . . " should read "the upper bound of the 2-sided $(1-2\alpha)\times 100\%$ CI for the treatment effect has to be below the margin Δ to declare that noninferiority has been shown . . . "

Error in Figure: In the Original Contribution entitled "Long-term Renal Outcomes in Patients With Primary Aldosteronism" published in the June 14, 2006, issue of *JAMA* (2006;295:2638-2645), an error occurred in **FIGURE 3**. In the left panel, which reports creatinine clearance values, the scale of the y-axis is not correct, and the data are therefore not plotted correctly. The correct graph appears below.



No. of Patients					
GFR <105 mL/min per 1.73 m²	25	25	25	14	8
GFR >105 mL/min per 1.73 m²	25	25	25	14	8