Hypertension

ORIGINAL ARTICLE

Efficacy and Safety of Treatment With Low Doses of Spironolactone in Patients With Primary Aldosteronism: A Retrospective Observational Study in a Tertiary Center

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BACKGROUND: Spironolactone is recommended as first-line therapy for patients with idiopathic primary aldosteronism. The aim of this study is to evaluate the impact of low and high doses of spironolactone on arterial blood pressure control, potassium levels, and the incidence of drug-related adverse effects.

METHODS: We retrospectively included 394 patients with primary aldosteronism receiving spironolactone. Patients were divided into 2 groups, according to the median prescribed dose in our population (50 mg, 25–75): subjects treated with doses ≤50 mg versus >50 mg.

RESULTS: The median follow-up after the introduction of spironolactone was 12 months, and 128 patients experienced adverse effects, with a proportion higher in men than in women (44.70% versus 15.70%). The most frequently reported adverse effect was gynecomastia, followed by sexual dysfunction. Subjects receiving a dose >50 mg of spironolactone displayed a higher prevalence of adverse effects (39.1%) compared to the ≤50 mg group (29.3%); this effect was significantly different only in men (*P*=0.002). Patients in the low-dose group were treated with a higher number of antihypertensive drugs, especially diuretics. No significant differences were seen between the 2 subgroups in blood pressure control, potassium and renin levels, and occurrence of cardiovascular events at follow-up.

CONCLUSIONS: Treatment with low doses of spironolactone, in association with other antihypertensive drugs, is effective in achieving an appropriate blood pressure control in primary aldosteronism, while it improves adherence with lower adverse effects. These findings could help the clinician choose the best therapeutic option for each patient. ***(Hypertension.* 2026;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.24881.)** • **Supplement Material**.

Key Words: blood pressure ■ glomerular filtration rate ■ gynecomastia ■ hypertension ■ spironolactone

Primary aldosteronism (PA) is the most prevalent cause of secondary hypertension, affecting 6% of the general hypertensive population.[1] Its prevalence increases with the severity of hypertension, reaching up to 20% in the more severe or resistant cases.[2] It is, however, underdiagnosed worldwide, even though it is a severe disease with increased risk of cardiovascular complications, which can be treated with specific treatments.[3]

The pathophysiological effects of aldosterone excess in triggering cardiovascular and renal damage through inflammation and fibrosis[4,5] underscore the heightened risk of cardio- and cerebrovascular events and renal morbidity in patients with PA—due to either an aldosterone-producing adenoma or a bilateral adrenal hyperplasia—when compared with patients with primary hypertension, irrespective of blood pressure (BP) levels.[6–8] Steroidal

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

We evaluated the impact on arterial blood pressure control and on the incidence of spironolactone-related adverse effects of medical treatment with low and high doses of spironolactone on a cohort of 394 patients with primary aldosteronism.

What Is Relevant?

Treatment with doses of spironolactone ≤50 mg is efficient in maintaining an adequate blood pressure control with a low rate of drug-related adverse effects, especially in men, and therefore a better adherence to therapy.

Clinical/Pathophysiological Implications?

We aimed at providing the clinicians with useful data for the initiation and optimization of medical therapy in primary aldosteronism. We suggest a potential therapeutic approach for the management of primary aldosteronism in men.

Nonstandard Abbreviations and Acronyms

AE	adverse effects
BP	blood pressure
eGFR	estimated glomerular filtration rate
IQR	interquartile range
MRA	mineralocorticoid receptor antagonists
ODBP	office diastolic blood pressure
OSBP	office systolic blood pressure
PA	primary aldosteronism

MRA (mineralocorticoid receptor antagonists), with spironolactone as the primary choice, are recommended by guidelines to block the noxious effects of aldosterone in patients with bilateral forms of PA or unilateral forms where adrenalectomy could not be performed due to the patient's decision or in elderly patients where BP improvement is less probable.[9] The PAMO consensus recently published underlines the fact that spironolactone should be considered as a targeted medical treatment and does not count as an antihypertensive drug in the classification of the consensus.[10] By blocking the genomic effects of aldosterone on its receptor and thus its downstream consequences, especially at the level of the distal nephron,[11–13] spironolactone reduces BP, normalizes potassium concentrations, and decreases vascular stiffness and left ventricular hypertrophy in patients with PA.[14,15] Despite the well-established benefits of MRA in heart failure with reduced ejection fraction,[16] postmyocardial infarction[17,18] and diabetic nephropathy,[19–21] the precise impact on lowering cardiovascular events remains a matter of debate in hypertension and PA. Although some studies support the protective effects of MRA against cardiovascular and renal events,[22,23] there is conflicting evidence suggesting that MRA may be less effective than surgery in preventing such events.[2,24]

Historically, spironolactone at high daily doses of 1 to 2 mg/kg was prescribed in patients with PA.[25–28] However, achieving these target doses is challenging in clinical practice, due to the dose-dependent spironolactone-induced adverse effects (AE), particularly gynecomastia and sexual dysfunction, because of its nonselective effect on the androgen and progesterone receptors.[16,29] Another steroidal MRA, eplerenone, which is more selective on the mineralocorticoid receptor and devoid of such AE, is proposed as an alternative, but this drug was shown to be much less effective than spironolactone in reducing BP in patients with PA on a milligram per milligram basis.[28] International guidelines[9,29,30] have thus proposed initiating treatment with spironolactone in first line and with low doses to reduce the burden of drug-induced AE while maintaining effective BP control.[31,32] Despite the widespread use of this strategy in clinical practice, its impact on BP control and hypokalemia reversal in a large population is not well established.

In our referral academic center, the prescribed doses have been progressively decreased in recent years to lower the incidence of AE and to achieve better adherence to treatment. The aim of this work, therefore, is to evaluate whether this strategy may have influenced BP control and potassium values and reduced the incidence of spironolactone-related AE in a large cohort of patients with PA.

METHODS

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

Design of the Study

We retrospectively analyzed the records of all patients with PA referred to our ESH Excellence Center of Hypertension in Paris from January 2001 to December 2020. Clinical, biochemical, hormonal, and radiological data at baseline and at follow-up were extracted from the electronic health record database. The study was approved by the French Independent Ethics Committee, CCP IDF II (IRB 2012-A00508-35), and written informed consent was obtained from all participants.

Patients were initially referred to our Hypertension center for the evaluation of resistant, severe, or complicated hypertension, hypertension with the presence of spontaneous or diuretic-induced hypokalemia, presence of adrenal incidentaloma on computed tomography scan/magnetic resonance imaging, hypertension diagnosed before 40 years, or for adrenal venous sampling when PA had been diagnosed elsewhere. The diagnosis of PA was performed as previously published[33] and according to international guidelines[9] and to SFE/SFHTA/AFCE Consensus on PA,[34] with at least 2 aldosterone-to-renin ratio measurements above the threshold, and either elevated aldosterone levels or unsuppressed aldosterone after saline infusion test. The diagnosis of PA was confirmed during weekly multidisciplinary rounds. For this retrospective analysis, we included only patients with at least 1-month follow-up after initiating spironolactone; we excluded those who underwent adrenalectomy and those without follow-up data.

Group Stratification

Patients were categorized into 2 groups (high dose: >50 mg/d; low dose: ≤50 mg/d) based on the median daily dose of spironolactone (50 mg, interquartile range [IQR], 25–75) prescribed in our cohort.

Clinical, Biochemical, Hormonal Assessment

Seated office systolic and diastolic BP (OSBP/ODBP) were calculated by the average of 3 measurements taken by a trained nurse after 5 minutes of rest using a validated semiautomatic manometer. Out-of-office BP was assessed by either 24-hour ambulatory BP measurement or standardized home BP measurements. Resistant hypertension was defined as OSBP ≥140 mm Hg or ODBP ≥90 mm Hg while being treated with at least 3 antihypertensive medications, including a diuretic, according to guidelines.[35]

History of cardiovascular events (coronary artery disease, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, atrial fibrillation), the presence of left ventricular hypertrophy at echocardiography—defined as a left ventricular mass index >115 g/m^2 in men and >95/m^2 in women, as well as a diagnosis of obstructive sleep apnea syndrome were retrieved from the electronic health record.

Baseline evaluation was performed during the first visit in our unit.

Laboratory Assays

Biochemical and hormonal determinations were performed in the same laboratory throughout the years of the study and were defined previously.[33] Sodium, potassium, and creatinine concentrations were determined by standard methods. The estimated glomerular filtration rate (eGFR) was calculated by using the MDRD formula,[36] and chronic kidney disease was defined by eGFR <60 mL/min per 1.73 m^2.[37]. Diabetes was defined using American Diabetes Association criteria.[38] Hypokalemia was defined as a serum potassium concentration <3.5 mmol/L.

Outcomes

The primary outcomes included: the decrease in OSBP/ODBP at follow-up and, when available, out-of-office BP measurements; the changes in plasma potassium concentrations, and the occurrence and the type of spironolactone-related AE. Secondary analyses included: the antihypertensive medication burden, including the total number of antihypertensive medications, the daily defined dose of medications[39] and the use of diuretics; the increase in plasma renin concentrations; the eGFR changes; the prevalence of cardiovascular events at follow-up.

The follow-up evaluation was performed at the final visit after a period during which the patient was administered a fixed prescribed dose of spironolactone, before any cessation or dose adjustment. This phase was used for the analysis of all the primary and secondary outcomes, with the exception of the evaluation of the occurrence of cardiovascular events. For this analysis, a second follow-up phase was conducted, extending the evaluation to the whole period during which the patient was exposed to mineralocorticoid receptor antagonist treatment, considering also modifications in spironolactone dosage or switch to eplerenone.

Statistical Analysis

Quantitative variables are reported as median (interquartile range) or as mean±SD, and categorical data as numbers (percentage). Comparison between the low dose and the high dose group was performed by a nonparametric Mann-Whitney *U* test for independent variables. Changes in BP and potassium adjusted on baseline were analyzed using ANOVA with repeated measures with Bonferroni correction. Multivariable sex-adjusted linear and logistic regression models were applied to assess the association between spironolactone dose and primary outcomes; potential confounders were included as interaction terms to avoid reporting bias. Patients with missing baseline or follow-up data were excluded from comparisons of delta-variation and multivariable regression analyses. A 2-sided $P<0.05$ was considered significant. IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY) was used for statistical analyses.

RESULTS

Baseline Characteristics of the Population

Patients 'selection is reported in Figure 1. We included 394 patients with PA (166 women, 42.1%). The median age was 48 years (IQR, 41–56), and the median body mass index was 29.0 kg/m^2 (IQR, 26.1–32.0). In our population, 340 patients (86.3%) had a past or ongoing history of hypokalemia, and the median hypertension duration at PA diagnosis was 105 months (IQR, 42–193). Median OSBP/ODBP was 146 mm Hg (IQR, 135–161)/92 mm Hg (IQR, 85–101) and 146 mm Hg (IQR 136–159) and 95 mm Hg (IQR 87–102) on out-of-office BP measurement, despite being treated with 2.4±1.3 antihypertensive medications at baseline. A total of 74/394 (18.8%) of patients had resistant hypertension, 52/394 (13.2%) had chronic kidney disease, and 181/386 subjects (46.9%) had left ventricular hypertrophy at baseline. The majority of cases were bilateral

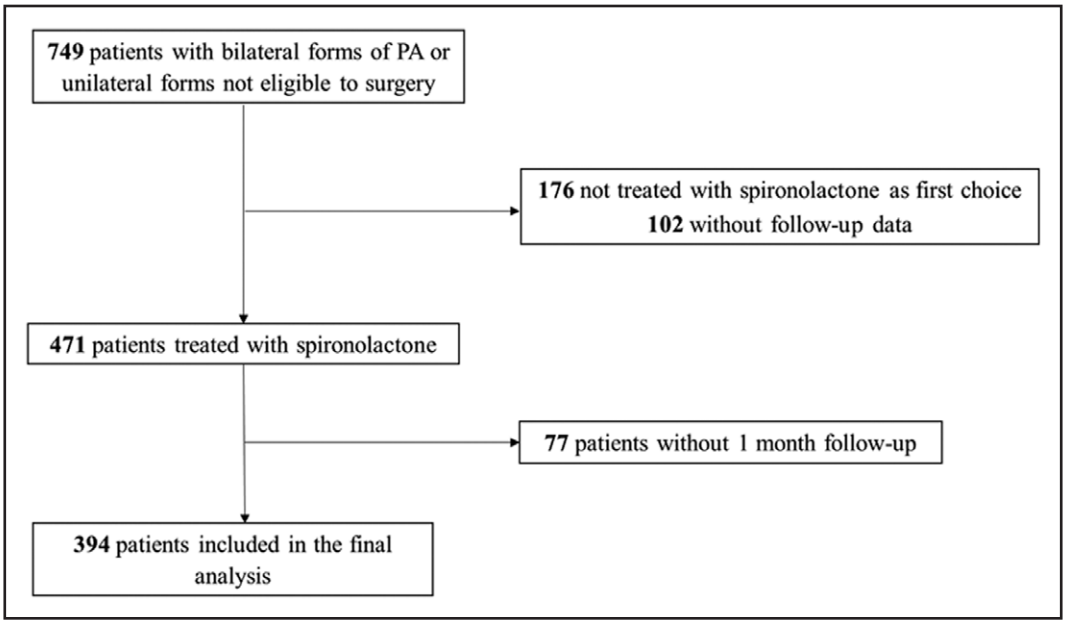

Figure 1. Flow-chart of the included patients.
PA indicates primary aldosteronism.

forms (343 patients); only 23 patients had unilateral aldosterone secretion at adrenal venous sampling but were unwilling or unable to perform surgery; finally, in 28 cases, adrenal venous sampling was either not performed or unsuccessful.

Compared with patients prescribed a low dose of spironolactone ≤50 mg/d, those prescribed a high dose of >50 mg/d were more frequently women (68 [53.1%] versus 98 [36.8%]; *P*=0.002). Subjects treated with high doses displayed: (1) lower baseline potassium values (3.4 mmol/L; IQR, 3.1–3.8) compared with those prescribed a dose ≤50 mg/d (3.6 mmol/L, 3.3–3.8; *P*=0.006) and (2) a more florid aldosterone secretion (plasma aldosterone concentration, 791 pmol/L [599–1098] versus 566 pmol/L [433–867], *P*<0.001; aldosterone-to-renin ratio 139 [100–200] versus 102 [78–152], *P*<0.001; urinary free aldosterone excretion 76 nmol/24 h [50–109] versus 64 nmol/24 h [47–90], *P*=0.012).

All results are detailed in Table 1.

BP Control and Hypokalemia Reversal During Follow-Up

The median follow-up after spironolactone initiation with the same dose was 12 months (IQR, 4–29 months), with 199 (50.5%) patients followed for more than a year. The median (IQR) dose of spironolactone was 50 mg (25–50) in the low dose group and 75 mg (75–100) in the high dose one. The length of follow-up with the same fixed dosage of spironolactone was not significantly different between the low-dose group (12 months; IQR, 4–22) and the high-dose one (12 months; IQR, 3–49; *P*=0.306).

In covariance analysis, no differences were observed between patients treated with high and low doses with respect to baseline and follow-up BP and potassium levels (*P*=0.618 for SBP, *P*=0.980 for DBP, *P*=0.555 for potassium). Also, no differences were seen with regard to persistence of uncontrolled BP and hypokalemia at follow-up in men or women according to the dose of spironolactone prescribed (Supplemental Material, Tables S1 and S2). Similar results were observed in a subanalysis of patients presenting with high rates of aldosterone at baseline, using a cutoff of plasma aldosterone concentration ≥555 pmol/L as suggested by the Expert Consensus on the Primary Aldosteronism Severity Classification,[40] as detailed in Table S3.

No statistically significant differences were seen between the 2 subgroups in BP measurements and potassium levels at follow-up: OSBP and ODB were, respectively, 130 mm Hg (IQR, 120–140) and 80 mm Hg (IQR, 73–88) in subjects receiving ≤50 mg of spironolactone and 129 mm Hg (IQR, 117–142) and 80 mm Hg (IQR, 73–87) in those treated with >50 mg of spironolactone; similarly, out-of-office measurements were 128 mm Hg (IQR, 120–136)/81 mm Hg (IQR, 75–86) in the low dose group and 129 mm Hg (IQR, 121–140)/83 mm Hg (IQR, 78–89) in the high dose group (*P*=0.351 for OOSBP and *P*=0.177 for OODBP). Moreover, 110 patients (30.6%) still had uncontrolled hypertension, and 41 (11.4%) patients had resistant hypertension at follow-up, without significant differences between the 2 groups. Hypokalemia was reported in 25 patients out of 333 (7.5%), with 19 patients (8.6%) in the low dose group and 6 (5.4%) in the high dose group (*P*=0.303). Median potassium concentration was 4.1 mmol/L (IQR, 3.8–4.4)

Table 1. Clinical and Biochemical Characteristics of the Patients at Baseline

Characteristics		Total population (n=394)		Spironolactone dose ≤50 mg (n=266)		Spironolactone dose >50 mg (n=128)	*P* value
Women	394	166 (42.1%)	266	98 (36.8%)	128	68 (53.1%)	0.002
Age, y	394	48 (41–56)	266	48 (41–55)	128	49 (42–56)	0.272
History of hypokalemia	394	340 (86.3%)	266	225 (84.6%)	128	115 (89.8%)	0.155
Duration of HTN at PA diagnosis, mo	394	105 (42–193)	266	90 (38–185)	128	126 (51–208)	0.081
Resistant HTN	394	74 (18.8%)	266	49 (18.4%)	128	25 (19.5%)	0.792
LVH at echocardiography	386	181 (46.9%)	261	124 (47.5%)	125	57 (45.6%)	0.725
History of CV events	394	107 (27.2%)	266	82 (30.8%)	128	25 (19.5%)	0.018
History of OSAS	394	53 (13.5%)	266	39 (14.7%)	128	14 (10.9%)	0.310
History of dyslipidemia	394	157 (39.8%)	266	109 (41.0%)	128	48 (37.5%)	0.509
History of diabetes	394	82 (20.8%)	266	55 (20.7%)	128	27 (21.1%)	0.924
CKD	394	52 (13.2%)	266	40 (15.0%)	128	12 (9.4%)	0.120
Year of visit	394	2016 (2009–2018)	266	2017 (2015–2019)	128	2010 (2005–2016)	<0.001
BMI, kg/m^2	394	29.0 (26.1–32.0)	266	29.0 (26.1–32.0)	128	28.9 (26.0–32.0)	0.951
Number of antihypertensive drugs	389	2.4±1.3	265	2.5±1.3	124	2.3±1.3	0.196
DDD	214	2.3 (1.0–4.0)	153	2.5 (1.0–4.0)	61	2.0 (1.0–4.0)	0.578
Office SBP, mm Hg	385	146 (135–161)	261	146 (134–160)	124	150 (137–165)	0.110
Office DBP, mm Hg	385	92 (85–101)	261	91 (85–102)	124	93 (87–101)	0.336
Out-of-office SBP, mm Hg	188	146 (136–159)	138	144 (135–157)	50	148 (139–164)	0.097
Out-of-office DBP, mm Hg	188	95 (87–102)	138	95 (87–101)	50	95 (87–103)	0.535
Plasma potassium, mmol/L	391	3.5 (3.2–3.8)	263	3.6 (3.3–3.8)	128	3.4 (3.1–3.8)	0.006
Hypokalemia <3.5 mmol/L	391	170 (43.5%)	263	103 (39.2%)	128	67 (52.3%)	0.014
Plasma sodium, mmol/L	387	141 (140–143)	260	141 (140–143)	127	141 (139–143)	0.068
Plasma creatinine, µmol/L	391	79 (68–94)	263	81 (69–95)	128	78 (65–94)	0.098
eGFR, mL/min per 1.73 m^2	391	82 (68–96)	263	82 (68–96)	128	83 ((68–99)	0.615
eGFR <60 mL/min per 1.73 m^2	391	62 (15.9%)	264	39 (14.8%)	127	23 (18.1%)	0.397
PRC, mIU/L	394	2.6 (1.1–5.3)	266	2.5 (1.1–5.2)	128	2.7 (1.1–6.4)	0.274
PAC, pmol/L	394	666 (472–955)	266	566 (433–867)	128	791 (599–1098)	<0.001
ARR	394	110 (82–167)	266	102 (78–152)	128	139 (100–200)	<0.001
Post-confirmatory test PAC, pmol/L	230	179 (112–298)	173	174 (110–273)	57	223 (113–373)	0.012
Urinary aldosterone, nmol/24 h	369	68 (49–99)	247	64 (47–90)	122	76 (50–109)	<0.001

Data are expressed as median (interquartile ranges) or as a number (percentage). The number of antihypertensive drugs is expressed as mean±SD. ARR indicates aldosterone-to-renin ratio; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DDD, defined daily dose; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVH, left ventricular hypertrophy; OSAS, obstructive sleep apnea syndrome; PA, primary aldosteronism; PAC, plasmatic aldosterone concentration; PRC, plasma renin concentration; and SBP, systolic blood pressure.

in the first group and 4.1 mmol/L (IQR, 3.7–4.4) in the latter, with a *P*=0.871. The eGFR at follow-up did not differ significantly between the 2 groups: 74 mL/min per 1.73 m^2 (IQR, 60–88) in the low dose versus 69 mL/min per 1.73 m^2 (IQR, 55–85) in the high dose (*P*=0.090), although a higher proportion of patients treated with >50 mg of spironolactone had a reduction of eGFR below 60 mL/min/1.73 m^2 (40/112, 35.7%) compared with those treated with ≤50 mg (53/216, 24.5%; *P*=0.033) and a greater reduction of GFR values from baseline (-13±19 mL/min per 1.73 m^2 in the high dose versus −7±22 mL/min per 1.73 m^2 in the low dose, *P*=0.007; Table 2).

Waterfall plots showing changes in BP and potassium levels from baseline in the 2 groups are illustrated in Figures S1 and S2 (Supplemental Material).

The similar BP and potassium levels at the last follow-up visit were achieved with patients in the low dose group being treated with a higher number of antihypertensive drugs compared with those in the high dose group (3.3±1.3 versus 2.8±1.5, respectively, *P*=0.001), especially through the use of diuretics, including thiazide, thiazide-like, and loop diuretics (122 patients, 46.6% versus 41 patients, 32.8%, respectively, *P*=0.010). The daily defined dose was numerically higher in the low dose versus the high dose group: 3.7 (IQR, 1.9–5.3) and 3.0 (IQR, 2.0–5.0), respectively, without reaching statistical significance (*P*=0.466). Among the 70 patients with an assessment of renin concentrations, there was no significant difference regarding the dose of spironolactone (14.3 mIU/L (IQR, 4.3–77.7) in the low dose group

Table 2. Clinical and Biochemical Characteristics of the Patients at Follow-Up

Characteristics		Total population (n=394)		Spironolactone dose ≤50 mg (n=266)		Spironolactone dose >50 mg (n=128)	*P* value
Cross-sectional estimates							
Length of follow-up with the same dosage of spironolactone, mo	394	12 (4–29)	266	12 (4–22)	128	12 (3–49)	0.306
Spironolactone dose, mg	394	55.1±30.7 50 (25–75)	266	38.5±13.0 50 (25–50)	128	90.0±28.1 75 (75–100)	<0.001
Follow-up ≥12 mo	394	199 (50.5%)	266	133 (50.0%)	128	66 (51.6%)	0.771
Incidence of spironolactone adverse effects	394	128 (32.5%)	266	78 (29.3%)	128	50 (39.1%)	0.053
Number of antihypertensive drugs	387	3.1±1.4	262	3.3±1.3	125	2.8±1.5	0.001
DDD	372	3.3 (2.0–5.3)	255	3.7 (1.9–5.3)	117	3.0 (2.0–5.0)	0.466
Use of diuretics*	387	163 (42.1%)	262	122 (46.6%)	125	41 (32.8%)	0.010
Potassium supplementation and use of potassium-sparing diuretics	387	25 (6.5%)	262	21 (8.0%)	125	4 (3.2%)	0.080
Hypokalemia <3.5 mmol/L	333	25 (7.5%)	222	19 (8.6%)	111	6 (5.4%)	0.303
Plasma potassium, mmol/L	333	4.1 (3.8–4.4)	222	4.1 (3.8–4.4)	111	4.1 (3.7–4.4)	0.871
Plasma creatinine, µmol/L	328	92 (77–112)	216	92 (79–112)	112	94 (75–113)	0.934
GFR, mL/min per 1.73 m²	328	72 (57–87)	216	74 (60–88)	112	69 ((55–85)	0.090
eGFR < 60 mL/min per 1.73 m²	328	93 (28.4%)	216	53 (24.5%)	112	40 (35.7%)	0.033
Office SBP, mm Hg	360	130 (119–141)	244	130 (120–140)	116	129 (117–142)	0.498
Office DBP, mm Hg	360	80 (73–87)	244	80 (73–88)	116	80 (73–87)	0.752
Out-of-office SBP, mm Hg	204	128 (120–137)	153	128 (120–136)	51	129 (121–140)	0.351
Out-of-office DBP, mm Hg	204	82 (76–87)	153	81 (75–86)	51	83 (78–89)	0.177
Uncontrolled BP†	360	110 (30.6%)	244	76 (31.1%)	116	34 (29.3%)	0.724
Resistant HTN	360	41 (11.4%)	244	31 (12.7%)	116	10 (8.6%)	0.254
PRC, mIU/L	70	15.2 (4.4–47.0)	42	14.3 (4.3–77.7)	28	16.3 (5.6–35.6)	0.806
Delta variations from baseline							
Number of antihypertensive drugs	383	0.7±1.4	261	0.8±1.3	122	0.5±1.6	0.038
DDD	208	0.5±2.2	149	0.5±2.2	59	0.5±2.5	0.675
Plasma potassium, mmol/L	330	0.6±0.6	219	0.5±0.6	111	0.7±0.6	0.090
eGFR, mL/min per 1.73 m²	327	−9±21	215	−7±22	112	−13±19	0.007
Office SBP, mm Hg	353	−17±25	240	−16±26	113	−19±26	0.119
Office DBP, mm Hg	353	−11±17	240	−11±18	113	−12±16	0.737

The first section of the table displays clinical and biochemical data presented as cross-sectional estimates; the second section shows changes from baseline for all the primary outcomes. Data are expressed as median (interquartile ranges) or as a number (percentage). The number of antihypertensive drugs and the dose of spironolactone are expressed as mean±SD. BP indicates blood pressure; DBP, diastolic blood pressure; DDD, defined daily dose; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HTN, hypertension; PRC, plasma renin concentration; and SBP, systolic blood pressure.

*Diuretics include thiazides, thiazide-like, and loop diuretics.

†Uncontrolled BP stands for office blood pressure persistently > 140/90 mm Hg.

versus 16.3 mIU/L (IQR, 5.6–35.6) in the high dose; Table 2).

AE During Follow-Up

Overall, spironolactone-related AE occurred in 128 patients (32.5%) after a median follow-up of 12 months (IQR, 4–29 months), with a nearly 3-fold higher prevalence in men compared with women (44.70% versus 15.70%; *P*<0.001). Gynecomastia or mastodynia (14.2%) and erectile dysfunction or sexual impotence (10.9%) were the most frequently reported AE, leading to spironolactone discontinuation in 44 (16.5%) of those experiencing gynecomastia and in 28 (21.9%) of those complaining of erectile dysfunction. Menstrual irregularities were reported by 6/166 (3.6%) of women, causing drug withdrawal in 2 patients (Table 3).

The AE were dose–related (high dose: 39.1% versus low dose: 29.3%; *P*=0.053), with a significant difference in men (high dose: 37/60, 61.7% versus low dose: 65/168, 38.7%; *P*=0.002), especially those receiving a dose of spironolactone inferior to 25 mg/die, where the reduction was more pronounced (Table 4; Figure S3; Table S4). No significant differences were observed in women (high dose: 13/68, 19.1% versus low dose: 13/98, 13.3%, *P*=0.308; Table S2). Men in the high-dose group discontinued spironolactone due to related AE more frequently than in the low-dose group (45.0%

Table 3. Prevalence of Spironolactone-Related Adverse Effects (AE) in the Population and Proportion of Treatment Withdrawal Due to Spironolactone-Related AE; Comparison of the Prevalence of AE Between Men and Women

	Total population (n=394)		Prevalence of AE		
	Prevalence of AE	Treatment withdrawal due to AE	Men (n=228)	Women (n=166)	*P* value
All adverse effects	128 (32.5%)	75 (58.6%)	102 (44.7%)	26 (15.7%)	<0.001
Gynecomastia and mastodynia	56 (14.2%)	44 (78.6%)	55 (24.1%)	1 (0.6%)	<0.001
Inability to achieve or maintain an erection	43 (10.9%)	28 (65.1%)	43 (18.9%)	n.a.	n.a.
Menstrual irregularities	6 (1.5%)	2 (33.3%)	n.a.	6 (3.6%)	n.a.
Hyperkalemia	12 (3.0%)	3 (25.0%)	5 (2.2%)	7 (4.2%)	0.374
Renal dysfunction or worsening of renal function	6 (1.5%)	0 (0.0%)	3 (1.3%)	3 (1.8%)	0.700
Skin eruptions	2 (0.5)	1 (50.0%)	1 (0.4%)	1 (0.6%)	0.999
Others/not specified	16 (4.1%)	6 (37.5%)	8 (3.5%)	8 (4.8%)	0.515

Results are expressed as n (%). The category others/not specified includes neurological disorders (eg, mental confusion, headache, drowsiness, lethargy), digestive disorders (such as diarrhea, abdominal cramping, nausea, vomiting), and subjective intolerance to the drug. AE indicates adverse effects; and n.a., not applicable.

versus 25.0%, respectively; *P*=0.004). There was no dose-related increase in AE rate in women, who had an overall lower incidence of AE, and the discontinuation rate of spironolactone was not statistically significantly different in the low-dose and high-dose group (Tables S1 and S2). No significant differences were observed in spironolactone dose or adverse event rates between women aged ≤50 and >50 years as a proxy for premenopausal and postmenopausal status (Table S5).

Of note, in the multivariable regression analysis stratified by sex (Table S6), the occurrence of AE at follow-up was associated with spironolactone dose only in male

Table 4. Clinical and Biochemical Characteristics of Men at Follow-Up

Characteristics		Men (n=228)		Spironolactone dose ≤50 mg (n=168)		Spironolactone dose >50 mg (n=60)	*P* value
Duration of spironolactone use, mo	228	10 (4–22)	168	11 (4–21)	60	10 (2–31)	0.789
Spironolactone dose, mg	228	49.3±29.2	168	35.7±18.3	60	87.3±28.3	<0.001
Follow-up ≥12 mo	228	104 (45.6%)	168	78 (46.4%)	60	26 (43.3%)	0.679
Incidence of spironolactone AE	228	102 (44.7%)	168	65 (38.7%)	60	37 (61.7%)	0.002
Incidence of gynecomastia	228	55 (24.1%)	168	38 (22.6%)	60	17 (28.3%)	0.374
Incidence of erectile dysfunction	228	43 (18.9%)	168	25 (14.9%)	60	18 (30.0%)	0.010
Treatment withdrawal due to AE	228	69 (30.3%)	168	42 (25.0%)	60	27 (45.0%)	0.004
Number of antihypertensive drugs	223	3.5±1.3	166	3.6±1.2	57	3.2±1.5	0.026
DDD	213	4.3 (2.7–5.8)	161	4.5 (2.6–5.8)	52	4.0 (2.9–6.0)	0.886
Use of diuretics*	223	114 (51.1%)	166	91 (54.8%)	57	23 (40.4%)	0.059
Potassium supplementation and use of potassium-sparing diuretics	224	18 (8.0%)	166	16 (9.6%)	58	2 (3.4%)	0.168
Hypokalemia <3.5 mmol/L	196	18 (9.2%)	146	16 (11.0%)	50	2 (4.0%)	0.168
Plasma potassium, mmol/L	196	4.1 (3.8–4.4)	146	4.1 (3.8–4.4)	50	4.3 (3.7–4.5)	0.546
Plasma creatinine, µmol/L	194	97 (86–120)	144	96 (85–117)	50	106 (92–131)	0.093
GFR, mL/min per 1.73 m²	194	73 (56–86)	144	75 (60–88)	50	69 (51–81)	0.074
eGFR <60 mL/min per 1.73 m2	194	54 (27.8%)	144	35 (24.3%)	50	19 (38.0%)	0.063
Office SBP, mm Hg	205	131 (121–141)	151	132 (122–141)	54	130 (117–142)	0.429
Office DBP, mm Hg	205	80 (72–87)	151	80 (72–87)	54	77 (70–85)	0.412

Data are expressed as median (interquartile ranges) or as a number (percentage). The dose of spironolactone and the number of anti-hypertensive drugs are expressed as mean±SD. AE indicates adverse effects; DBP, diastolic blood pressure; DDD, defined daily dose; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; and SBP, systolic blood pressure.

*Diuretics include thiazides, thiazide-like, and loop diuretics.

patients with an odds ratio of 1.015, thus meaning an increase of 1.5% in the likelihood of developing an AE for each 1 mg of spironolactone (*P*=0.005).

Hyperkalemia and worsening of renal function were observed in 3.0% and 1.5% of subjects, respectively, with no sex-related differences. A hyperkalemia necessitating spironolactone withdrawal occurred only in 3 patients; 2 of them had chronic kidney disease and were treated with a dose of spironolactone of 75 mg, while the third was treated with 50 mg and had normal renal function.

All reported AE are shown in Table 3.

Cardiovascular Events at Follow-Up

A total of 8 patients experienced cardiovascular events during the follow-up period (low dose group: n=3 versus high dose group: n=5, *P*=0.119). We then extended the evaluation of the occurrence of cardiovascular events to the whole observation time, regardless of the dose of spironolactone and the switch to eplerenone for some patients. After a median observation time of 37 months (IQR, 19–78), a total of 17 cardiovascular events were reported, including 7 patients with acute ischemic stroke or transient ischemic attack, 5 subjects with coronary artery disease, 3 patients with heart failure, and 2 with atrial fibrillation.

DISCUSSION

This study evaluates the management of medical treatment and the optimization of spironolactone dosage in a large cohort of patients with PA. We demonstrated that men with PA treated with low doses of spironolactone (≤50 mg/d) had the same rate of BP control and potassium levels at follow-up and no difference regarding the occurrence of cardiovascular events than patients treated with a higher dose, with a reduced prevalence of spironolactone-related AE. While some clinical settings may initiate spironolactone at doses as low as 12.5 mg/d, especially in milder phenotypes, most patients in our low-dose group received 25 to 50 mg, which is consistent with both real-world prescribing patterns and European position paper on PA.[29]

Bilateral secretion of aldosterone is the most common form of PA, accounting for about 60% of all cases,[41] and benefits from medical therapy with MRA, which is also indicated in PA patients with unilateral forms not undergoing adrenalectomy. The aim of pharmacological treatment in PA is not only BP control and restoration of normokalemia, but also prevention of cardiovascular and renal damage.[22] Recent studies underlined that medically treated patients could develop a higher risk of cardiovascular events if compared with those treated surgically, especially if the blockade of the mineralocorticoid receptor is insufficient or inadequate.[42] In the study by Hundemer et al,[42] the augmented risk of cardiovascular events in medically treated patients was limited to those whose renin levels remained suppressed after the introduction of MRA. In our cohort, we could observe a rise in renin concentrations at follow-up compared with baseline in both groups, but no differences were seen in renin levels at follow-up between the low and high dose groups. Similarly to the subgroup analyses performed by Hundemer et al, where only a small subset of individuals was evaluated, it should be acknowledged that data about renin concentrations at follow-up were available only in a minority of patients in our study, and potential confounders, such as other medications, could have impacted the renin rise. Also, since a proportion of patients in our cohort still had unsuppressed renin after spironolactone introduction, it could not be excluded a low adherence to treatment in these patients.

Besides, in our cohort, after an adequate follow-up, with a controlled BP, only 17 patients experienced cardiovascular events. It is, therefore, essential that further confirmations follow, also taking into account that titration of MRA doses according to renin levels in clinical practice could be limited by the occurrence of dose-dependent AE of spironolactone. In our study, the overall prevalence of AE was higher in men treated with high doses of spironolactone than in those treated with low doses, while there was no difference for women. In male individuals, similarly to the proportions reported in previous studies,[25,43] gynecomastia and sexual dysfunction were experienced by almost 40% of subjects and required the withdrawal of the treatment in a high number of cases. It must be acknowledged that a percentage of about 30% of men described AE also at low doses of spironolactone. On the contrary, in women, the prevalence of AE did not change significantly at different doses, and the percentage of women complaining of menstrual irregularities did not reach 4%, a condition which may be more frequent since both clinicians and patients tend to underestimate the correlation between the symptoms and the assumption of the drug. Besides, the rate of hyperkalemia during MRA treatment in our cohort was low (3.0%), similar to the proportions reported in recently published studies on large cohorts of patients with PA.[10] This rate is higher in patients with heart failure or resistant hypertension, with a rate close to 20%.[44]

Finally, as stated by previous studies,[31] we confirmed that an optimal BP control could be achieved by administering low doses of spironolactone, as no differences were seen at follow-up between the 2 groups in office and out-of-office BP measurements. This goal could be obtained by a combination therapy with other antihypertensive drugs, namely diuretics, whose use was significantly more frequent in the low doses group (46.6%) than in the high doses one (32.8%). We could not assess if the MR blockade was the same in both groups; however, both dose groups achieved potassium normalization, suggesting that aldosterone blockade was sufficient in the kidney in both groups to prevent potassium wasting.

Therefore, from a practical point of view, different approaches could be proposed and discussed with the patients. In male subjects, we would suggest starting with a low dose of spironolactone combined with other antihypertensive drugs, if needed; then assess the efficacy of the treatment at 4 to 6 weeks, evaluating BP control, potassium values, drug-tolerance and, if feasible, testing drug adherence or renin levels (only in those patients who do not receive other antihypertensive drugs that could interfere with renin measurements). If spironolactone is well tolerated, but BP control is nonoptimal or potassium levels remain low, the dose of spironolactone could be increased, or another potassium-sparing diuretic could be added. If spironolactone is not tolerated, switching to eplerenone could be considered (Figure 2). It should be underlined that eplerenone is not used widely in France and in other European countries because it is not authorized for hypertension, and it can only be prescribed in PA patients with a proven intolerance of spironolactone. Besides, the efficacy of eplerenone in BP control is lower than that of spironolactone.[28] In female patients, spironolactone could be initiated at higher doses, but a proper assessment of drug tolerance should be regularly conducted, bearing in mind that the burden of AE could be underestimated.

Our results are limited by the retrospective design of the study, and by the absence of a randomized protocol, and the existence of bias, as patients receiving higher doses of spironolactone were more frequently women with higher rates of aldosterone and lower potassium levels at baseline, and were also managed earlier than those with lower doses. However, the subanalysis in male patients showed the same results. Second, we acknowledge that some of the outcomes' evaluations could be undermined by the length of follow-up and that a longer observation time would be useful to assess long-term AE and cardiovascular events. Moreover, the number of follow-up visits per patient was not available, which may have affected the assessment of outcomes. Furthermore, the treatment adherence was not assessed by analytic methods, but only through medical reports; the sodium consumption of the patients of this study was not assessed either.

PERSPECTIVES

In our study, we demonstrated that medical therapy with low doses of spironolactone in patients with PA could allow an optimal management of BP control and reduce the burden of spironolactone-related AE, especially in men. Our analysis, conducted on a large population of individuals, could help clinicians propose a personalized therapeutic approach to the patients according to compliance with the treatment and the BP targets. A prospectively designed study, with a long

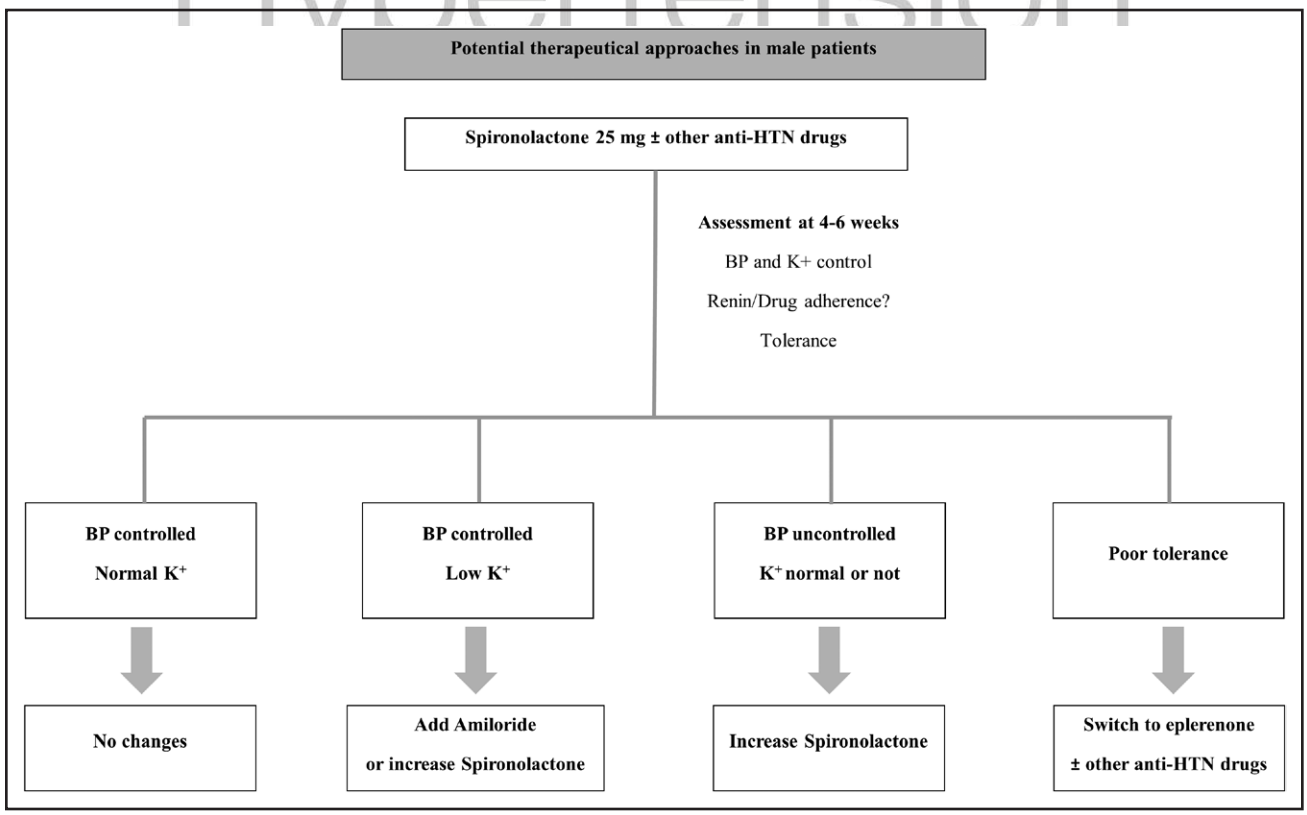

Figure 2. Flow-chart for the potential therapeutical approaches suggested in men.
BP indicates blood pressure; and HTN, hypertension.

follow-up, is necessary to evaluate the implications of medical treatment in patients with PA, to define the best way to assess compliance with the therapy, and to estimate the incidence of cardiovascular events in the long-term.

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None.

Supplemental Material

Tables S1–S5
Figures S1–S3

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