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Prevalence of Hypokalemia and Primary Aldosteronism in 5100 Patients Referred to a Tertiary Hypertension Unit

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Prevalence of Hypokalemia and Primary Aldosteronism in 5,100 patients referred to a tertiary hypertension unit.

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ABSTRACT

Primary aldosteronism (PA) was considered a rare disorder almost always associated with hypokalemia. The widespread screening of patients with hypertension unveiled an increased prevalence of PA with normokalemic hypertension the prevailing phenotype. Many studies have reported the prevalence of hypokalemia in patients with PA, conversely the prevalence of PA in patients with hypokalemia is unknown. In this retrospective observational study, we define the prevalence of hypokalemia in referred patients with hypertension and the prevalence of PA in patients with hypokalemia and hypertension. Hypokalemia was present in 15.8% of 5,100 patients with hypertension whereas 76.9% of these patients were normokalemic. PA prevalence in this cohort was significantly higher than in a cohort of 1,672 unselected patients with hypertension in primary care from the PATO study (7.8% *vs*. 5.9%, *P*=0.011). The prevalence of PA in patients with hypokalemia was 28.1% and increased with decreasing serum potassium concentrations up to 88.5% of patients with spontaneous hypokalemia and serum potassium concentrations below 2.5 mmol/L. A multivariate regression analysis demonstrated the association of hypokalemia with the occurrence of cardiovascular events independent of PA diagnosis. An association of PA with the occurrence of cardiovascular events and target organ damage independent of hypokalemia was also demonstrated. In conclusion, our results confirm that PA is a frequent cause of secondary hypertension in patients with hypokalemia and the presence of hypertension and spontaneous hypokalemia are strong indications for a diagnosis of PA. Finally, we show that PA and hypokalemia are associated with an increased risk of cardiovascular events.

Keywords: hypokalemia, potassium, primary aldosteronism, essential hypertension, cardiovascular events.

ABBREVIATION LIST: PA, Primary Aldosteronism; CV, Cardiovascular; ARR, Aldosterone-to-Renin Ratio; PRA, Plasma Renin Activity; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CKD, Chronic Kidney Disease; LVH, Left Ventricular Hypertrophy; APA, Aldosterone Producing Adenoma; EH, Essential Hypertension.

INTRODUCTION

Potassium is the most abundant cation in human body and the maintenance of potassium ion homeostasis across the cell membrane is of fundamental importance for cell function, particularly in excitable tissues, such as nerves, cardiac and skeletal muscles [1]. Current recommendations define the normal lower potassium limit from 3.5 to 3.8 mmol/L and the upper limit from 5.0 and 5.5 mmoL [2].

Hypokalemia is a common electrolyte disorder in clinical practice [1;3]. The prevalence of hypokalemia in hospitalized patients is between 6.7 and 21% [4-6]. This high variability can be explained by the different cut-offs selected for diagnosis and by characteristics of enrolled cohorts. Potassium depletion is also frequent in patients with hypertension. Recent data from a nationwide registry reported a prevalence of 3.8% [3]; this study also demonstrated an increased all-cause mortality for potassium levels < 4.1 or > 4.7 mmol/L [3].

Diuretic-induced renal loss and a diagnosis of primary aldosteronism (PA) are commonly considered as frequent causes of hypokalemia in patients with hypertension [3;7-9]. The incidence of hypokalemia in patients receiving diuretics is reported between 7.2 and 56.4% [10;11]. Conversely, the prevalence of diuretic-induced hypokalemia in patients with hypertension is unknown.

PA is characterized by an inappropriate secretion of aldosterone relative to suppressed plasma renin levels. The consequent excessive activation of the mineralocorticoid pathway produces deleterious effects, such as volume expansion, hypertension, and an increased risk of cardiovascular (CV) events. An early diagnosis and targeted treatment could reduce this excess risk [12;13]. Until the 1990s, PA was considered a rare disorder, accounting for less than 1% of patients with hypertension, almost always associated with spontaneous hypokalemia [14-16]. The introduction of the aldosterone-to-renin ratio (ARR) and the widespread screening of patients with hypertension led to a 5-to-15-fold increase in the diagnosis of PA [17] with prevalence estimates ranging from 1 to 29.8% in referral centers and from 3.2 to 12.7% in primary care practice [18], depending on different settings, patient cohorts and diagnostic criteria. The wide use of the ARR led to an increased detection of milder forms of PA. Reflecting this change, normokalemic hypertension became the most common phenotype of PA, with a prevalence comprised between 63 to 91% [17]. Indeed, hypokalemia was detected in 0-37.5% of patients with PA in primary care studies and 0-67% in referral centers [18]. Prevalence of PA increases with the severity of hypertension, from 3.9-6.6% [19;20] in stage 1, up to 20% in patients with resistant hypertension [21]. The prevalence of hypokalemia also increased to 45.6-72% in this subgroup of patients, consistent with a more severe phenotype [21;22].

A large number of studies investigated the prevalence of hypokalemia in patients with PA. Surprisingly, the prevalence of PA in patients with hypertension and hypokalemia is unknown [8]. The aim of our study was to investigate the prevalence of hypokalemia in patients referred to a tertiary hypertension unit and to identify the prevalence of PA in patients with hypokalemia. In addition, considering the relevance of potassium imbalance to cardiovascular disease, we assessed the cardiovascular risk of patients with normokalemia *versus* patients with hypokalemia, independent of the diagnosis of PA.

METHODS

Patient selection

Between 2007 and 2018, 7,110 patients were referred to our tertiary hypertension unit and of these 5,100 had at least two visits to our center, concluded the diagnostic work-up for secondary hypertension and were selected for inclusion to the study. Medical records of patients were reviewed by three independent reviewers, who were blinded to patients' identification and diagnosis and evaluated clinical data and cardiovascular risk indicators. For each patient, clinical (age, sex, duration of hypertension, systolic blood pressure [SBP] and diastolic blood pressure [DBP], weight, and BMI) and biochemical parameters (sodium, potassium, creatinine, glucose, total cholesterol, HDL, triglycerides, PRA and aldosterone) were assessed. We considered the lowest available serum potassium concentration to define hypokalemia ($K^+ < 3.7$ mmol /L) and the highest to define hyperkalemia ($K^+ > 5.2$ mmol/L). Subjects with both hypokalemia and hyperkalemia were classified in the group with hypokalemia. In most cases (36 of 42 patients), subjects displaying both hypokalemia and hyperkalemia were patients with PA that had hypokalemia at diagnosis that subsequently developed hyperkalemia after adrenalectomy or therapy with mineralocorticoid receptor antagonists. When potassium measurements were all comprised between 3.7 and 5.2 mmol/L, patients were considered in the group with normokalemia and the first available measurement was used in the analysis. For each patient, clinical and biochemical parameters closest to the selected potassium measurement were considered in the analysis. For patients with hypokalemia, we determined when possible, the factor(s) responsible for the reduction in potassium levels (PA, diuretic-induced hypokalemia, reno-vascular hypertension, Cushing syndrome, laxative use/diarrhea, licorice or grapefruit abuse, monogenic forms of low-renin hypertension).

The entire cohort was also compared with a previously described population of 1,672 unselected primary care patients with hypertension [20].

Cardiovascular risk indicators

We considered as CV events (occurring after the considered potassium measurement) sustained arrhythmias (atrial fibrillation, atrial flutter, sustained ventricular tachycardia, and ventricular fibrillation), coronary heart disease (myocardial infarction and unstable angina requiring angioplasty), heart failure requiring hospitalization, stroke (ischemic stroke or transient ischemic attack). Other reported events were pre-eclampsia, aortic dissection, acute kidney injury and hypertensive encephalopathy. Chronic kidney disease (CKD) was defined if eGFR was lower than 60 mL/min [23]; diabetes, metabolic syndrome, and dyslipidemia were defined according to guidelines [24-26]. Left ventricular hypertrophy (LVH) was assessed by left ventricular mass index calculated with the formula: 0.8 * 1.04 * [(interventricular septum + left ventricular internal diameter + inferolateral wall thickness)^3 - left ventricular internal diameter^3] + 0.6 gr. LVH was defined as a left ventricular mass index >115 g/m^2 (men) or >95 g/m^2 (women) [27]. Microalbuminuria was diagnosed in presence of urine albumin concentration of 30–300 mg/24 h or by an albumin to creatinine ratio of 30–300 mg/g [27].

Diagnostic criteria

PA was diagnosed in agreement with the Endocrine Society guideline [8]. An aldosterone-to-renin ratio (ARR) greater than 30 $ng/dL/ng*mL^{-1}*h^{-1}$ together with an aldosterone level greater than 10 ng/dL were considered for a positive screening test; all patients with a positive screening test underwent confirmatory/exclusion testing through an intravenous saline loading test or a captopril challenge test, as previously described [20]. Patients with a confirmed diagnosis of PA underwent subtype differentiation through CT scanning and adrenal venous sampling. Other forms of secondary hypertension associated with hypokalemia (reno-vascular hypertension, Cushing syndrome, Liddle syndrome) were diagnosed according available guidelines [27;28].

Statistical analysis

IBM SPSS Statistics 22 (*IBM Corp., Armonk, New York, USA*) was used for statistical analyses. Data were analyzed with the Kolmogorov–Smirnov test to determine their distributions. Normally distributed variables are expressed as mean ± standard deviation and were analyzed by ANOVA one-way and Bonferroni post-hoc tests. Non-normally distributed variables are expressed as median [interquartile range] and were analyzed by Mann-Whitney's and Kruskall-Wallis. Categorical variables are expressed as absolute number and proportion (percentage, %) and were analyses by Chi-square and Fisher tests. Multivariate logistic regression was used to determine odds ratios (ORs) and assess the association between hypokalemia and cardiovascular risk indicators. An OR greater than 1 indicates an increased likelihood of the evaluated variable, whereas an OR less than 1 a decreased likelihood. *P*-values of less than 0.05 were considered significant.

RESULTS

Hypokalemia: prevalence, etiology and associated CV events

After the exclusion of patients with hyperkalemia (n = 374), the final cohort was composed of 4,726 patients, including 3,922 normokalemic and 804 hypokalemic patients (Figure 1). Demographic and clinical features of patients included in the analysis are summarized in Table 1. Overall, the mean age was 50 ± 13 years, 53.4% were men. The prevalence of hypokalemia was 15.8% (804 of 5,100 patients).

The main causes of hypokalemia were diuretic therapy or a diagnosis of PA (Table 2). The prevalence of PA was 28.1% (226 of 804 patients); 8.3% had an aldosterone producing adenoma (APA) and 19.0% were diagnosed as bilateral PA. Diuretic-induced hypokalemia was detected in 357 patients (44.4%): 40.9% of patients used thiazide diuretics and 4.3% loop diuretics. The other considered causes were reno-vascular hypertension, Cushing syndrome, Liddle syndrome, laxatives/diarrhea, licorice or grapefruit abuse, which justified 7.3% of hypokalemia cases. Finally, in 248 patients

(30.8%) we could not identify the cause of hypokalemia. Compared with normokalemic patients, patients with hypokalemia were older (52 ± 12.8 *versus* 49 ± 13.1 years; $P < 0.001$), with a longer known duration of hypertension (10 [4-19] *versus* 7 [3-13] years; $P < 0.001$) and higher SBP (158 ± 25 *versus* 154 ± 21.6 years; $P < 0.001$). As expected, aldosterone values were higher, and potassium and PRA levels were lower in patients with hypokalemia. In addition, glucose and triglycerides, were significantly higher, whereas HDL levels were lower in patients with hypokalemia ($P < 0.001$ for all comparisons; Table 1).

For all patients included in the analysis, we evaluated the occurrence of CV events, target organ damage and the diagnosis of CKD, diabetes, metabolic syndrome, and/or dyslipidemia (Table 1). Comparing patients with hypokalemia *versus* normokalemia, we demonstrated a higher prevalence of CV events (10.7% *versus* 6.3%; $P < 0.001$). In detail, patients with hypokalemia displayed more frequently arrhythmias (3.4% *versus* 1.8%; $P = 0.006$), heart failure (1.0% *versus* 0.4%; $P = 0.032$), and stroke (3.3% *versus* 1.1%; $P < 0.001$). There was no difference regarding the age of patients at the event (58 ± 13.3 *versus* 56 ± 14.1 years; $P = 0.223$). Moreover, patients with hypokalemia displayed a significantly higher prevalence of CKD (8.6% *versus* 3.2%; $P < 0.001$), diabetes (10.4% *versus* 7.9%; $P = 0.025$), metabolic syndrome (46.0% *versus* 31.9%; $P < 0.001$), LVH (61.9% *versus* 54.3%; $P = 0.001$), and microalbuminuria (20.1% *versus* 15.3%; $P = 0.005$).

To further characterize the CV risk of these patients, we performed a multivariate logistic regression analysis, evaluating associations between hypokalemia, and cardiovascular events, CKD, diabetes, metabolic syndrome, LVH, or microalbuminuria; we considered sex, age, duration of hypertension, SBP, and a diagnosis of PA, as possible confounding factors (Table 3). We confirmed the association of hypokalemia with cardiovascular events (OR 1.37; 95% CI 1.06-1.77; $P = 0.017$), CKD (OR 1.75; 95% CI 1.22-2.52; $P = 0.003$), and metabolic syndrome (OR 1.59; 95% CI 1.32-1.90; $P < 0.001$). Of note, the same analysis demonstrated the association between PA and cardiovascular events (OR 1.53; 95% CI 1.12-2.10; $P = 0.007$), CKD (OR 1.80; 95% CI 1.18-2.75; $P = 0.007$), diabetes (OR

1.68; 95% CI 1.19-2.39; $P = 0.003$), metabolic syndrome (OR 1.78; 95% CI 1.31-2.34; $P < 0.001$), LVH (OR 1.32; 95% CI 1.01-1.74; $P = 0.034$), and microalbuminuria (OR 1.66; 95% CI 1.19-2.34; $P = 0.003$), independent of serum potassium concentrations and the other considered confounding factors.

Prevalence of primary aldosteronism

The prevalence of PA in the entire cohort was 7.8% (396 of 5,100 patients) compared with 28.1% in patients with hypokalemia and 4.3% in patients with normal potassium levels. In patients with diuretic-induced or spontaneous hypokalemia, the prevalence was 16.5% (59 of 357 patients) and 37.4% (167 of 447 patients), respectively (Figure 2A and Supplemental Table S1). The prevalence of PA progressively increased from 0.8%, with serum potassium of 5.0 to 5.2 mmol/L, up to 76.7% in patients with serum potassium concentrations below 2.5 mmol/L (Figure 2B). Considering only patients with spontaneous hypokalemia, the prevalence of PA increased from 21.8% in patients with serum potassium of 3.5-3.6 mmol/L up to 88.5% in patients with serum potassium concentrations below 2.5 mmol/L. In patients with PA, 42.9% were normokalemic and 57.1% had hypokalemia, making hypokalemic hypertension the more common phenotype in our cohort.

Essential hypertension (EH) was the main cause of hypertension in patients with normokalemia (94.7%; 3,669 of 3,922) and hypokalemia (69.8%; 605 of 804). Considering only patients with EH, 86.9% displayed normokalemia and 13.1% hypokalemia. In addition, normal serum potassium concentrations were the most frequent findings also in patients with Cushing syndrome, pheochromocytoma, and reno-vascular hypertension (75.0%, 72.7%, and 67.6% of patients with normokalemia, respectively; Supplemental Table S2 and Figure S1).

Finally, to evaluate if selection bias influenced the data of our cohort, we compared patient data from this study with that from the 1,672 unselected patients with hypertension in primary care from the PATO cohort (Supplemental Table S1 and S3) [20]. Compared with our selected cohort, patients

from the PATO study were younger (46 ± 9 years; $P < 0.001$), with a shorter known duration of HTN (3 [1-7] years; $P < 0.001$) and lower BP values (147 ± 15 / 94 ± 8 mmHg; $P < 0.01$). The prevalence of diabetes and LVH was lower (respectively, 4.0% - $P < 0.001$ and 33.3% - $P < 0.001$) and patients displayed significantly higher levels of HDL and lower levels of glucose, total cholesterol, and triglycerides ($P < 0.01$ for all comparisons).

The overall prevalence of PA was lower in the PATO study compared with the present cohort (5.9% *versus* 7.8% patients; $P = 0.011$; Figure 2A), whereas we did not observe any significant differences in PA prevalence in normokalemic (4.5% *versus* 4.3%; $P = 0.764$), and hypokalemic patients (27.4% *versus* 28.1%; $P = 0.862$), and neither among patients with diuretic-induced (19.1% *versus* 16.5%; $P = 0.655$), or spontaneous hypokalemia (33.9% *versus* 37.4%; $P = 0.603$). Finally, stratifying patients for potassium levels, the distribution of patients with a diagnosis of PA was similar to our cohort ($P > 0.05$ for all comparisons; Figure 2B).

DISCUSSION

In this retrospective analysis of 5,100 referred patients with hypertension, we report the prevalence, clinical and biochemical characteristics of subjects with hypokalemia. For the first time we establish the prevalence of PA in hypokalemic patients with hypertension and demonstrate the association of hypokalemia and PA with an unfavorable CV outcome.

The prevalence of hypokalemia in the cohort with hypertension reported herein was 15.8%. To date, a single study screened a large cohort of 44,799 hospitalized patients with hypertension from a national registry, reporting a prevalence of 3.8% [3]. Differences in strategy for patient selection and the definition of hypokalemia (< 3.5 mmol/L *vs.* < 3.7 mmol/L) may explain this wide variance between our study and the previous report. In addition, the observational study of Krogager et al.,

defined hypertension by the use of at least two concomitant anti-hypertensive medications, which may have led to the misclassification of several patients.

In our cohort the main causes of hypokalemia were the use of diuretics or PA. Diuretic-induced renal potassium loss is attributed to the inhibition of water, sodium and chloride reabsorption in the loop of Henle or in the distal tubule, as well as to increased aldosterone secretion due to volume depletion [29]. A total of 7.2% of the chlortalidone-treated patients with hypertension in the Systolic Hypertension in the Elderly Program (SHEP) were hypokalemic [11], compared with 8.5% of patients treated with chlortalidone for 4 years in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial [30] and with 56.4% of 447 referred patients receiving hydrochlorothiazide [10]. The incidence of hypokalemia in patients with hypertension receiving diuretics is well described [7], but the prevalence of diuretic-induced hypokalemia has never been systematically investigated. In our study, diuretics were the putative cause of potassium depletion in 44.4% of patients with hypokalemia receiving thiazide diuretics (40.9%) and/or loop diuretics (4.3%).

PA was the second cause of hypokalemia in our cohort. The prevalence of PA was 28.1% in patients with hypokalemia increasing to 37.4% in cases of spontaneous hypokalemia. The detection rate of PA gradually increased with decreasing serum potassium concentrations, with a maximum prevalence of 88.5% for patients with spontaneous hypokalemia and serum potassium below 2.5 mmol/L. Although spontaneous or diuretic-induced hypokalemia were originally considered prerequisite for screening patients for PA [31], several studies have since demonstrated that hypertension with normokalemia is common in patients with PA (reviewed in Käyser et al. [18] and Buffolo et al. [16]). This has been demonstrated convincingly in patients in primary care, where the mean prevalence of hypokalemia is 20.9% [18;20;32;33], compared with a mean prevalence of 43.4% in referral centers, when studies which enrolling more than 100 patients are considered [17-

19;22;34;35]. In our study, 57.1% of PA patients displayed hypokalemia, consistent with estimates in referred patients and in agreement with a more florid phenotype.

In the overall cohort, the prevalence of PA was higher compared with the unselected primary care patients with hypertension in the PATO study (7.8 *vs* 5.9%), whereas no differences were found between the two hypertensive populations either after stratification for potassium levels [20]. Of note, only 6.3% of the PATO cohort displayed hypokalemia, corresponding to around half that in the present study. These data confirm PA as a frequent cause of secondary hypertension in referred and primary care patients, and support screening for PA in most patients with hypertension, independent of serum potassium concentrations [18;20].

Finally, we demonstrated a higher prevalence of CV events, CKD, diabetes, metabolic syndrome, LVH, and microalbuminuria in patients with hypokalemia. Considering the high prevalence of PA in these patients, we hypothesize that hypokalemia could explain part of the excess risk of CV events associated with PA [12;36]. In the multivariate analysis, after correction for possible confounders, such as sex, age, duration of hypertension and BP levels, hypokalemia was associated with CV events, CKD, and metabolic syndrome independent of a diagnosis PA, whereas PA was associated with CV events, CKD, diabetes, metabolic syndrome, LVH, and microalbuminuria independent of hypokalemia.

Several observational studies have demonstrated the association of abnormal potassium concentrations with increased mortality, major CV events, and hospitalization rates in different selected cohorts [9;37-39]. In all cases, studies observed a high risk of adverse outcomes in patients with hypokalemia [1;9;39].

Few studies have focused on patients with hypertension, reporting similar associations between serum potassium concentrations and outcomes [2;3;29]. Of note, serum potassium below 3.5 mmol/L is

associated with a 2.1-fold increased risk of all-cause mortality in patients with hypertension [3]. In accordance with these findings, in our cohort hypokalemia was associated with CV events independent of sex, age, duration of HTN, systolic BP and diagnosis of PA.

Patients with PA displayed an increase of CV events and target organ damage, in agreement with previous reports [12;20;36;40;41]. In patients with PA, the association between hypokalemia and CV risk is not entirely dependent on a more severe blood pressure phenotype; indeed, the multivariate analysis showed that PA and hypokalemia were independently associated with the occurrence of CV events.

The strengths of our study are the systematical assessment of hypokalemia in a large cohort of patients with hypertension and the use of strict criteria for the diagnosis of PA. Medical records were independently reviewed by three investigators who were blind to patients' diagnosis, thus excluding any adjudication bias. Moreover, this is the first study reporting the prevalence of PA among patients with hypokalemia.

The main limitation is the retrospective observational design resulting in the exclusion of 2,010 of 7,110 patients because the diagnostic work-up was not concluded. A further limitation is that we cannot determine if the association of increased CV events with hypokalemia and PA diagnosis is caused by decreased potassium concentrations or is simply a marker of associated pathologies.

In conclusion, arterial hypertension is frequently associated with PA and hypokalemia; PA is particularly frequent among hypokalemic hypertensive patients and its prevalence gradually increases with the decrease of potassium levels; indeed, 1 of 3 patients with hypokalemia was diagnosed as PA in our study. Finally, PA and hypokalemia are independently associated with the occurrence of CV events.

PERSPECTIVES

Normokalemia does not exclude the diagnosis of PA, nevertheless the presence of hypokalemia and hypertension strongly suggests this condition and is associated with a worse CV risk profile. Clinicians and general practitioners should focus attention on risks of hypokalemia in patients with a diagnosis of EH and PA. The reported prevalence of PA in patients with hypokalemia should to be confirmed in large prospective multi-center cohorts. Future studies may elucidate further the association between hypokalemia and PA with increased CV risk and target organ damage.

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Conflict(s) of Interest/Disclosure(s): nothing to disclose.

NOVELTY AND SIGNIFICANCE

What is New?

- We reported for the first time the prevalence of PA in a cohort of referred patients with hypertension and hypokalemia;
- PA and hypokalemia are independently associated with an increased risk of cardiovascular events;

What is Relevant?

- The prevalence of hypokalemia is 15.8% among referred patients with hypertension;
- Main causes of hypokalemia are diuretic therapy (44.4%) or a diagnosis of PA (28.1%);
- The prevalence of PA gradually increases with decreasing of potassium levels, up to 88.5% in patients with spontaneous hypokalemia and serum potassium below 2.5 mmol/L;

Summary

Hypokalemia is frequent in patients with hypertension. The presence of hypertension and spontaneous/diuretic-induced hypokalemia strongly suggests a diagnosis of PA, which is associated with an increased cardiovascular risk independent of potassium levels.

Table 1 *– Patients Characteristics*

Variable	Total cohort	Patients with Normokalemia	Patients with Hypokalemia	*P-Value*
Clinical characteristics				
Age (years)	50 ± 13.1	49 ± 13.1	52 ± 12.8	<0.001
Sex (Male; %)	2522 (53.4)	2087 (53.2)	436 (54.2)	0.635
Duration of HTN (years)	7.0 [3.0-14.0]	7.0 [3.0 – 13.0]	10.0 [4.0 – 19.0]	<0.001
SBP (mmHg)	155 ± 22.2	154 ± 21.6	158 ± 25.0	<0.001
DBP (mmHg)	95 ± 11.9	95 ± 11.8	95 ± 12.9	0.125
BMI (Kg/m^2)	26.4 ± 4.4	26.3 ± 4.4	26.5 ± 4.4	0.280
Biochemical characteristics				
K^+ (mmol/L)	4.1 ± 0.5	4.3 ± 0.3	3.3 ± 0.3	<0.001
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.772
Glucose (mg/dL)	97 ± 21.9	97 ± 21.9	100 ± 21.6	<0.001
Cholesterol Tot (mg/dL)	214 ± 40.9	214 ± 40.6	214 ± 43.0	0.868
HDL (mg/dL)	54 ± 15.2	54 ± 15.2	52 ± 15.2	0.003
Triglycerides (mg/dL)	128 ± 79.9	127 ± 79.4	137 ± 82.5	0.017
PRA (ng/mL/h)	1.2 [0.4 – 3.3]	1.3 [0.5 – 3.3]	0.9 [0.3 – 2.9]	<0.001
Aldosterone (ng/dL)	18.4 [11.8 – 27.5]	17.6 [11.4 – 26.4]	22.0 [14.3 – 33.4]	<0.001
Cardiovascular profile				
CV event (yes; %)	332 (7.0)	246 (6.3)	86 (10.7)	<0.001
Age at event (years)	56.3 ± 13.9	55.8 ± 14.1	57.5 ± 13.3	0.223
Arrhythmias (yes; %)	99 (2.1)	72 (1.8)	27 (3.4)	0.006
CAD (yes; %)	64 (1.4)	50 (1.3)	14 (1.8)	0.290
Heart failure (yes; %)	24 (0.5)	16 (0.4)	8 (1.0)	0.032
Stroke (yes; %)	71 (1.5)	45 (1.1)	26 (3.3)	<0.001
Other events (yes; %)	74 (1.6)	63 (1.6)	11 (1.4)	0.627
CKD (yes; %)	193 (4.1)	124 (3.2)	69 (8.6)	<0.001
Diabetes (yes; %)	376 (8.4)	293 (7.9)	83 (10.4)	0.025
Metabolic Syndrome (yes; %)	1438 (34.6)	1070 (31.9)	368 (46.0)	<0.001
Dyslipidemia (yes; %)	3314 (74.8)	2721 (74.9)	593 (74.1)	0.649
LVH at echo (yes; %)	1832 (55.8)	1437 (54.3)	395 (61.9)	0.001
Microalbuminuria (yes; %)	445 (16.3)	329 (15.3)	116 (20.1)	0.005

Legend to Table 1 – Clinical and biochemical parameters of patients included in the analysis (N = 4,726). The table reports data recorded in the visit closest to the considered potassium value (see methods), cardiovascular profile (events and target organ damage), and the comparison between patients with normokalemia (N = 3,922) or hypokalemia (N = 804). HTN, Hypertension; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PRA, Plasma Renin Activity; CV, Cardio-

Vascular; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; LVH, Left Ventricular Hypertrophy. Differences were considered significant for *P*-values < 0.05.

Table 2 *– Causes of Hypokalemia*

Etiology	**N (%)**
Primary aldosteronism (yes; %)	226 (28.1)
Aldosterone Producing Adenoma	67 (8.3)
Bilateral Primary Aldosteronism	153 (19.0)
Undetermined	6 (0.8)
Diuretic-induced hypokalemia (yes; %)	357 (44.4)
Thiazide Diuretics	329 (40.9)
Loop Diuretics	34 (4.3)
Other causes (yes; %)	59 (7.3)
Reno-Vascular Hypertension	13 (1.6)
Cushing syndrome	6 (0.8)
Liddle syndrome	1 (0.1)
Laxative/Diarrhea	9 (1.1)
Licorice/Grapefruit	17 (2.2)
No identified causes	248 (30.8)

Legend to Table 2 – Causes and prevalence of hypokalemia in our cohort. The table reports number of patients and percentages referred to the cohort with hypokalemia (N = 804).

Table 3 *– Associations of hypokalemia and primary aldosteronism with cardiovascular and metabolic complications and organ damage*

Variables	Sex (ref. male)	Age (years)	Duration of HTN (years)	Systolic BP (mmHg)	PA diagnosis (ref. present)	Hypokalemia (ref. present)
Cardiovascular Events	**1.15** (0.93-1.43) *0.189*	**1.04** (1.03-1.05) *< 0.001*	**1.01** (0.99-1.02) *0.131*	**1.01** (0.99-1.01) *0.254*	**1.53** (1.12-2.10) *0.007*	**1.37** (1.06-1.77) *0.017*
Chronic Kidney Disease	**1.31** (0.95-1.81) *0.097*	**1.06** (1.04-1.08) *< 0.001*	**1.01** (0.99-1.02) *0.578*	**1.01** (1.01-1.02) *0.001*	**1.80** (1.18-2.75) *0.007*	**1.75** (1.22-2.52) *0.003*
Diabetes	**1.07** (0.84-1.35) *0.595*	**1.04** (1.02-1.05) *< 0.001*	**1.01** (0.99-1.02) *0.268*	**1.01** (1.01-1.02) *< 0.001*	**1.68** (1.19-2.39) *0.003*	**0.96** (0.71-1.30) *0.796*
Metabolic Syndrome	**1.48** (1.28-1.72) *< 0.001*	**1.02** (1.02-1.03) *< 0.001*	**1.01** (1.01-1.03) *0.001*	**1.01** (1.01-1.01) *< 0.001*	**1.78** (1.31-1.44) *< 0.001*	**1.59** (1.32-1.90) *< 0.001*
Left Ventricular Hypertrophy	**2.42** (2.05-2.87) *< 0.001*	**1.04** (1.03-1.04) *< 0.001*	**1.01** (0.99-1.02) *0.236*	**1.02** (1.01-1.02) *< 0.001*	**1.32** (1.01-1.74) *0.034*	**1.15** (0.93-1.43) *0.197*
Microalbuminuria	**1.48** (1.17-1.88) *0.001*	**0.99** (0.98-1.00) *0.171*	**1.01** (0.99-1.02) *0.315*	**1.01** (1.01-1.02) *< 0.001*	**1.66** (1.19-2.34) *0.003*	**1.21** (0.91-1.61) *0.188*

Legend to Table 3 – Multivariate logistic regression analysis: association between PA and hypokalemia with cardiovascular events, CKD, diabetes, metabolic syndrome, LVH at echocardiography, and microalbuminuria. Sex, age, duration of HTN (hypertension), and systolic BP (blood pressure) were considered as possible confounding factors. The table reports the OR (odds ratio) in bold, the 95% confidence interval (in brackets) and the *P*-value in italics. Differences were considered significant for *P*-values < 0.05.

FIGURE LEGENDS

Figure 1 – Study Flow Chart

Legend to Figure 1 – From 7,110 patients referred to a tertiary hypertension unit, we selected 5,100 patients for the analysis: 374 hyperkalemic (7.3%), 3,922 normokalemic (76.9%), and 804 hypokalemic patients (15.8%).

Figure 2 – Prevalence of Primary Aldosteronism

Legend to Figure 2 – Prevalence of Primary Aldosteronism (PA) in different cohorts. Black bars represent all patients included in the analysis (N = 4,726), grey bars represent the PATO study cohort (N = 1,672). (A) Comparison of PA prevalence in patients with hypokalemia and normokalemia. (B) Prevalence of PA stratified for lowest serum potassium concentrations. Differences were considered significant for *P*-values < 0.05. **P*-value < 0.05.

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