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Incidence of Primary Aldosteronism in Patients with Hypokalemia (IPAHK$^+$): Study Design and Baseline Characteristics

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ABSTRACT

Hypokalemia plays a central role for case finding, course, treatment decision, and prognosis of patients with primary aldosteronism. However, to date there is a lack of high-level evidence about the incidence of primary aldosteronism in hypokalemic patients. The IPAHK$^+$ study is an epidemiological, cross-sectional, monocentric study to provide evidence on the incidence of PA in a hypokalemic population. The aim of the current analysis was to describe the baseline characteristics of the first 100 patients eligible for study inclusion. The recruitment of patients with hypokalemia (≤ 3 mmol/l) is carried out continuously on a referral-basis by the central laboratory of the University Hospital Zurich through an automated suitability testing and data delivery system. The careful evaluation of the first 100 reported patients was based on the available reporting system. Out of 28 140 screened patients, 222 (0.79 %) were identified with a serum potassium value of ≤ 3 mmol/l (mean 2.89 ± 0.02 mmol/l). Mean potassium levels were slightly lower in non-hypertensive subjects compared to hypertensive subjects (mean difference 0.07 mmol/l, p = 0.033), while no significant difference was found between the sexes and patients with and without the diagnosis of primary aldosteronism, atrial fibrillation, or the use of diuretics. The incidence of PA was 4 % in the total population studied and 7.5 % in the subgroup of hypertensive patients. In conclusion, the continuous enrollment of patients from the IPHAK$^+$ hypokalemia registry into the IPAHK$^+$ trial will provide evidence about the actual incidence of primary aldosteronism in a hypokalemic outpatient population.

ABBREVIATIONS

ABPM	Ambulatory blood pressure measurement
APA	Aldosterone producing adenoma
ARR	Aldosterone-to-renin ratio
BAH	Bilateral adrenal hyperplasia
BMI	Body mass index
CCT	Captopril challenge test
ECG	Electrocardiogram
HYRENE	Hypertension Research Network
IQR	Interquartile range
MR	Mineralocorticoid receptor
NCCR Kidney.CH	The National Centre of Competence in Research Kidney Control of Homeostasis
PA	Primary aldosteronism
REDCap	Research Electronic Data Capture
RAAS	Renin-angiotensin-aldosterone system
SIT	Saline infusion test
USZ	University Hospital Zurich

Introduction

Primary aldosteronism (PA) comprises a group of endocrine disorders with inadequate oversecretion of aldosterone decoupled from the physiological regulatory circuits. Bilateral adrenal hyperplasia (BAH) and aldosterone producing adenoma (APA) represent the most frequent causes of PA with 70 and 30 %, respectively, while adrenal carcinoma and hereditary disorders are rare findings (< 1 % each) [1]. In the setting of low levels of renin and angiotensin II, aldosterone mediated activation of renal mineralocorticoid receptors (MR) results in considerable sodium and secondary fluid retention. The reabsorption of sodium in the aldosterone-sensitive distal portions of the nephron further provides a sustained driving force for the luminal secretion of potassium and hydrogen in equal quantities. Thus, PA typically results in arterial hypertension and facultative hypokalemia and metabolic alkalosis. With a prevalence of 5–12 % in hypertensive patients, PA constitutes the most common endocrine cause of secondary hypertension [2–6]. Despite this high prevalence, PA remains underappreciated particularly in primary care, due to imprecise and therefore difficult to apply screening indications as well as the necessity of complex, multi-step, error-prone and cost-intensive diagnostics. An improvement and simplification of disease recognition, however, would be of particular importance from both, a patient and health economic perspective. Compared to essential hypertension, PA is associated with worse cardiovascular morbidity and mortality due to the systemic effects of aldosterone excess [7]. Since effective targeted drug therapies and potentially even curative surgical treatments exist, an early diagnosis could prevent or at least delay the development of PA-associated long-term complications in a large number of cases.

Against this background, the "Incidence of Primary Aldosteronism in Patients with Hypokalemia" (IPAHK$^+$) study was designed with the long-term perspective to increase the detection rate of PA by improving the evidence level of current screening recommendations, that are largely based on cohort-specific prevalences. Specifically, screening for PA is indicated in patients with moderate (prevalence 8 %), severe (13 %) and drug-resistant hypertension (17–23 %) [8]. Furthermore, patients with adrenal incidentaloma (2 %) or sleep apnea syndrome (34 % among newly diagnosed hypertensive patients) should be evaluated for the disease [8]. Last but not least, also patients with spontaneous or diuretic-induced hypokalemia and simultaneous hypertension are screening candidates [8]. The link between hypokalemia and PA is plausible from a pathophysiological point of view and proven by numerous studies [8–11]. However, prevalence data of PA in a hypokalemic population independent of other factors such as hypertension are still missing. Hypokalemia is of particular importance in the context of the disease with respect to pre-analytics, differential diagnosis, course of disease, treatment and prognosis [8, 9]. The IPAHK$^+$ trial, which was launched in October 2019, will provide the first high-level evidence data on the incidence of PA in an unselected hypokalemic outpatient cohort. This information could ultimately allow more targeted screening recommendations to be made, ideally based on specific potassium levels. In addition, we expect to gain insights into whether different potassium levels correlate with specific features of the disease.

Here, we describe the baseline characteristics of the first 100 patients eligible for study participation.

Design and Methods

IPAHK$^+$ was designed as an epidemiological cross-sectional study including patients with defined hypokalemia (≤ 3.0 mmol/l) conducted at the University Hospital Zurich (USZ), Switzerland. The recruitment of patients is carried out continuously on a referral-basis by the central laboratory of the hospital through an automated suitability testing and data delivery system.

Eligibility Criteria

Male and female outpatients of the University Hospital Zurich over 18 years of age with a serum potassium level ≤ 3.0 mmol/were defined eligible to participate in the study if they had signed a general informed consent. The cut-off value for hypokalemia was chosen with the intention to include only patients with moderate to severe hypokalemia as mild hypokalemia often also occurs in otherwise healthy individuals.

Key exclusion criteria include inpatients, pregnant or lactating women, comorbidities resulting in a life expectancy of less than one year and the inability to follow the procedures of the study.

Objectives

The primary objective of this study is to determine the incidence of PA in outpatients from the USZ with a random serum potassium level ≤ 3 mmol/l in the presence or absence of hypertension. Secondarily, the study aims to assess whether the incidence of PA correlates with different serum potassium levels. Beyond that, evidence will be gathered whether the level of hypokalemia correlates with the extent of clinical and metabolic characteristics of PA. These include the stage of hypertension, the history of cardiovascular events such as myocardial infarction, strokes and atrial fibrillation, the occurrence of muscle weakness and evidence of hyponatremia or hypomagnesemia.

Final diagnosis

The diagnosis of PA in this study follows the internationally recommended routine procedure. Each step in this multistep process is performed as previously described [8]. A prerequisite for meaningful results of all tests is the prior adaption of the participants' drug regime according to the clinical standard to prevent interference with the renin-angiotensin-aldosterone system (RAAS). If needed to maintain hypertension control, the established therapy is therefore temporarily switched to Verapamil slow-release 120–240 mg twice daily and/or Doxazosin 4–8 mg once daily for one or four weeks, depending on the original medication [8]. In addition, the participants are given oral potassium supplements to provide normokalemic conditions for testing, whenever necessary as hypokalemia can lead to false negative sreening results. During blood collection, care is taken to minimize factors that may induce hemolysis (e. g., fist clenching, late release of the tourniquet, aspiration, etc.) as this can mask hypokalemia due to incorrectly high potassium levels [12].

The calculation of the aldosterone-to-renin ratio (ARR) serves as the gold standard for the screening for PA. Aldosterone and renin are measured with chemiluminescence assays (CLIA) from DiaSorin with the Liasion XL analyzer. If aldosterone is > 50 ng/l and the ARR > 11.5 ng/mU (thresholds defined by the manufacturer DiaSorin) a subsequent confirmatory test will either confirm or rule out the diagnosis. Many different test methods are established for this latter purpose. For IPAHK+, the saline infusion test (SIT) is primarily used. An aldosterone level above 60 ng/l after saline infusion in the sedentary patient confirms the diagnosis of PA, provided that the renin concentration is simultaneously suppressed and serum-cortisol did not increase [8]. Only if there are contraindications for the implementation of a SIT or if the results from the SIT are ambiguous a captopril challenge test (CCT) is used as an alternative. A decline in aldosterone to less than 30 % of baseline after 120 minutes is consistent with the diagnosis of PA [8].

Independently of the study, patients with newly diagnosed PA were offered further diagnostics for subtype differentiation (adrenal imaging, adrenal vein catheter sampling) and adequate treatment.

Data collection

Study related data are collected and managed using REDCap electronic data capture tools hosted at the University Hospital Zurich. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies [13].

Results

Study recruitment started on 1 October 2019 and is ongoing. By 30 December 2019, a total of 100 patients eligible for study participation were registered through the electronic reporting system. Up to this point, 28 140 ambulatory potassium measurements were performed of which 0.79 % were found to be ≤ 3.0 mmol/l (▶ **Fig. 1**). Of 222 hypokalemia reports, a total of 122 were excluded: 64 patients had not signed the general consent form, in further 34 cases, multiple measurements were registered in patients who had already been included, and 22 patients suffered from concomitant diseases that did not allow study participation or resulted in a life expectancy of less than one year.

▶ **Table 1** Baseline characteristics of the first 100 patients in the IPAHK+ hypokalemia registry.

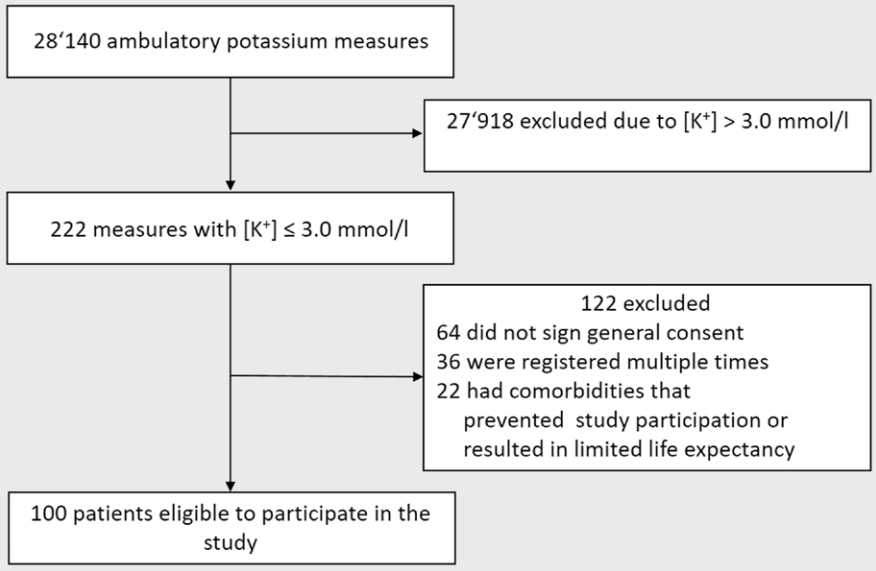
IPAHK+ Registry (n = 100)	
Age (years) median [range]	57 [22; 92]
Sex distribution male/female (%)	53/47
Hypertension (%)	53
Atrial fibrillation (%)	7
Primary aldosteronism (%)	4
Use of diuretics (%)	37
Use of laxatives (%)	12
Use of MR-agonists (%)	12
Potassium supplementation (%)	20
K+ mean (mmol/l) [range]	2.9 [2.3, 3.0]
K+ ≤ 3.0 mmol/l (%)	100
K+ ≤ 2.9 mmol/l (%)	46
K+ ≤ 2.8 mmol/l (%)	29
K+ ≤ 2.7 mmol/l (%)	13
K+ ≤ 2.6 mmol/l (%)	8
K+ ≤ 2.5 mmol/l (%)	5
K+ ≤ 2.4 mmol/l (%)	3
K+ ≤ 2.3 mmol/l (%)	2

The first 100 patients registered had a median age of 57 years with the youngest being 22 years and the oldest 92 years (▶ **Table 1**). Sex distribution was balanced with 53 % men and 47 % women. Baseline potassium measurements were performed in the central laboratory on patients of 22 different outpatient clinics of the USZ. Most patients were from the Department of Medical Oncology and Hematology (20 %), Gastroenterology (12 %) and Cardiology (11 %). Nine percent of patients each came from the interdisciplinary emergency unit and the Clinic for Nephrology. Eighteen other departments accounted for the total 39 percent remaining patients. The exact proportions of the respective medical departments are shown in ▶ **Fig. 2**.

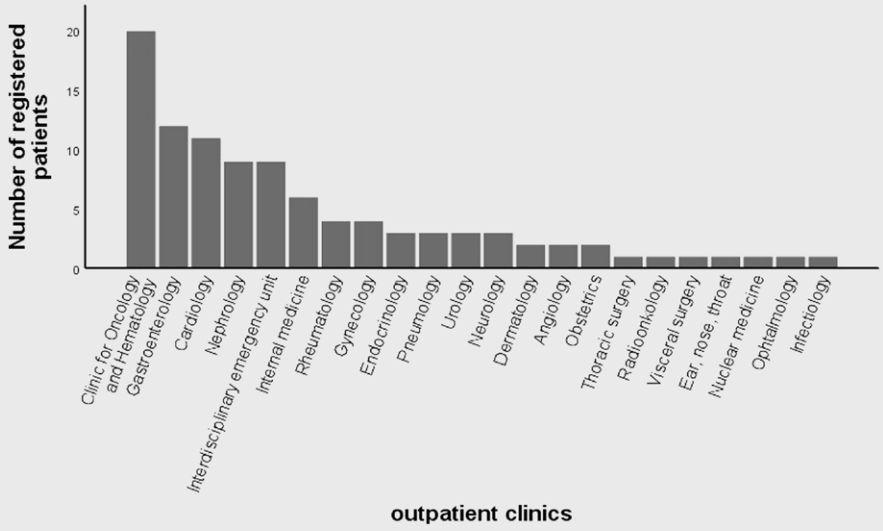
Serum potassium distribution

The mean serum potassium value was 2.89 ± 0.02 mmol/l (range 2.3–3.0 mmol/l) independent of sex (2.92 vs. 2.87 mmol/l in males and females, p = 0.17). More than half of the included patients (54 %) had a potassium value of exactly 3.0 mmol/l. The number of reported patients decreases steadily with the extent of hypokalemia (▶ **Fig. 3a, b**). Overall, 92 % of all measurements were in a range between 3.0 and 2.7 mmol/l, while only 5 % of patients had severe hypokalemia with values lower than 2.6 mmol/l.

Twenty percent of patients were on oral potassium supplementation with an average daily dosage of 52.5 mmol. Twelve percent of patients took MR antagonists.



▶ **Fig. 1** Overview on exclusion and inclusion of patients in the IPAHK+ trial.



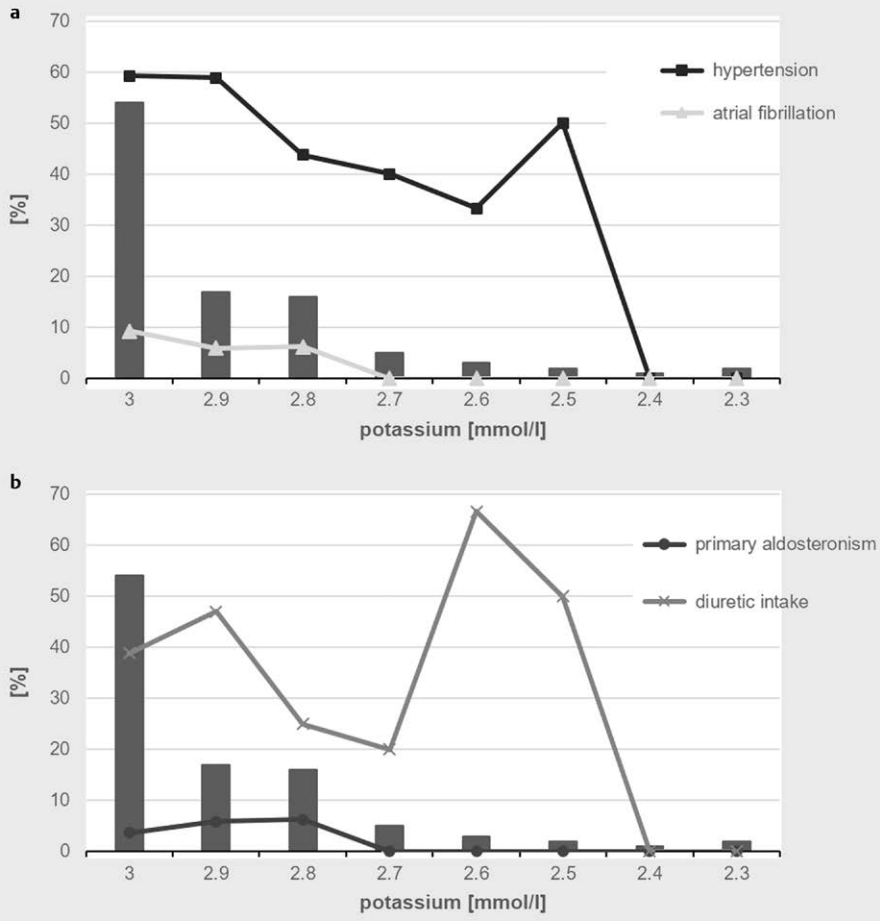
▶ **Fig. 2** Proportion of reported patients from the different medical departments.

Co-morbidities

The percentage of patients with a history of arterial hypertension was 53 %. Seven percent of the first 100 study patients had a history of atrial fibrillation. The proportion of hypertensive patients and patients with atrial fibrillation related to the different potassium levels is provided in ▶ **Fig. 3a**. Notably, the percentage of hypertensive patients, but also of atrial fibrillation decreased with decreasing potassium levels. However, the intake of oral potassium supplements and potassium-sparing diuretics was higher in the group of hypertensives than in non-hypertensives (24.5 vs. 14.9 % and 15.1 vs. 8.5 %, respectively). The same was seen when comparing the two subgroups of patients with and without atrial fibrillation (28.6 vs. 19.4 % and 14.3 vs. 10.8 %, respectively).

Causes of hypokalemia

The current evaluation suggests that hypokalemia-inducing drugs were the most common cause of hypokalemia in the study population: 55 % of all patients had been prescribed at least one potentially hypokalemia-inducing drug with a leading usage of diuretics at 37 %. Twelve percent of the patients were on laxatives. These two groups of drugs therefore accounted for the majority of potentially hypopotassemia-promoting drugs. Glucocorticoids and various immunomodulary drugs accounted for a significantly smaller share.



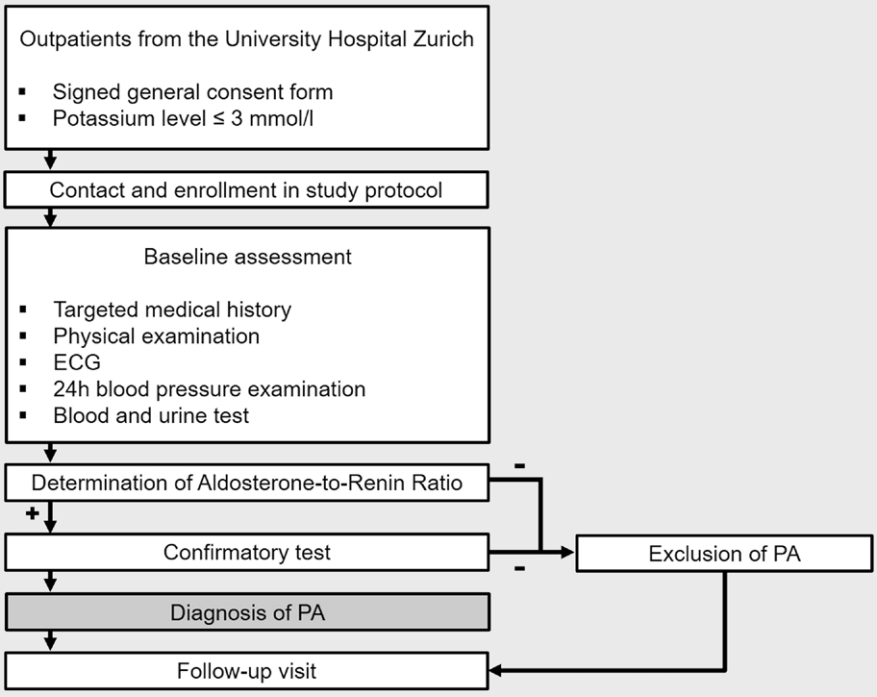
▶ **Fig. 3** Percentage of the different potassium levels within the total population studied. **a**: indicates the percentage of hypertension (■) and atrial fibrillation (▲) within groups of different potassium levels. **b**: shows the percentage of PA (●) and diuretic medication (x) within groups of different potassium levels.

After drug-related causes, acute or chronic gastrointestinal losses account for the second most common cause of hypokalemia in the study population, with a proportion of 9 %. In third place among the most common causes of hypokalemia in the population studied was PA with a prevalence of 4 %. Within the subgroup of hypertensive patients, the prevalence was as high as 7.5 %. ▶ **Fig. 3b** shows the percentage of patients with diuretic use and those diagnoses with PA related to the different potassium levels. More rare causes were renal losses due to Gitelman disease (2 %) or renal tubular acidosis type 1 (1 %) and a decreased intake of potassium due to eating disorders (2 %).

Discussion

Herein, we introduce the IPAHK⁺ hypokalemia cohort and report baseline characteristics of the first 100 patients eligible for IPAHK⁺ study enrollment. Numerous previous studies have provided information on the prevalence of hypokalemia in cases of confirmed diagnosis of primary hyperaldosteronism [11, 14–18]. Based on these evaluations, a hypokalemic course of the disease is expected in 9–37 % of cases [11]. In contrast, high-level evidence about the prevalence of PA in a hypokalemic population is missing. To our knowledge, the IPHAK⁺ trial is the first prospective study investigating the incidence of PA in a hypokalemic population. Although hypokalemic PA only accounts for the smaller proportion of the disease, it is of major importance because of its impact on pre-analytics, the diagnostic pathway, treatment and prognosis [8, 9].

Along with hyponatremia, hypokalemia is one of the most common electrolyte disorders. The prevalence of mild hypokalemia (3.0–3.5 mmol/l) in outpatients is reported to be 14 % [19]. Lower values have a significantly lower prevalence. Indeed, in the total of 28 140 outpatient potassium measurements performed at the USZ between October and December 2019, the rate of hypokalemia less than or equal to 3.0 mmol/l was 0.79 %. As expected, case numbers decreased sharply with further decreasing potassium levels. The mean potassium level was 2.9 mmol/l irrespective of sex. With a share of 20 %, most of the reports were attributable to the Oncology and Hematology department, followed by the Department for gastroenterology (12 %), cardiology (11 %), nephrology and the interdisciplinary emergency unit (11 % each). Obviously, this ranking



▶ **Fig. 4** IPAHK⁺ study design and patient flow.

is potentially biased by the total number of potassium measurements in each clinical setting. Ophthalmologists, for example, are likely to check potassium levels less frequent than cardiologists, for example, due to lack of indication. In addition, however, the patient population of the departments are characterized by various dyselectrolytemia predisposing factors such as polymorbidity, malnutrition and polypharmacy. The aforementioned properties favor an inadequate supply of potassium, impaired potassium distribution between intra- and extracellular space and in particular, increased gastrointestinal or renal excretion of potassium, which finally results in hypokalemia [20, 21].

Subgroup comparison revealed a marginally but significantly lower mean potassium level in non-hypertensive compared with hypertensive patients. In addition, the percentage of hypertensive patients decreased successively with decreasing potassium levels. This is initially surprising, since hypokalemia per se promotes the development of hypertension at different levels [22–26]. Based on these findings, one would have expected lower potassium values in patients suffering from hypertension and a higher proportion of hypertensive patients with decreasing potassium. However, the comparatively higher intake of oral potassium supplements and potassium-sparing diuretics in the group of hypertensive patients may represent a relevant confounder and plausible explanation. Interestingly, no significant differences in mean potassium levels were found in patients with and without atrial fibrillation or PA.

The current evaluation suggests that hypokalemia-inducing drugs were the most common cause of hypokalemia in the study population, followed by acute or chronic gastrointestinal disorders and PA. The prevalence of PA in the study population was at least 4 %. In relation to all patients with hypertension, PA even accounts for at least 7.5 %. In a current retrospective observational study from Italy, the prevalence of PA in outpatients with hypokalemia and hypertension was reported to be as high as 28.1 % [27]. The lower rate in our study is most likely due to the low proportion of screening examinations. It is likely that very few study candidates ever received an appropriate screening examination regarding PA. In order to obtain meaningful data and allow for subgroup analysis we therefore aim to recruit a minimum of 1000 candidates undergoing a standardized screening assessment. To achieve this goal we began to enroll patients continuously in the IPAHK⁺ study protocol (▶ **Fig. 4**). Patients are invited to a baseline visit in which all relevant basic characteristics are assessed. This includes a targeted medical history and physical examination as well as a 24-hour ambulatory blood pressure measurement (ABPM) and an electrocardiogram (ECG). In addition, we perform urine examinations in spot and 24-hour collection urine and blood tests. The diagnosis of PA follows internationally recommended routine procedure including adaptation of antihypertensive medication (slow-release verapamil 120–240 mg twice daily and/or Doxazosin 4 to 8 mg once daily for one or four weeks, depending on the initial medication) for the determination of the aldosterone-to-renin ratio (ARR) [8]. In addition, participants are provided with oral potassium supplements to achieve normokalemic conditions for testing. Saline infusion test (SIT) is used as a subsequent confirmatory test [8]. Independently of the study, patients with newly diagnosed PA are offered further diagnostics for subtype differentiation (adrenal imaging, adrenal vein catheter sampling) and adequate treatment. Irrespective of whether PA was found or not, a final follow-up one year after study enrollment is scheduled that includes re-assessment of the baseline characteristics and adverse events.

The study in its current stage has several limitations. The main weakness of the study is the patient selection. Patients with hypertension or chronic or unclear hypokalemia are likely to be motivated to participate in the study. Conversely, patients who do not have hypertension or those with known plausible cause of their hypokalemia, or only one-time low potassium are more likely to decline participation in the study because the personal benefit is considered to be low. The risk of selection bias may thus arises from the predominant inclusion of patients with already elevated pretest probability for PA into the trial. This in turn may ultimately lead to an overestimation of the disease in a hypokalemic population. Another limitation is the monocentric design of the study whereby the involvement of further international study centers is planned in order to enhance the power of the study by greater diversity and cohort size.

In conclusion, we have reported the baseline characteristics of the first 100 suitable candidates for inclusion in the IPAHK⁺ trial. The prevalence of PA was 4 % in the total study population and 7.5 % in the subgroup of hypertensives. However, guideline-compliant screening of all patients with spontaneous or diuretic-induced hypokalemia ≤ 3.0 mmol/l would likely result in a significantly higher rate of PA. In the coming years, the IPAHK⁺ study will therefore fill a long-standing knowledge gap by providing evidence on the incidence of PA in a hypokalemic population. It will also investigate whether the degree of hypokalemia correlates with various features of the disease such as symptomatology, disease severity, and subgroup differentiation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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