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Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice

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Prevalence and Clinical Phenotype of Primary Aldosteronism in Primary Care Hypertensives

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Brief title: hyperaldosteronism in primary care

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Abstract
Background. Despite being widely recognized as the most common form of secondary hypertension, the true prevalence of primary aldosteronism (PA) and its main subtypes, aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), among the general hypertensive population remains a matter of debate.
Objectives. To determine the prevalence and clinical phenotype of PA in a large cohort of unselected hypertensive patients, consecutively referred to our Hypertension Unit, by 19 general practitioners from Torino, Italy.
Methods. Patients were screened for PA using the serum aldosterone to plasma renin activity ratio after withdrawal from all interfering medications and PA was diagnosed according to the Endocrine Society guidelines. The diagnosis was confirmed/excluded by an i.v. saline infusion test or captopril challenge test and subtype differentiation was performed by adrenal CT scanning and adrenal vein sampling (AVS) using strict criteria to define both successful cannulation and lateralization of aldosterone production.
Results. A total of 1,672 primary care hypertensive patients, 569 newly diagnosed hypertensives and 1,103 patients already diagnosed with arterial hypertension, were included in the study. A total of 99 patients (5.9%) were diagnosed with PA and conclusive subtype differentiation by AVS was made in 91 patients (27 patients with an APA and 64 patients with BAH). The overall prevalence of PA increased with the severity of hypertension, from 3.9% in hypertensives stage I to 11.8% in hypertensives stage III. Patients with PA more frequently displayed target organ damage and cardiovascular events compared to non-PA hypertensives, independent of confounding variables.
Conclusions. The results from the present study demonstrated that PA is a frequent cause of secondary hypertension even in the general hypertensive population and indicates that the majority of hypertensive patients should be screened for PA.

Keywords: Primary aldosteronism, aldosterone-producing adenoma, bilateral adrenal hyperplasia

Abbreviation list
AC = aldosterone concentration
APA = aldosterone-producing adenoma
AVS = adrenal vein sampling
ARR = serum aldosterone to plasma renin activity ratio
BAH = bilateral adrenal hyperplasia
CV events = cardiovascular events
GP = general practitioner
HT = hypertension
LREH = low renin essential hypertensives
MRA= mineralocorticoid receptor antagonist
PA = primary aldosteronism
PATO = primary aldosteronism in Torino

Condensed Abstract
The prevalence of primary aldosteronism (PA) among general hypertensive population remains unknown. We screened 1,672 primary care hypertensives and 5.9% were diagnosed with PA (27

with an aldosterone-producing adenoma and 64 with bilateral adrenal hyperplasia). PA prevalence increased with the severity of hypertension, from 3.9% in hypertensives stage I to 11.8% in stage III. PA patients more frequently displayed target organ damage and cardiovascular events compared to non-PA hypertensives. The study demonstrated that PA is a frequent cause of secondary hypertension in the general hypertensive population and indicates that the majority of hypertensive patients should be screened for PA.

Introduction

Primary aldosteronism (PA) is a heterogeneous group of disorders characterized by hypertension and aldosterone overproduction relatively autonomous from the renin-angiotensin system. The importance of a correct diagnosis of PA is demonstrated by the increased risk of cardiovascular and cerebrovascular complications and the increased rate of metabolic syndrome of patients with PA compared to primary hypertensives with matched cardiovascular risk profiles (1–3). According to the Endocrine Society Guidelines (4, 5) the diagnosis of PA is a three-step process comprising screening, confirmatory testing and subtype differentiation. The latter is necessary to distinguish the two most common PA subtypes: unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), and thereby stratify patients to the recommended therapeutic management (unilateral adrenalectomy or medical therapy with mineralocorticoid receptor antagonists, MRA).

Until the late 1990's, PA was suspected only in the presence of overt and spontaneous hypokalemia resulting in low estimated prevalences from 1% to 2% (6, 7). The subsequent wide application of the aldosterone to renin ratio (ARR) as a screening test to unselected hypertensive patients resulted in a 5 to 15-fold increase in the diagnosis of PA (8, 9). A large number of studies have investigated the prevalence of PA and have reported wide variations of estimates in patients referred to hypertension units (1 to 29.8%) and in primary care patients (3.2 to 12.7%) (10) depending on the characteristics of the selected population and the diagnostic method employed. In particular, prevalence of PA increases with the severity of hypertension, from 2% in patients with grade 1 hypertension (11), to 20% among resistant hypertensives (12). However, the majority of studies were conducted in tertiary hypertension units and referral bias is likely to have influenced the results. For this reason, the true prevalence of PA among the general

hypertensive population and the importance of extending the measurement of the ARR in most hypertensive patients, are still a matter of debate.

The present study was aimed at determining the prevalence and clinical phenotype of PA and its main subtypes, APA and BAH, in a large cohort of 1,672 unselected hypertensive patients, consecutively referred to our Hypertension Unit, without applying any selection criteria, by 19 general practitioners (GPs) from Torino, Italy.

Methods

Study design

The protocol of the PATO (Primary Aldosteronism in TOrino) study was approved by the ethical committee of the University of Torino and written informed consent was obtained from all patients participating to the study. To avoid any selection bias, the study population was recruited directly from 19 GPs in Torino, Italy. All patients were aged 18 to 60 and affected by arterial hypertension (newly diagnosed or previously diagnosed hypertensives) consecutively presenting to the GP's office from 2009 to 2014 were invited to participate; 1672 patients were included in the study and the overall response rate was 51%.

All patients who agreed to participate were contacted by telephone by a physician from our Hypertension Unit to collect medical and pharmacological history and to schedule Visit 1. In absence of any medical condition requiring mandatory medication, all the drugs interfering with the renin-angiotensin-aldosterone system were withdrawn, as detailed below. During Visit 1 the patients underwent physical examination including blood pressure (BP) measurement, familial medical and pharmacological history and blood samples for plasma renin activity (PRA) and aldosterone measurement were collected.

Patients

The group of 19 GPs participating to the Primary Aldosteronism in TOrino (PATO) study cared for a total of 23,067 patients, 13,090 of which were aged 18-60 years; 3,272 were hypertensive (either newly diagnosed or with pre-existing hypertension) and were invited to participate to the study. A final cohort of 1,672 patients was included in the PATO study. Some information about the patients that were not-recruited is available in the supplemental file and Online Table 1.

The diagnosis of hypertension (HT) was made by three consecutive BP measurements in the sitting position using a mercury sphygmomanometer, according to European Society of Hypertension (ESH) guidelines (13). The diagnosis of PA was made according to the recommendation of the Endocrine Society Guidelines (4). In particular, patients were screened for PA using the serum aldosterone concentration (AC) to plasma renin activity (PRA) ratio (ARR); all interfering medications were withdrawn for at least 4 weeks (6 weeks for diuretics and MRA) and hypokalemia, if present, was corrected with K^+ supplements. A calcium channel blocker and/or doxazosin, which are known to have minimal effect on the ARR, were used to control BP when discontinuation of all antihypertensive medications was not feasible because of the risk of uncontrolled HT (4). The cut-off level considered to be a positive ARR was 30 (ng/dL/ng·mL^{-1}·h^{-1}) (830 pmol/L/ng·mL^{-1}·h^{-1}), together with an aldosterone level greater than 10 ng/dL (277 pmol/L). The diagnosis of PA was confirmed (Visit 2, Figure 1) by an i.v. saline loading test (2 liters of 0.9% NaCl infused over 4 h), which was considered positive if post-test aldosterone levels were greater than 5 ng/dl (138.7 pmol/L) (14). Captopril challenge test was used to confirm the diagnosis of PA in those patients with a contra-indication to acute volume expansion (i.e. poorly controlled hypertension, chronic kidney failure, heart failure, previous cardiovascular events). Captopril (50 mg) was administered orally and PRA and aldosterone

were measured after 2 hours. PA was confirmed if the ARR post testing was greater than 30 ng/dL/ng·mL^{-1}·h^{-1}. Subtype differentiation was performed as previously reported (15). Finally, long PCR for glucocorticoid remediable aldosteronism testing was performed in all confirmed PA patients.

PRA levels were classified as follows: low renin, if PRA was < 1 ng·mL^{-1}·h^{-1}; normal renin, if PRA levels were comprised between 1 and 4 ng·mL^{-1}·h^{-1} and high renin if PRA levels were above 4 ng·mL^{-1}·h^{-1}. Hypokalaemia was defined as serum potassium < 3.6 mEq/L. We considered the following cardiovascular events: myocardial infarction and unstable angina requiring angioplasty (in the text grouped together under coronary artery disease - CAD), stroke or transient ischemic attack (in the text together under stroke), sustained arrhythmias (atrial fibrillation, atrial flutter, sustained ventricular tachycardia, and ventricular fibrillation) demonstrated by electrocardiogram, and heart failure (HF) requiring hospitalization (2). Definitions of cut-offs for target organ damage is provided in the supplemental file. Since other forms of secondary hypertension were not systematically excluded, patients without PA were considered as non-PA hypertensive patients (apparent essential hypertensives).

Biochemical measurements

Blood samples for AC and PRA measurements were collected in the morning between 7 am and 9 am at the Città della Salute e della Scienza di Torino University Hospital centralized laboratory with the patients in the sitting position. PRA and AC were measured by RIA as described previously (16). AC was assessed by solid-phase radioimmunoassay ALDOCTK-2 (DiaSorin, Saluggia, Italy) and PRA using the RENCTK RIA kit (DiaSorin, Saluggia, Italy) according to the manufacturer's instructions. The analytical sensitivity was 0.1 ng/mL/h (16).

Statistical analysis

IBM SPSS Statistics 21 (SPSS INC, Chicago, IL) was used for statistical analyses. Data were analyzed with the Kolmogorov-Smirnov test to determine their distributions. Results are expressed for continuous variables with a normal distribution as mean ± standard deviation and with non-normal distributions as median (25th-75th percentile). Statistical significance between groups was calculated in normally distributed data by Student t-test for independent samples and in non-normally distributed data by Kruskal-Wallis and Mann-Whitney *U* test. One-way ANOVA followed by a Bonferroni test was used to compare quantitative variables between groups and χ^2 test or the Fisher exact test for qualitative variables. Multivariate logistic regression analysis was performed in order to correct for confounding variables (age, male gender, duration of hypertension, systolic blood pressure, BMI, HDL cholesterol, smoking habit, diabetes and PA diagnosis).

Results

Additional results material is available in the supplemental file. Between 2009 and 2014 a total of 1,672 patients agreed to participate and were included in the study. The design of the study, comprising the diagnostic work-up for PA, is shown in **Figure 1.**

Clinical and demographical features of the included patients are summarized in **Table 1.** Overall, the average systolic and diastolic BP (SBP and DBP) levels were 147 ± 15 mmHg and 94 ± 8 mmHg respectively; 67.8% (1,133/1,672) of the patients displayed hypertension stage I, 24.7% (413/1,672) hypertension stage II and 7.5% (126/1,672) hypertension stage III. Of the 1,672 included patients, 569 were newly diagnosed hypertensives, and 1,103 were previously diagnosed hypertensives at the time of recruitment. Clinical and biochemical parameters of these two subpopulations are shown in Online Table 2. Unsurprisingly, patients with newly diagnosed

hypertension were younger, with lower SBP levels and displayed a lower prevalence of cardiovascular events compared to established hypertensives.

Following diagnostic work-up, comprising screening, confirmatory testing and subtype differentiation, a total of 99 patients (5.9%) resulted to be affected by PA. Specifically, 33 of the 99 PA diagnoses were in the newly diagnosed hypertensive group (5.8% prevalence) and 66 diagnoses of PA were in the subgroup of patients with a pre-existing diagnosis of hypertension (6.0% prevalence). A conclusive subtype diagnosis was achieved by AVS in 91 patients: 27 (27%) had an APA and 64 (65%) had BAH whereas in 8 patients (8%) the subtype was undetermined because AVS was not performed or not diagnostic. No complications occurred during AVS procedures. The overall prevalence of PA and its subtypes according to the severity of hypertension was 3.9% in hypertension stage I (21 % APA, 68% BAH and 11% undetermined), 9.7% in hypertension stage II (30% APA, 62.5% BAH and 7.5% undetermined) and 11.8% in hypertension stage III (40% APA and 60% BAH) as detailed in Figure 2. The prevalence of hypokalaemia (defined as serum $K^+ < 3.6$ mEq/L) was 6.8% (105/1544) in the overall study population, 5.3% (77/1,447) amongst the non-PA hypertensives and 29.3% (29/99) in the PA subgroup (52% in APA and 22% in BAH, p=0.013).

Screening test for suspected PA

Of the 1,672 patients included in the analysis, according to PRA values, 34% displayed low renin (including PA patients and low renin essential hypertension, LREH), 57% normal renin and 9% high renin levels (for further evaluations, normal and high renin patients are combined). The LREH category was composed of two subgroups of patients, those with PRA < 1 ng/ml/h and ARR < 30 (negative screening test, n=331) and those with PRA < 1 ng/mL/h and ARR > 30 (positive screening test and negative confirmatory testing, n=133).

A total of 232 patients (13.8%) had an ARR > 30 together with an absolute AC > 10 ng/dL (positive screening test) and underwent confirmatory testing (187 i.v. saline loading test and 45 captopril challenge test).

Comparison between PA and non-PA patients

Clinical and biochemical parameters of patients according to the final diagnosis (PA vs non-PA) are summarized in **Tables 1, 2, 3** and in Online Table 3. Patients with PA displayed higher SBP and DBP than non-PA and, in agreement with the classical PA phenotype, higher serum aldosterone levels and lower PRA and K^+ levels. Metabolic syndrome was more frequent in PA patients than non-PA and, further, they displayed greater waist circumference, lower HDL cholesterol, higher fasting plasma glucose and hypertriglyceridemia was more prevalent. For target organ damage, PA patients presented more frequently with left ventricular hypertrophy (evaluated by electrocardiogram and/or echocardiography) and microalbuminuria; furthermore, PA patients also displayed a higher rate of CV events at diagnosis compared with non-PA hypertensives. Interestingly, in a multivariate logistic regression model, the diagnosis of PA was a strong factor associated with the occurrence of CV events in our study population aged 18 to 60 years (OR=2.1; 95% IC=1.1-3.9), after correction for age, sex, duration of hypertension, SBP, BMI, HDL cholesterol, smoking habit and the presence of diabetes mellitus (Online Table 4). Accordingly, the diagnosis of PA was a strong factor associated with the occurrence of left ventricular hypertrophy (OR=2.1; 95% IC=1.3-3.2), after correction for age, duration of hypertension and SBP (Online Table 5) and with microalbuminuria (OR=2.6; 95% IC=1.5-4.4), after correction for age, duration of hypertension, SBP and the presence of diabetes mellitus (Online Table 6).

Comparison between APA and BAH patients

AVS was successfully performed in 91 patients, displaying unilateral aldosterone overproduction in 27 patients (1.6% of the total study population) and bilateral secretion in 64 (3.8% of the study population). Overall, APA patients were characterized by higher serum aldosterone levels, higher ARR and a trend towards lower K^+ levels compared to BAH patients (**Table 4**). Of note, no significant differences in the total number of CV events at diagnosis was observed between the two subgroups. However, the low number of APA patients could have affected the results and limits any conclusions to be drawn.

Patient subgroups according to renin profiling

Comparison of clinical and biochemical parameters of the different subpopulations according to the renin profile are shown in Online Tables 6 and 7. Interestingly, patients with LREH and patients with normal-high renin values display a similar clinical phenotype in terms of K^+ levels, prevalence of metabolic syndrome, TOD and CV events, despite higher SBP levels in LREH subpopulation.

Subsequently, we compared the clinical and biochemical features between LREH patients who tested positive to the ARR and LREH with a negative screening test. As expected, PRA levels were lower and aldosterone levels higher in the LREH patients who tested positive at ARR, but these two populations did not differ significantly in terms of other clinical parameters and in particular displayed a similar prevalence of TOD and CV events at diagnosis.

Discussion

Additional discussion -is available in the Online Appendix. Arterial hypertension affects up to 30% of the Italian population aged 35-74 years (17) and represents the single most important contributor to the global burden of disease and mortality (18). Despite this, only a minority of hypertensive patients attain optimal blood pressure control (19). This is due in part to

the underdiagnosis and targeted treatment of underlying secondary forms of hypertension such as PA.

The introduction of the ARR as a screening test for PA prompted a large number of studies investigating the prevalence of PA in different populations. In particular, 12 studies have been conducted on patients from primary care centers (10, 20, 21), which represent an apparently unselected hypertensive population, reporting a wide variation in PA prevalence, ranging between 3.2% and 13%. Nevertheless, as suggested by the heterogeneity of the results, these studies could have been biased by the various criteria adopted for patient selection and diagnosis. In fact, only 2 of these studies were published after the release of the Endocrine Society Guidelines for diagnosis and treatment of PA, in 2008 (4). Furthermore, only one study was performed in more than 1,000 patients (22), subtype differentiation was not performed systematically with AVS and target organ damage and cardiovascular events were not evaluated. Recently, a survey on the knowledge and application of the Endocrine Society PA guidelines by GPs in Italy and Germany, demonstrated a low rate of PA diagnosis (1% and 2%, respectively) in primary care hypertensive patients (23).

In this study, we prospectively investigated the prevalence of PA and its main subtypes, APA and BAH, in a large cohort of 1,672 unselected hypertensives consecutively recruited by 19 GPs in Torino, Italy. We observed an overall PA prevalence of 5.9% and an APA was found in 27% of the patients diagnosed with PA (1.6% of the total study population) (Central Illustration). Interestingly, similar estimates of PA prevalence were observed between the newly diagnosed and the established hypertensives, thereby excluding the occurrence of any referral or selection bias for patients with established hypertension. Importantly, PA prevalence was not rare even in patients with relatively mild hypertension (3.9% in stage I and 9.7 in stage II, with a consistent

proportion of the potentially curable unilateral PA). It should be noted that, in addition to the hypertensive population with overt PA (5.9%), a further 8% of patients (133/1672) displayed an inappropriate aldosterone production for the renin status, despite being still suppressible with a saline load and 231 (13.8%) patients had an ARR between 20 and 30. This population of hypertensive patients has been shown to respond particularly well to therapy with MRA (24, 25).

In the present study we demonstrate 1) the prevalence of PA is largely underestimated in the general hypertensive population and 2) a wider application of the simple ARR screening test would benefit a consistent proportion of hypertensive patients by offering the possibility of surgical cure or of a targeted pharmacotherapy. Spontaneous or diuretic-induced hypokalemia, traditionally considered as a prerequisite for pursuing diagnostic tests for PA (26), was detected in 6.8% of the hypertensive population and in 28.9% of our PA cohort, making normokalemic hypertension the most common presentation of the disease, as previously observed in a study including centers from 5 continents (9).

In our study, patients affected by PA presented a more severe clinical phenotype, as demonstrated by the increased prevalence of the disease according to the severity of hypertension, in agreement with earlier reports (2, 11). We also observed an increased rate of cardio- and cerebro-vascular events in PA patients compared with non-PA hypertensives, that were at least partly independent of blood pressure levels, consistent with previous studies in selected hypertensive populations (2, 27, 28). Similarly, target organ damage (left ventricular hypertrophy and microalbuminuria) was also associated with PA in part independent of confounding variables.

The present study suggests that the majority of the hypertensive patients should be screened with the simple ARR test, in agreement with the Japanese Endocrine Society guidelines

(29). Some concern could arise from the consequences that a widespread use of the ARR could determine in term of performance of confirmatory/exclusion tests, which are poorly standardized, and for the expensive and invasive subtype diagnosis procedures (using CT scanning and AVS). However, it has been shown that PA diagnosis and treatment is feasible and economically convenient (30,31). Furthermore, an alternative strategy with patients displaying high ARR and relatively mild hypertensive disease could be the recommendation of strict adherence to the reduction of sodium intake (32) and the use of low-doses of MRA (5).

A strength of our study is the diagnosis of PA following the recommendations of the Endocrine Society Guidelines (4, 5), the screening of all patients using the ARR and confirmation of the diagnosis of PA in all patients. The ARR is the most reliable means to screen for PA, but a unique cut-off is difficult to define due to the wide variability of laboratory assays and population-specific characteristics (4, 5). In order to increase the sensitivity of the test, we adopted 30 ($ng/dL/ng \cdot mL^{-1} \cdot h^{-1}$) as cut-off to define a positive screening test, in addition to a minimum AC of 10 ng/dL, instead of the less sensitive, but most specific cut-off routinely used in our hypertension unit (ARR > 40 and AC > 15 ng/dL). Moreover AVS was performed in all PA patients and strict criteria were employed to define both successful cannulation of the adrenal glands and lateralization of aldosterone production (15,33); our study is also the first that investigate in primary care hypertensives the presence of target organ damage and the rate of cardiovascular events. Another strength of the present study is that the distribution of the different pattern of PRA levels (low, normal and high renin hypertension) in our hypertensive patients did not differ significantly compared to another extensively studied general hypertensive population (34): therefore, our PA prevalence findings are confidently representative of the general unselected hypertensive population. Limitations of the study are: 24 hour ambulatory

blood pressure monitoring levels were not available and therefore blood pressure levels subdivision could be affected by the white coat effect; only 51% of all hypertensive patients were recruited for study participation and only information about 31% of the patients not recruited was available; since other secondary forms of hypertension were not excluded, patients who did not have PA possibly had, in a minority of cases, another secondary cause of hypertension.

The present study demonstrates that PA is a frequent cause of secondary hypertension even in the general hypertensive population and indicates that the majority of hypertensive patients should be screened for PA (29). Early diagnosis is critical to obtain cure in patients who are adrenalectomized for unilateral PA (35) and fundamental to prevent the development of target organ damage (36). Unfortunately, aldosterone and renin measurements are rarely requested by GPs (23) and PA is often diagnosed by specialists following years of uncontrolled hypertension (2). Our results also support the view that aldosterone excess determines an increase in organ damage and cardiovascular events, supporting the extensive screening of the hypertensive population to address PA patients to the therapy, preferably adrenalectomy for unilateral forms and pharmacological therapy with MRA for bilateral forms.

PERSPECTIVES

Competency in medical knowledge

Primary aldosteronism, including the potentially curable aldosterone producing adenoma, is a common form of secondary hypertension in primary care hypertensive patients and it is associated with an increase in target organ damage, cardiovascular complications and metabolic syndrome.

Translational Outlook

Further studies are warranted to explore whether the early detection of primary aldosteronism, including mild forms of the disease, will result in a reduction of cardio- and cerebrovascular events associated to this clinical condition.

References

1. Milliez P, Girerd X, Plouin P-F, Blacher J, Safar ME, Mourad J-J. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J. Am. Coll. Cardiol. 2005;45:1243–48.

2. Mulatero P, Monticone S, Bertello C, et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J. Clin. Endocrinol. Metab. 2013;98:4826–33.

3. Fallo F, Veglio F, Bertello C, et al. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J. Clin. Endocrinol. Metab. 2006;91:454–9.

4. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 2008;93:3266–81.

5. Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2016;101:1889-916.

6. Kaplan NM. Hypokalemia in the Hypertensive Patient: With Observations on the Incidence of Primary Aldosteronism. Ann. Intern. Med. 1967;66:1079–90.

7. Andersen, G.S. Toftdahl, D.B. Lund, J.O. Strandgaard, S. Nielsen PE. The incidence rate of phaeochromocytoma and Conn's syndrome in Denmark, 1977-1981. J. Hum. Hypertens. 1988;2:187–9.

8. Gordon, Richard D; Klemm, Shelley A; Stowasser, Michael; Tunny, Terry I; Storie, William I; Rutherford JC. How common is primary aldosteronism? Is it the most frequent cause of curable hypertension? J. Hypertens. 1993;11:S310–1.

9. Mulatero P, Stowasser M, Loh K-C, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J. Clin. Endocrinol. Metab. 2004;89:1045–50.

10. Käyser SC, Dekkers T, Groenewoud HJ, et al. Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: a Systematic Review and Meta-regression Analysis. J. Clin. Endocrinol. Metab. 2016; 101:2826-35.

11. Mosso L, Carvajal C, González A, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003;42:161–5.

12. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism Among Black and White Subjects With Resistant Hypertension. Hypertension 2002;40:892–6.

13. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH / ESC Guidelines for the management of arterial hypertension. Eur. Heart J. 2013:2159–219.

14. Mulatero P, Milan A, Fallo F, et al. Comparison of confirmatory tests for the diagnosis of primary aldosteronism. J. Clin. Endocrinol. Metab. 2006;91:2618–23.

15. Monticone S, Viola A, Rossato D, et al. Adrenal vein sampling in primary aldosteronism: towards a standardised protocol. Lancet. Diabetes Endocrinol. 2014;8587:1–8.

16. Burrello J, Monticone S, Buffolo F, et al. Diagnostic accuracy of aldosterone and renin measurement by chemiluminescent immunoassay and radioimmunoassay in primary aldosteronism. J. Hypertens. 2016;34:1–8.

17. http://www.epicentro.iss.it/ben/pre_2002/settembre02/2.htm#BEN.

18. Poulter NR, Prabhakaran D, Caulfield M. Hypertension. Lancet 2015;386:801–12.

19. Banegas JR, López-García E, Dallongeville J, et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J. 2011; 32: 2143-52.

20. Hannemann A, Wallaschofski H. Prevalence of primary aldosteronism in Patient's cohorts and in population based studies - a review of the current literature. Horm. Metab. Res. 2012;44:157–62.

21. Jansen PM, Boomsma F, van den Meiracker AH, et al. Aldosterone-to-renin ratio as a screening test for primary aldosteronism - The Dutch ARRAT study. Neth. J. Med. 2008;66:220-8.

22. Fogari R, Preti P, Zoppi A, Rinaldi A, Fogari E, Mugellini A. Prevalence of primary aldosteronism among unselected hypertensive patients: a prospective study based on the use of an aldosterone/renin ratio above 25 as a screening test. Hypertens. Res. 2007;30:111–7.

23. Mulatero P, Monticone S, Burrello J, Williams TA, Veglio F, Funder JW. Guidelines for Primary Aldosteronism: Uptake by Primary Care Physicians in Europe. J. Hypertens. 2016;34:2253-7.

24. Williams B, Macdonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. Lancet 2015;386:2059–68.

25. Ori Y, Chagnac A, Korzets A, et al. Regression of left ventricular hypertrophy in patients with primary aldosteronism/low-renin hypertension on low-dose spironolactone. Nephrol. Dial. Transplant. 2013;28:1787–93.

26. Kaplan NM. Cautions over the current epidemic of primary aldosteronism. Lancet 2001;357:953–4.

27. Savard S, Amar L, Plouin P-F, Steichen O. Cardiovascular Complications Associated With Primary Aldosteronism: A Controlled Cross-Sectional Study. Hypertension 2013;62:331–6.

28. Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch. Intern. Med. 2008;168:80–5.

40. Nishikawa T, Omura M, Satoh F, et al. Guidelines for the diagnosis and treatment of primary aldosteronism -The Japan Endocrine Society 2009-. Endocr. J. 2011;58:711–21.

41. Sywak, M; Pasieka L. Long-term follow-up and cost benefit of adrenalectomy in patients with primary aldosteronism. Britsh J. Surg. 2001;89:1587–92.

42. Sato M, Morimoto R, Seiji Y, et al. Cost-Effectiveness Analysis of the Diagnosis and Treatment of Primary Aldosteronism in Japan. Horm. Metab. Res. 2015;47:826–32.

43. Williams JS, Williams GH, Raji A, Jeunemaitre X, Brown NJ, Hopkins PN. Prevalence of primary hyperaldosteronism in mild to moderate hypertension without hypokalaemia. 2006:129–36.

44. Sealey JE, Gordon RD, Mantero F. Plasma renin and aldosterone measurements in low renin hypertensive states. Trends Endocrinol. Metab. 2005;16:86–91.

45. Monticone S, Satoh F, Viola A, et al. Aldosterone suppression on contralateral adrenal during adrenal vein sampling does not predict blood pressure response after adrenalectomy. J. Clin. Endocrinol. Metab. 2014;99:4158–66.

46. Sawka AM, Young WF, Thompson GB, et al. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med. 2001;135:258-61.

47. Catena C, Colussi G, Lapenna R, et al. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. Hypertension. 2007;50:911-8.

Figure legends.

Central illustration. Prevalence of primary aldosteronism in primary care hypertensives and target organ damage. A. Diagnostic flow-chart of the study and prevalence of primary aldosteronism and its subtypes in primary care patients. Prevalence of primary aldosteronism resulted to be 5.9% in a cohort of 1672 primary care hypertensive patients, 27% had an aldosterone producing adenoma, 64% had bilateral adrenal hyperplasia and in 8% of the patients the final diagnosis was undetermined. B. Prevalence of target organ damage and cardiovascular events in primary aldosteronism and essential hypertensive patients. Patients affected by primary aldosteronism dispalyed a higher prevalence of target organ damage than non-PA hypertensives with similar risk profile.

Figure 1: Design of the PATO study. The diagnosis of primary aldosteronism was made following the Endocrine Society recommendations. 1672 hypertensive patients from primary care centers were included in the study and screened for primary aldosteronism: 232 patients had a positive screening test and underwent confirmatory testing (i.v. saline loading test or captopril challenge test). A final subtype diagnosis was achieved by AVS in 91 patients. AC = aldosterone concentration; APA = aldosterone producing adenoma; AVS = adrenal vein sampling; ARR = aldosterone to renin ratio; BAH = bilateral adrenal hyperplasia; CT = computed tomography; LREH = low renin essential hypertension; PA = primary aldosteronism; PRA = plasma renin activity.

Figure 2: Prevalence of primary aldosteronism subtypes in hypertension stage I to III. Prevalence of primary aldosteronism increased with the severity of hypertension (from 3.9% in stage I hypertension to 11.8% in stage III hypertension). The proportion of aldosterone

producing adenomas was higher in hypertension stage III patients compared to hypertensives stage I and stage II. APA = aldosterone producing adenoma; BAH = bilateral adrenal hyperplasia; Undet = undetermined.

Table 1. Clinical and biochemical parameters of patients included in the PATO Study

Variable	PA (n = 99)	Non-PA (n=1573)	P value
Sex (male/female)	59/40	886/687	0.5
Age (years)	49±7	46±9	<0.001
Duration of hypertension (years)	5 [1-10]	3 [1-7]	0.08
Systolic BP (mmHg)	153±17	147±14	<0.001
Diastolic BP (mmHg)	97±9	94±8	0.001
Smoking habit (Y/N/previous)	23/57/19	362/933/271	0.9
Serum K^+ (mEq/L)	3.8±0.5	4.3±0.4	<0.001
PRA (ng/mL/h)	0.3 [0.2-0.5]	1.6 [0.8-2.6]	<0.001
Serum aldosterone (ng/dL)	31 [22-42.9]	18.4 [12.5-26]	<0.001
ARR (ng/dL/ng·mL/h)	102 [64-166]	12 [7-21]	<0.001
Serum creatinine (mg/dL)	0.9±0.2	0.9±0.2	1
Uric acid (mg/dL)	5.2±1.7	5.2±1.4	0.8

PA= primary aldosteronism; EH= essential hypertension; BP = blood pressure; PRA = plasma renin activity; K^+= potassium; ARR= serum aldosterone to PRA ratio. Variables are indicated as mean± standard deviation (if normally distributed) or as median [25th -75th] (for variables without normal distribution), unless otherwise indicated.

Table 2. Clinical and biochemical parameters of patients included in the PATO Study

Variable	PA (n=99)	Non-PA (n=1573)	P value
BMI ($Kg \cdot m^{-2}$)	26.9±4.7	26.1±4.3	0.07
Waist circumference (cm)	95±14	92±13	0.03
Glucose (mg/dL)	97±25	93±20	0.05
Total cholesterol (mg/dL)	203±38	207±40	0.3
HDL (mg/dL)	53±18	56±16	0.05
Triglycerides (mg/dL)	132±79	120±74	0.1
LDL (mg/dL)	124±35	128±36	0.3
Diabetes (Y/N/IFG)	5/76/12	55/1182/177	0.8
Metabolic syndrome (Y/N)	44/53 (45.4%)	441/1037 (29.8%)	<0.001
Hypercolesterolemia (Y/N)	54/40 (57.4%)	780/673 (53.7%)	0.5
Hypertrigliceridemia (Y/N)	32/63 (33.7%)	330/1112 (22.9%)	0.016

PA= primary aldosteronism; EH= essential hypertension; BP = blood pressure; PRA = plasma renin activity; BMI = body mass index; IFG = impaired fasting glucose; HDL= high density lipoprotein; LDL= low density lipoprotein; Y= yes; N= no. Variables are indicated as mean± standard deviation, unless otherwise indicated.

Table 3. Target organ damage and cardiovascular events rate in PA and EH patients.

Variable	PA (n=99)	Non-PA (n=1537)	P value
LVH ECG (Y/N)	20/68 (22.7%)	113/1074 (9.5%)	<0.001
LVH Echo (Y/N)	50/43 (53.8%)	390/839 (31.7%)	<0.001
Microalbuminuria (Y/N)	22/60 (26.8%)	150/1018 (12.8%)	<0.001
Aortic root (mm)	35.0±4.7	32.2±4.3	<0.001
CV events at diagnosis (Y/N)	15/84 (15.2%)	94/1479 (6%)	<0.001

PA= primary aldosteronism; EH= essential hypertension; LVH = left ventricular hypertrophy; CV= cardiovascular; ECG= electrocardiography; Echo= echocardiography. Variables are indicated as mean ± standard deviation, unless otherwise indicated.

Table 4. Clinical and biochemical parameters, prevalence of organ damage and cardiovascular events in APA and BAH patients

Variable	APA (n=27)	BAH (n=64)	P value
Sex (male/female)	12/15	43/21	0.04
Age (years)	49±7	49±7	0.8
Duration of hypertension (years)	6 [3-8]	4 [1-10]	0.2
Systolic BP (mmHg)	156±19	153±17	0.5
Diastolic BP (mmHg)	98±9	97±9	0.6
Serum K^+ (mEq/L)	3.65±0.7	3.91±0.4	0.07
PRA (ng/mL/h)	0.3 [0.2-0.5]	0.3 [0.2-0.5]	0.9
Serum aldosterone (ng/dL)	43.2 [33.3-54.4]	29.5 [20.8-36.4]	<0.001
ARR (ng/dL/ng/mL/h)	115.8 [78.1-243.0]	92.0 [55.4-149.8]	0.02
Serum creatinine (mg/dL)	0.86±0.2	0.92±0.2	0.2
BMI ($Kg \cdot m^{-2}$)	26.4±4.6	27.5±4.6	0.3
Waist circumference (cm)	92.7±12.4	97.1±14.6	0.2
Glucose (mg/dL)	94±19	99±28	0.4
Total cholesterol (mg/dL)	197±29	206±51	0.3
HDL (mg/dL)	54±19	51±16	0.3
Triglycerides (mg/dL)	131±67	140±86	0.6
LDL (mg/dL)	115±28	128±37	0.1
Diabetes (N/Y/IFG)	23/0/4	46/5/7	0.3
Metabolic syndrome (Y/N)	12/15 (44.4%)	32/30 (51.6%)	0.5

LVH ECG (Y/N)	4/19 (17.4%)	16/42 (27.6%)	0.3
LVH Echo (Y/N)	17/9 (65.4%)	31/28 (52.5%)	0.3
Microalbuminuria (Y/N)	6/15 (28.6%)	16/37 (30.2%)	0.9
Aortic root (mm)	34.8±4.4	35.4±4.0	0.6
CV events at diagnosis (Y/N)	3/24 (11.1%)	12/52 (18.8%)	0.4

APA= aldosterone-producing adenoma; BAH= bilateral adrenal hyperplasia; BP = blood pressure; PRA = plasma renin activity; BMI = body mass index; K^+ = potassium; ARR= aldosterone to PRA ratio; IFG = impaired fasting glucose; HDL= high density lipoprotein; LDL= low density lipoprotein; LVH= left ventricular hypertrophy; CV= cardiovascular. Variables are indicated as mean± standard deviation (if normally distributed) or as median [25th -75th] (for variable without normal distribution), unless otherwise indicated.