

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Primary aldosteronism in the primary care setting

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1676794> since 2018-09-19T13:09:35Z

Published version:

DOI:10.1097/MED.0000000000000408

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

1 **Primary Aldosteronism in the Primary Care Setting**

2 Fabrizio Buffolo¹, Silvia Monticone¹, Martina Tetti¹, Paolo Mulatero¹

3 ¹ Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, Via
4 Genova 3, 10126, University of Torino, Italy.

5 **Corresponding author:**

6 Paolo Mulatero, MD, Division of Internal Medicine and Hypertension, Department of Medical
7 Sciences, University of Torino, Via Genova 3, 10126, Torino, Italy.

8 e-mail: paolo.mulatero@unito.it

9 Phone: +390116336959 Fax: +390116336931

10 **Key words:** aldosterone, primary aldosteronism, aldosterone producing adenoma, bilateral adrenal
11 hyperplasia, primary care

12 **Word count** 2084 words

13 **Abstract**

14 *Purpose of review.* The aim of the present manuscript is to provide an overview of the most updated
15 studies on the prevalence of primary aldosteronism in primary care and to compare these figures with
16 the actual rate of diagnosis in clinical practice and with the prevalence of PA in specific subgroup of
17 patients.

18 *Recent findings.* Over the last 20 years the clinical spectrum of low renin hypertension and primary
19 aldosteronism has changed dramatically. Once considered only in the presence of severe hypertension
20 and hypokalemia, it is now well known that PA is not uncommon even in patients with mild forms of
21 hypertension and/or normokalaemia. Moreover, recent evidence points towards a large proportion of

1 normotensive subjects as being affected by subclinical PA, which represents a strong risk factor for
2 incident hypertension. Moreover, PA patients are exposed to an increased risk of cardio- and cerebro-
3 vascular events and metabolic comorbidities compared with patients affected by essential
4 hypertension. Disappointingly, primary aldosteronism remains a largely underdiagnosed and under-
5 treated disorder.

6 *Summary.* These recent findings further highlight the importance of widening the spectrum of patients
7 who should be screened for PA, to reduce the cardiovascular risk associated with this medical
8 condition.

9 *Key words:* aldosterone, primary aldosteronism, aldosterone producing adenoma, bilateral adrenal
10 hyperplasia, primary care

11 **Introduction**

12 The 2016 *Lancet* commission on hypertension highlighted that missing a diagnosis of secondary
13 hypertension is one of the most important reasons for the unacceptably low control rate of blood
14 pressure levels in patients with hypertension [1]. Although the 2016 Endocrine Society (ES) guideline
15 suggests screening for primary aldosteronism (PA) all patients with hypertension and high risk of PA,
16 [2**], which account for more than half of the hypertensive population, the diagnosis of PA is still
17 largely inadequate [3*].

18 Recently, the PATO (primary aldosteronism in Torino) study reported a PA prevalence of about 6%
19 in a large cohort of unselected patients with hypertension referred by general practitioners (GPs). PA
20 prevalence increased with the severity of hypertension, but notably 44% of the identified cases were
21 affected by stage I hypertension (that is systolic blood pressure level comprised between 140-160
22 mmHg and/or diastolic levels comprised between 90-100 mmHg) [4*]. These data are particularly
23 relevant for the observed significant association between PA and a higher risk of cerebro- and cardio-

1 vascular events, cardiac organ damage and metabolic comorbidities compared with patients with
2 essential hypertension, independent of blood pressure levels [5*]. In fact, the identification of patients
3 with PA and a correct subtype diagnosis are important to offer a prompt and specific treatment
4 (surgical cure or targeted pharmacotherapy) which has been demonstrated not only to significantly
5 improve blood pressure and correct electrolyte abnormalities [6*,7**], but even to revert target organ
6 damage [8,9] and reduce the cardiovascular associated risk [7**].

7 **Prevalence of primary aldosteronism among patients with hypertension**

8 Over the last 25 years many studies investigated the prevalence of PA in primary care settings and in
9 referral centres. Although diagnostic criteria varied widely between different studies, especially in
10 those performed before the publication of the first ES Guideline in 2008 [10], a median PA prevalence
11 of around 6% in primary care setting and 11% in referral centres is observed [11].

12 Prevalence of PA in primary care progressively increases with the severity of hypertension, from 2-
13 4% in mildest forms to 12-13% in the most severe forms, [4*,12] and from 7% in mildest forms to
14 19% in the most severe in referral centres [13]. In patients with resistant hypertension, PA reaches its
15 highest prevalence (up to 20%) [14].

16 A correct subtype diagnosis allows the identification of an aldosterone producing adenoma (APA) in
17 one third of PA cases and bilateral adrenal hyperplasia (BAH) in the remaining patients [4*,15].
18 Hypokalaemia, once considered a prerequisite to screen for PA, is observed in only 25-40% of
19 patients with confirmed PA [4*,11,15], and more frequently in patients with resistant hypertension
20 (45-70%) [16].

21 PA seems to be more prevalent in some specific subgroups, such as patients with hypertension and
22 obstructive sleep apnoea syndrome (OSAS) [17]: for this reason, the 2016 Guideline recommends
23 that PA screening should be extended also to this category of patients [2*].

1 The association between PA and a higher risk of developing type 2 diabetes was historically described
2 by Jerome Conn [18] and recently confirmed in a cross-sectional metanalysis [5*]. However, it is not
3 yet established if patients with type 2 diabetes should be systematically screened for PA or only
4 patients with concomitant severe hypertension, in which a high prevalence was observed [19].

5 Finally, patients with PA have a higher risk of atrial fibrillation (AF) [5*]. No prospective studies
6 have investigated the prevalence of PA in patients with AF; an ongoing study in patients with lone
7 AF will provide more information in the near future [20].

8 **Prevalence of primary aldosteronism and adrenalectomy in hospital registries**

9 Although widely recognised as the most common cause of secondary hypertension, PA is still largely
10 underdiagnosed. A recent survey performed among GPs from Italy and Germany, showed that ES
11 Guidelines are only partially known and applied in clinical practice [3*]. Renin and aldosterone
12 measurements were requested by GPs in only 7-8% of patients with hypertension [3*], in contrast
13 with the 50% recommended by the 2016 ES Guideline [2**] and potassium levels were measured by
14 only 43% of the GPs in Italy and 58% in Germany at diagnosis of hypertension [3*]. PA prevalence
15 reported in patients with hypertension was 2% from German GPs and 1% from Italian GPs.
16 Noteworthy, 36% of GPs in Italy have no patients with PA [3*].

17 The direct consequence of a poor knowledge and application of international guidelines is the low
18 prevalence of PA reported by hospital registries worldwide.

19 If the prevalence of PA is 5% and a prevalence of hypertension among adults is 20-30%, the
20 prevalence of PA should be 1-1.5% in the general population. However, recent analysis performed in
21 Italy and Island showed an estimated prevalence of PA from hospital registry between 1.0-2.2/10,000
22 individuals [21-22]. Patients with a diagnosis of PA in an ambulatory setting and who did not undergo
23 a subtype diagnosis with adrenal venous sampling or those who had a surgical adrenalectomy are

1 probably missed by this kind of registries. Nevertheless, even if we consider that patients with milder
2 PA are probably missed, the figures reported are much lower than expected.

3 Hypokalaemia was present in 53-100% of patients with PA recorded in European hospital registries
4 [22-24] and this probably reflects a selection for the most severe cases of PA and a low rate of
5 diagnosis of milder forms. A national survey performed in Japan in 2014 demonstrated unilateral
6 forms of PA in more than two thirds of cases [25]. Since it is known that patients with APAs display
7 a more severe phenotype compared to patients with BAH [4*], it is probable that even in Asia, milder
8 forms of PA are largely underdiagnosed.

9 Since one third of patients with PA have a unilateral form, which benefit from unilateral
10 adrenalectomy [6*], if we consider that 1-2% of individuals in general population have a new
11 diagnosis of hypertension each year, we would expect that the number of adrenalectomies should be
12 2-4/10,000 patients/year. However, the number of adrenalectomies performed for PA in an Italian
13 Hospital registry was much lower (1.0% of expected adrenalectomies in the period 2000-2015 in the
14 Italian region of Emilia Romagna).

15 **Prevalence of primary aldosteronism among individuals without hypertension**

16 Only few studies have evaluated the PA prevalence among individuals with normal blood pressure
17 levels. The first case of PA with normotension and hypokalaemia was described in 1972 in a patient
18 with aldosterone-producing carcinoma; subsequently, almost 30 cases of PA diagnosed in patients
19 without hypertension have been reported in the scientific literature [26]. Hypokalaemia was the
20 hallmark of all cases and most patients were symptomatic, female and relatively young, suggesting
21 that age and sex may play a protective role in the hemodynamic effects mediated by aldosterone
22 excess [27].

1 In 2011, Ito et al. [28] screened for PA in 44 patients with pre-hypertension and normal potassium
2 serum level, demonstrating a relatively high prevalence of PA (6.8%). Two of the three patients with
3 confirmed PA showed a unilateral form of PA and after unilateral adrenalectomy displayed a
4 reduction of blood pressure levels. A recent study observed a lower prevalence of PA (1.8%) [29].
5 However, only 17% of patients with a positive screening test underwent a confirmatory test,
6 suggesting that the real PA prevalence was likely higher than reported.

7 Other studies investigated the prevalence of aldosterone overproduction, beyond the strict criteria of
8 PA diagnosis, identifying a prevalence of 13-14% of patients with unsuppressible aldosterone
9 secretion [30,31]. Markou et al. used, as confirmatory test, a slightly modified version of the
10 fludrocortisone suppression test (FST), with different cut-off criteria compared to the ES Guideline
11 [2*] and with administration of oral dexamethasone to reduce the effect of ACTH on aldosterone
12 secretion [30]. Instead, Baudrand et al., performed the oral sodium loading test in all patients with
13 low plasma renin activity (PRA) levels, independent of a positive ARR at basal values [31].

14 Although genetic forms of PA are usually associated with a severe phenotype, in some kindreds with
15 familial hyperaldosteronism patients with the diagnosis of PA and normotension have been reported
16 [32-35].

17 **Renin-independent and subclinical aldosteronism**

18 Recent developments on the pathophysiology and molecular basis of aldosterone overproduction and
19 the study of the subclinical phase of autonomous aldosterone production, allowed the broadening of
20 the spectrum of low-renin conditions.

21 Brown et al. [36*], in a prospective longitudinal study, recently demonstrated that individuals with
22 normal blood pressure levels and suppressed renin activity, display a higher risk of developing
23 hypertension. Furthermore, only in subjects with suppressed renin, high aldosterone levels were

1 associated with a higher risk of incident hypertension [36*]. These data are in agreement with the
2 analysis of the Framingham Offspring Study that demonstrated an association between aldosterone
3 levels and the development of hypertension in patients with normal blood pressure levels [37,38].

4 The progressive increase of aldosterone secretion, until its production becomes independent of renin
5 regulation, results in normotensive aldosteronism. Patients with normotensive aldosteronism display
6 a >15 fold higher risk of developing hypertension than controls without PA [30].

7 Aldosterone levels are not detrimental *per se*: in a context of sodium deficiency, high aldosterone
8 levels are part of a homeostatic balance and do not increase the risk of aldosterone-associated
9 cardiovascular damage. On the other hand, high aldosterone levels in the presence of high salt-diet
10 are inappropriate and not “homeostatic”, leading to higher incidence of hypertension and
11 cardiovascular damage [5*,39].

12 In this context a potential significant role may be played by endogenous ouabain (EO). EO is a
13 hormone secreted by the adrenal cortex under the regulation of adrenocortical tropic hormone
14 (ACTH), angiotensin-II (via angiotensin receptor type 2) and sodium loading [40-42]. EO induces
15 vasoconstriction with consequent increase of vascular resistance and blood pressure levels, and
16 increases natriuresis [43]. When aldosterone levels are appropriately high, such as in conditions of
17 sodium deficiency, sodium balance is preserved and EO is not increased. By contrast, when
18 aldosterone is inappropriately high, the excessive sodium retention causes an increase of EO secretion
19 by adrenal cortex with consequent further increase in blood pressure levels [39]. These observations
20 explain the different predictive role of aldosterone levels observed in the study of Brown et al. In a
21 condition of renin-independent aldosteronism the homeostatic balance is lost and the sodium load is
22 excessive, leading to increase of EO with consequent development of hypertension. This is not the
23 case for condition in which aldosterone is physiologically regulated by the renin-angiotensin system.

1 The recent description of the aldosterone-producing cell clusters (APCCs) provided a potential basis
2 for the renin-independent aldosterone production. APCCs are clusters of subcapsular zona
3 glomerulosa-like cells and inner zona fasciculata-like cells of 0.2-1.5 mm of diameter which express
4 CYP11B2 (aldosterone synthase), but not CYP11B1 (11 β -hydroxylase, involved in the last step of
5 cortisol synthesis) [44,45].

6 Recent studies demonstrated that APCCs are relatively frequent even in the adrenal glands removed
7 from patients with normal blood pressure levels [46]. In particular, aging is associated with a decrease
8 in CYP11B2 expression in the normal zona glomerulosa and concomitant increase in APCCs,
9 explaining the common finding of a progressive reduction of renin level with age and relative increase
10 of aldosterone levels [47**]. Some APCCs harbour the same mutations associated with autonomous
11 aldosterone production in APAs [48-50], suggesting that they could be considered as precursors of
12 some types of APAs [51].

13 **Conclusions**

14 Patients with a unilateral form of PA treated with laparoscopic adrenalectomy, show a normalization
15 or significant reduction of blood pressure levels in 84% of cases and 94% having complete
16 biochemical cure [6*]. Patients with an absent or partial clinical response had a duration of
17 hypertension significantly longer than cured patients [6*]. Patients with PA are at higher risk of
18 developing cardiovascular complication and metabolic disturbances compared with patients with
19 essential hypertension [5*]. These observations underline the importance of an early diagnosis and
20 treatment of PA. The high prevalence of this condition, even in the general hypertensive population
21 and in patients with a mild hypertensive phenotype, point towards the necessity of widening the
22 number of patients with hypertension that should be screened early for PA. Unfortunately, the vast
23 majority of patients with PA, and particularly the mildest forms, will remain undiagnosed. Therefore,
24 although robust data from prospective randomized trials on the most appropriate treatment in patients

1 with low renin hypertension without a confirmed diagnosis of PA are currently lacking, the use of
2 specific drugs that block aldosterone effects in those patients could prevent the cardio-metabolic
3 effects of an excessive aldosterone production and should be considered in the early steps of
4 pharmacological treatment.

5 **Key points:**

- 6 • Recent studies reported a prevalence of PA of about 6% among unselected patients with
7 arterial hypertension, with the highest percentage in patients with the most severe degrees of
8 hypertension, but with a not negligible rate even in patients with mild hypertension.
- 9 • Among Italian and German general practitioners, PA is investigated in less than 20% of the
10 expected patients according to the recommendations of the ES Guideline.
- 11 • Analysis of hospital registries demonstrated unacceptably low rates of diagnosis of PA
12 compared to the expected prevalence and even lower rates of adrenalectomies compared to
13 the expected rate of diagnosis of unilateral forms of PA.
- 14 • The prevalence of PA among individuals with normal blood pressure levels and
15 normokalaemia is relatively high and, among individuals with normotension, high aldosterone
16 levels predict a high risk of developing hypertension, especially in the presence of low renin
17 levels.

18 **References**

- 19 1. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the
20 global burden of raised blood pressure on current and future generations: the Lancet Commission on
21 hypertension. *Lancet* 2016;388:2665–2712.

1 2. Funder JW, Carey RM, Mantero F et al. The Management of Primary Aldosteronism: Case
2 Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin*
3 *Endocrinol Metab.* 2016;101:1889–1916.

4 ** Updated version of the Endocrine Society Guideline giving practical recommendations regarding
5 the diagnosis and treatment of primary aldosteronism. According to the guideline 50% of patients
6 with arterial hypertension should be screened for primary aldosteronism.

7 3. Mulatero P, Monticone S, Burrello J, et al. Guidelines for primary aldosteronism: uptake by
8 primary care physicians in Europe. *J Hypertens.* 2016;34:2253–2257.

9 * This survey demonstrated a lack of knowledge of the ES guideline among general practitioners in
10 Germany and Italy, resulting in a large underestimation of the PA prevalence.

11 4. Monticone S, Burrello J, Tizzani D et al. Prevalence and Clinical Manifestations of Primary
12 Aldosteronism Encountered in Primary Care Practice. *J Am Coll Cardiol.* 2017;69:1811–1820.

13 * This study evaluated the prevalence of PA in a large cohort of unselected patients with arterial
14 hypertension referred by Italian general practitioners, demonstrating a PA prevalence of about 6% .

15 5. Monticone S, D’Ascenzo F, Moretti C et al. Cardiovascular events and target organ damage
16 in primary aldosteronism compared with essential hypertension: a systematic review and meta-
17 analysis. *Lancet Diabetes Endocrinol.* 2017; doi: 10.1016/S2213-8587(17)30319-4. [Epub ahead of
18 print].

19 * This metaanalysis demonstrated a significant association between primary aldosteronism and
20 cardiovascular and cerebrovascular events, target organ damage and metabolic comorbidities.

1 6. Williams TA, Lenders JWM, Mulatero P et al. Outcomes after adrenalectomy for unilateral
2 primary aldosteronism: an international consensus on outcome measures and analysis of remission
3 rates in an international cohort. *Lancet Diabetes Endocrinol.* 2017;9:689-699

4 * This articles define for the first time the clinical and biochemical criteria for success after
5 adrenalectomy; these criteria are also applied to a large cohort of patients. The authors reported a rate
6 of biochemical success after adrenalectomy in patients with a unilateral form of PA of 94% and a rate
7 of complete or partial clinical success in more than 80% of adrenalectomies in a large, multicenter
8 cohort.

9 7. Hundemer GL, Curhan GC, Yozamp N, et al. Cardiometabolic outcomes and mortality in
10 medically treated primary aldosteronism: a retrospective cohort study. *Lancet Diabetes Endocrinol.*
11 2017; doi: 10.1016/S2213-8587(17)30367-4. [Epub ahead of print]

12 ** This retrospective cohort study demonstrated that PA patients treated with MR antagonists are
13 exposed to an increased risk of incident cardiometabolic events and death compared with age-
14 matched patients with essential hypertension. The excess risk was limited to patients with persistent
15 suppressed renin activity despite MR treatment.

16 8. Catena C, Colussi G, Lapenna R et al. Long-term cardiac effects of adrenalectomy or
17 mineralocorticoid antagonists in patients with primary aldosteronism. *Hypertension.* 2007;50:911-
18 918

19 9. Rossi GP, Cesari M, Cuspidi C et al. Long-term control of arterial hypertension and regression
20 of left ventricular hypertrophy with treatment of primary aldosteronism. *Hypertension.* 2013;62:62-
21 69.

- 1 10. Funder JW, Carey RM, Fardella C et al. Case detection, diagnosis, and treatment of patients
2 with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol*
3 *Metab.* 2008;93:3266–3281.
- 4 11. Buffolo F, Monticone S, Burrello J et al. Is Primary Aldosteronism Still Largely
5 Unrecognized? *Horm Metab Res.* 2017; 49:908-914.
- 6 12. Mosso L, Carvajal C, González A et al. Primary aldosteronism and hypertensive disease.
7 *Hypertension.* 2003;42:161–165.
- 8 13. Rossi GP, Bernini G, Caliumi C et al. A prospective study of the prevalence of primary
9 aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol.* 2006;48:2293–2300.
- 10 14. Calhoun DA, Nishizaka MK, Zaman MA et al. Hyperaldosteronism among black and white
11 subjects with resistant hypertension. *Hypertension.* 2002;40:892–896.
- 12 15. Mulatero P, Stowasser M, Loh K-C et al. Increased diagnosis of primary aldosteronism,
13 including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab.*
14 2004;89:1045–1050.
- 15 16. Käyser SC, Dekkers T, Groenewoud HJ et al. Study Heterogeneity and Estimation of
16 Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis. *J Clin*
17 *Endocrinol Metab.* 2016;101:2826–2835.
- 18 17. Di Murro A, Petramala L, Cotesta D et al. Renin-angiotensin-aldosterone system in patients
19 with sleep apnoea: prevalence of primary aldosteronism. *J Renin-Angiotensin-Aldosterone Syst*
20 *JRAAS.* 2010;11:165–172.
- 21 18. Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J*
22 *Med.* 1965 ;273:1135–1143.

- 1 19. Mukherjee JJ, Khoo CM, Thai AC et al. Type 2 diabetic patients with resistant hypertension
2 should be screened for primary aldosteronism. *Diabetes Vasc Dis Res.* 2010;7:6–13.
- 3 20. Rossi GP, Seccia TM, Gallina V et al. Prospective appraisal of the prevalence of primary
4 aldosteronism in hypertensive patients presenting with atrial flutter or fibrillation (PAPPHY Study):
5 rationale and study design. *J Hum Hypertens.* 2013;27:158–163.
- 6 21. Rossi E, Perazzoli F, Negro A, Magnani A. Diagnostic rate of primary aldosteronism in
7 Emilia-Romagna, Northern Italy, during 16 years (2000-2015). *J Hypertens.* 2017;35:1691–1697.
- 8 22. Jonsdottir G, Gudmundsson J, Birgisson G, Sigurjonsdottir HA. Primary aldosteronism: from
9 case detection to histopathology with up to 6 years of follow-up. *J Clin Hypertens.* 2017;19:424–430.
- 10 23. Hanslik G, Wallaschofski H, Dietz A et al. Increased prevalence of diabetes mellitus and the
11 metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry. *Eur J*
12 *Endocrinol.* 2015;173:665–675.
- 13 24. Schirpenbach C, Segmiller F, Diederich S et al. The diagnosis and treatment of primary
14 hyperaldosteronism in Germany: results on 555 patients from the German Conn Registry. *Dtsch*
15 *Arztebl Int.* 2009;106:305–311.
- 16 25. Miyake Y, Tanaka K, Nishikawa T et al. Prognosis of primary aldosteronism in Japan: results
17 from a nationwide epidemiological study. *Endocr J.* 2014;61:35–40.
- 18 26. Ito Y, Takeda R, Takeda Y. Subclinical primary aldosteronism. *Best Pract Res Clin*
19 *Endocrinol Metab.* 2012 Aug;26(4):485–495.
- 20 27. Médeau V, Moreau F, Trinquart L et al. Clinical and biochemical characteristics of
21 normotensive patients with primary aldosteronism: a comparison with hypertensive cases. *Clin*
22 *Endocrinol.* 2008;69:20–28.

- 1 28. Ito Y, Takeda R, Karashima S et al. Prevalence of primary aldosteronism among
2 prehypertensive and stage 1 hypertensive subjects. *Hypertens Res.* 2011;34:98–102.
- 3 29. Karashima S, Kometani M, Tsujiguchi H et al. Prevalence of primary aldosteronism without
4 hypertension in the general population: Results in Shika study. *Clin Exp Hypertens.* 2017;19:1–8.
- 5 30. Markou A, Pappa T, Kaltsas G et al. Evidence of primary aldosteronism in a predominantly
6 female cohort of normotensive individuals: a very high odds ratio for progression into arterial
7 hypertension. *J Clin Endocrinol Metab.* 2013;98:1409–1416.
- 8 31. Baudrand R, Guarda FJ, Fardella C et al. Continuum of Renin-Independent Aldosteronism in
9 Normotension. *Hypertension.* 2017;69:950–956.
- 10 32. Fallo F, Pilon C, Williams TA et al. Coexistence of different phenotypes in a family with
11 glucocorticoid-remediable aldosteronism. *J Hum Hypertens.* 2004;18:47–51.
- 12 33. Mulatero P, di Cella SM, Williams TA et al. Glucocorticoid remediable aldosteronism: low
13 morbidity and mortality in a four-generation italian pedigree. *J Clin Endocrinol Metab.*
14 2002;87:3187–3191.
- 15 34. Sukor N, Mulatero P, Gordon RD et al. Further evidence for linkage of familial
16 hyperaldosteronism type II at chromosome 7p22 in Italian as well as Australian and South American
17 families. *J Hypertens.* 2008;26:1577–1582.
- 18 35. Scholl UI, Stölting G, Nelson-Williams C et al. Recurrent gain of function mutation in calcium
19 channel *CACNA1H* causes early-onset hypertension with primary aldosteronism. *eLife.*
20 2015;4:e06315.

- 1 36. Brown JM, Robinson-Cohen C, Luque-Fernandez MA et al. The Spectrum of Subclinical
2 Primary Aldosteronism and Incident Hypertension: A Cohort Study. *Ann Intern Med.* 2017;167:630–
3 641.
- 4 ** In this prospective study the authors demonstrated that normotensive individuals with low renin
5 and high aldosterone levels display an increased risk for hypertension. This manuscript broadens the
6 spectrum of renin independent aldosteronism.
- 7 37. Vasani RS, Evans JC, Larson MG et al. Serum aldosterone and the incidence of hypertension
8 in nonhypertensive persons. *N Engl J Med.* 2004;351:33–41.
- 9 38. Newton-Cheh C, Guo CY, Gona P et al. Clinical and genetic correlates of aldosterone-to-renin
10 ratio and relations to blood pressure in a community sample. *Hypertension.* 2007;49:846–856.
- 11 39. Funder JW. Aldosterone and Mineralocorticoid Receptors-Physiology and Pathophysiology.
12 *Int J Mol Sci.* 2017;18(5).
- 13 40. Lorenz JN, Loreaux EL, Dostanic-Larson I et al. ACTH-induced hypertension is dependent
14 on the ouabain-binding site of the alpha2-Na⁺-K⁺-ATPase subunit. *Am J Physiol Heart Circ Physiol.*
15 2008;295:273–280.
- 16 41. Laredo J, Shah JR, Lu ZR, et al. Angiotensin II stimulates secretion of endogenous ouabain
17 from bovine adrenocortical cells via angiotensin type 2 receptors. *Hypertension.* 1997;29:401–407.
- 18 42. Hasegawa T, Masugi F, Ogihara T, Kumahara Y. Increase in plasma ouabainlike inhibitor of
19 Na⁺, K⁺-ATPase with high sodium intake in patients with essential hypertension. *J Clin Hypertens.*
20 1987;3:419–429.

- 1 43. Dostanic I, Paul RJ, Lorenz JN et al. The alpha2-isoform of Na-K-ATPase mediates ouabain-
2 induced hypertension in mice and increased vascular contractility in vitro. *Am J Physiol Heart Circ*
3 *Physiol.* 2005;288:477–485.
- 4 44. Nishimoto K, Nakagawa K, Li D et al. Adrenocortical zonation in humans under normal and
5 pathological conditions. *J Clin Endocrinol Metab.* 2010;95:2296–2305.
- 6 45. Gomez-Sanchez CE, Kuppusamy M, Reincke M, Williams TA.
7 Disordered CYP11B2 Expression in Primary Aldosteronism. 2017; 49:957-962.
- 8 46. Nishimoto K, Seki T, Hayashi Y et al. Human Adrenocortical Remodeling Leading to
9 Aldosterone-Producing Cell Cluster Generation. *Int J Endocrinol.* 2016;2016:7834356.
- 10 47. Nanba K, Vaidya A, Williams GH et al. Age-Related Autonomous Aldosteronism.
11 *Circulation.* 2017;136:347–355.
- 12 ** This work highlights that aging is associated with a pattern of increased APCC number and a
13 decreased expression of CYP11B2 (aldosterone synthase) in the adrenal zona glomerulosa.
- 14 48. Monticone S, Castellano I, Versace K et al. Immunohistochemical, genetic and clinical
15 characterization of sporadic aldosterone-producing adenomas. *Mol Cell Endocrinol.* 2015;411:146–
16 154.
- 17 49. Omata K, Yamazaki Y, Nakamura Y et al. Genetic and Histopathologic Intertumor
18 Heterogeneity in Primary Aldosteronism. *J Clin Endocrinol Metab.* 2017;102:1792–1796.
- 19 50. Nishimoto K, Tomlins SA, Kuick R, Cani AK, Giordano TJ, Hovelson DH, et al. Aldosterone-
20 stimulating somatic gene mutations are common in normal adrenal glands. *Proc Natl Acad Sci U S*
21 *A.* 2015 Aug 18;112(33):E4591–4599.

1 51. Nishimoto K, Seki T, Kurihara I, Yokota K, Omura M, Nishikawa T, et al. Case Report:
2 Nodule Development From Subcapsular Aldosterone-Producing Cell Clusters Causes
3 Hyperaldosteronism. J Clin Endocrinol Metab. 2016 Jan;101(1):6–9.

4 **Acknowledgements**

5 None

6 **Financial support and sponsorship**

7 None

8 **Conflict of interest**

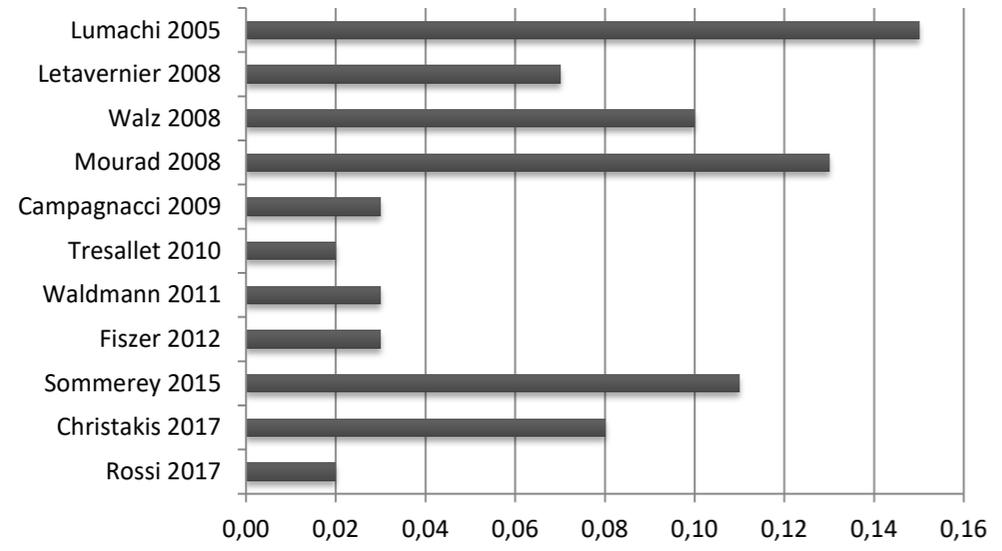
9 None

10

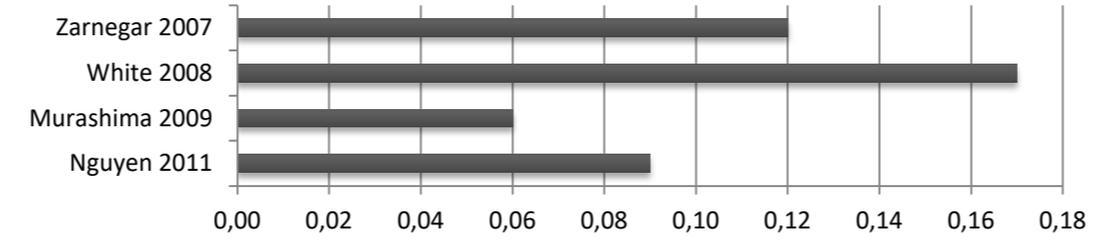
11

Incidence of adrenalectomies in patients with primary aldosteronism in expert centers

Europe



USA



Japan

