Review Article
Changes in the Perceived Epidemiology of Primary Hyperaldosteronism

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Primary aldosteronism has been considered a rare disease in the past years, affecting 1% of the hypertensive population. Subsequently, growing evidence of its higher prevalence is present in literature, although the estimates of disease range from 5 up to 20%, as in type 2 diabetes and resistant hypertension. The main reasons for these variations are associated with the selection of patients and diagnostic procedures. If we consider that hypertension is present in about 20% of the adult population, primary aldosteronism can no longer be considered a rare disease. Patients with primary aldosteronism have a high incidence of cardiovascular, cerebrovascular and kidney complications. The identification of these patients has therefore a practical value on therapy, and to control morbidities derived from vascular damage. The ability to identify the prevalence of a disease depends on the number of subjects studied and the methods of investigation. Epidemiological studies are affected by these two problems: there is not consensus on patients who need to be investigated, although testing is recommended in subjects with resistant hypertension and diabetes. The question of how to determine aldosterone and renin levels is open, particularly if pharmacological wash-out is difficult to perform because of inadequate blood pressure control.

1. Introduction
The history of primary aldosteronism (PA) is that of an uncommon cause of hypertension until up to 15 years ago. In 1954, Conn studied a 34-year-old female with high blood pressure, severe hypokalemia, and mild hypernatremia, discovering an averaged 22-fold higher mineralcorticoid activity per day in comparison with normotensive controls: this clinical condition reversed after the removal of a right adrenal mass. Thereafter, Conn stated in his presidential address “It is believed that these studies delineate a new clinical syndrome which is designated as primary aldosteronism.” Primary aldosteronism, as defined by Conn in 1955 [1], was widely thought to be present in approximately 1% of hypertensive patients [2, 3]. Today primary aldosteronism can be defined as a group of different disorders (Table 1), “in which aldosterone production is inappropriately high, relatively autonomous from the renin-angiotensin system, and non suppressible by sodium loading” [4]. Several studies suggest that PA is the most common cause of secondary hypertension, although the prevalence is variable from 5 to 20%, depending on patient selection and methods of diagnosis. There are changes in the perceived epidemiology of the disease because as Gordon observed “normokalemic primary aldosteronism has been known for 50 years, always there, but not recognized because patients were not tested for it” [5]. Recent studies highlight that only a minority of patients with PA presents with hypokalemia and normokalemic hyperaldosteronism is the most common presentation of the disease, particularly in the case of idiopathic hyperaldosteronism (IHA). Variability in the prevalence of PA can be due to differences in aldosterone to renin ratio (ARR) cutoff values, defects in the use of functional tests, or suboptimal sampling conditions such as the maintenance of some medications or bias in the selection of patients. Strong evidence supports the hypothesis that aldosterone plays a pivotal role in hypertension, even if the classical diagnosis of primary aldosteronism cannot be made. Finally, is the diagnosis of aldosteronism essential in the strategies we need to adopt in treating high blood pressure and related comorbidities?
Patients with primary aldosteronism (PA) are at risk of hypertension, which can induce a significant blood pressure increase over time. The addition of amiloride in the therapy for resistant hypertension is associated with an increase in sodium and fluid excretion, as it blocks the epithelial-sodium channel (ENaC) as an indirect aldosterone antagonist, opposing the upregulating action of mineralocorticoids on this channel (ENaC) as an indirect aldosterone antagonist. The Framingham study reported that serum aldosterone levels predicted the development of hypertension in normotensive subjects [13] and high ARR is predictive of the worsening of hypertension. The study of Newton-Cheh and coworkers [14] analyzed the progression and a 53% increased risk of hypertension. Dividing patients into quartiles of ARR, the upper quartile experienced BP progression and 16% developed hypertension. The study concluded that “The incidence of primary aldosteronism is probably much higher than the 1% currently quoted in texts, with earlier, normokalemic forms accounting for the majority of cases” [18].

### Table 1: Subtypes of primary aldosteronism [6].

| Subtype                                      | Percentage of Cases |
|----------------------------------------------|---------------------|
| Aldosterone-producing adenoma (APA)          | 35%                 |
| Bilateral idiopathic hyperplasia (IHA)       | 60%                 |
| Primary unilateral adrenal hyperplasia       | 2%                  |
| Pure aldosterone-producing adrenocortical carcinoma | 1%               |
| Familial hyperaldosteronism                  |                     |
|   Type I = glucocorticoid remediable aldosteronism | <1%               |
|   Type II = familial APA or IHA              | <2%                 |
| Ectopic aldosterone-producing adenoma or carcinoma | <0.1%             |

### 2. Materials and Methods

#### 2.1 Data Sources and Searches

We conducted a search on the PubMed database for epidemiological studies on primary aldosteronism using terms to identify clinical settings as follows: [(Primary Aldosteronism] AND [epidemiology] AND [hospital setting] OR [general population] OR [essential hypertension] OR [refractory hypertension] OR [diabetes] OR [aldosterone antagonist] OR [angiotensin II receptor antagonist] OR [angiotensin converting enzyme inhibitors]). The search was limited to articles published up to February 2011. A subsequent search was performed for clinical trials using terms for identification as follows: [(aldosteronism] AND [target organ damage] OR [heart] OR [kidney] OR [endothelium] OR [mesangium]). Clinical trials with an active treatment period of ≥4 weeks were included.

### 3. Aldosterone and Hypertension

Mineralcorticoid antagonists are extremely efficient in the treatment of hypertension [7]. Eplerenone is able to reduce blood pressure in unselected patients with mild to moderate hypertension [8], with an add-on effect if patients are treated with ACEi [9], and its effect on uncontrolled hypertensive patients on ACE-I or ARB was not predicted by the baseline value of aldosterone/PRA (ARR) ratio [10]. Of note, aldosterone receptor antagonists need to be used with care, because they can induce an increase of potassium especially if renal function is impaired. In the case of renin angiotensin aldosterone system (RAAS) inhibition monotherapy, mineralcorticoid antagonists increase the level of potassium marginally but, in the case of dual RAAS inhibition, when associated with ACEi/ARB, a higher incidence of serum potassium >5.5 mmol/L has been reported in up to 5.6% of patients [11]. Amiloride blocks the epithelial-sodium channel (ENaC) as an indirect aldosterone antagonist, opposing the upregulating action of mineralocorticoids on this transport and, consequently, reduces the sodium and fluid overload. The addition of amiloride in the therapy for resistant hypertension can induce a significant blood pressure decrease in low-renin hypertensive patients [12]. Is it aldosteronism or inappropriately high levels of aldosterone?

A method for answering this question is another question: are aldosterone levels able to predict future hypertension, supporting a causal role? The Framingham Offspring Study reported that serum aldosterone levels predicted the development of hypertension in normotensive subjects [13] and high ARR is predictive of the worsening of hypertension.

### 4. Epidemiology of Primary Aldosteronism

If we consider the relationship between primary aldosteronism and hypertension, we are moving into the field of awareness that increased levels of aldosterone in relation to normal range are an important cause of secondary hypertension (Table 2). How frequent is primary aldosteronism? The Harvey Lecture of Conn held in 1967 reports “While we were theorizing about the possible existence of normokalemic primary aldosteronism and before we have actually described it, we had suggested on the basis of autopsy report and other indirect evidence, that primary aldosteronism could actually involve as many as 20 percent of people with “essential hypertension.” Although our own work in this regard is far from complete, it appears that the determined value will not be as high as predicted. At present 10 percent appear to be more realistic” [17].

At the beginning of the 1990s, Gordon et al. reported that 12% of 52 individuals enrolled in a hypertensive drug trial were positive for primary aldosteronism. The diagnosis was made after the determination of ARR and by using a suppression test, namely, fludrocortisone acetate administration plus oral salt loading. Remarkably, none of the 6 patients in this study presented hypokalemia. The study concluded that “The incidence of primary aldosteronism is probably much higher than the 1% currently quoted in texts, with earlier, normokalemic forms accounting for the majority of cases” [18].
One year later, in 1994, the same authors reported in 199 patients referred to the Hypertension Clinic of Brisbane a prevalence of 8.5% up to probably 12% [19]. The characteristics of these patients were hypertension and normokalemia; that is, the diagnosis was made in patients without a clinical suspicion of primary aldosteronism. The cutoff value of serum aldosterone/plasma renin activity ratio (SA/PRA = suspicion of primary aldosteronism. The cutoff is, the diagnosis was made in patients without other criteria, while diagnosis of highly probable PA was established for a ratio higher than 25. To confirm the diagnosis, the fludrocortisone test was performed while the suppression test was not executed; therefore, the difference with the general population can be considerable.

More recently, the Framingham Offspring Study [14] reported aldosterone/plasma-renin concentration ratio exceeding 26 ng/L per mU/L in 7.9% and 23.1% of untreated hypertensive men and woman, respectively, and in 24.6% and 31.1% of men and woman on β-blockers. In this study, ARR was measured only once, sodium intake was not standardized, and suppression tests were not executed;
therefore, a limit to this epidemiological observation was present, although it does reflect a large community-based investigation.

The Bussolengo Study [21] was carried out in a primary care setting. A sampling of 1462 patients referred by general practitioners, aged 35–74 years, were randomly selected and studied. 412 patients were identified as hypertensive (28.2%) and 287 gave their consent to blood analysis (69.6%). Direct active renin and aldosterone were measured in these hypertensive subjects. The aldosterone/active renin ratio (AARR) was considered positive for values >32 pg/mL, which corresponded to AARR > 50 ng/dL/ng/mL/h. This last cutoff has a relatively high sensitivity and specificity for the diagnosis of aldosteronism [30]. About one of three patients (32.4%) had an elevated AARR. The study cannot demonstrate clearly the prevalence of hyperaldosteronism in a general hypertensive population, because confirmatory tests were not performed and a prudent practice could be the repetition of AARR, but the suggestion that a large population can reap benefits from antialdosterone drug therapy does arise.

A large study was carried out by Rossi et al. [22] on 1125 hypertensive patients referred to 14 specialized hypertension clinics throughout Italy. Plasma renin activity and plasma aldosterone were measured at baseline and again 60 minutes after administration of 50 mg of captopril. The subjects then had a saline suppression test, and 126 patients were identified as presumed PA, corresponding to 11.2%. Taking into account patients with primary aldosteronism, an aldosterone producing adenoma (APA) was found in 54 of them, 43% of cases, with the remainder considered to have idiopathic hyperaldosteronism (IHA). Different results on PA prevalence were reported by Williams and coworkers [23]. They observed a low prevalence of primary aldosteronism in a group of 347 hypertensive volunteers: they analyzed ARR, plasma, and urine aldosterone, on different salt diet regimens. Only 3.4% of patients were diagnosed with PA. The large difference in prevalence with the other studies brings to light the question of patient selection, because subjects with plasma potassium <3.5 mEq/L were excluded, as well as patients with diastolic BP > 110 mmHg while on two or more medications. The analysis of these two last studies follows up on the question suggested by Kaplan [31]: is there really an unrecognized epidemic of aldosteronism? The Rossi study could be limited by a number of problems, as Kaplan observes, one of them being related to the fact that only one set of ARR was performed; on the other hand, the Williams study could have the bias that patients were excluded from the study on the basis of low plasma potassium and resistant hypertension. The bias of patient selection in the Williams study could be reasonably evoked, because it is clearly demonstrated that primary aldosteronism is more prevalent in essential hypertensives classified as stage 2 and 3 JNC VI [32].

Three years after Kaplan’s observations, a recent study by Rossi [33] demonstrated that ARR has a good reproducibility, contrary to the previously claimed poor reproducibility [34].

As Gordon observes in answering the question “primary aldosteronism—actual epidemics or false alarm?,” “Epi-
demics is an inappropriate term”, but, at the same time, PA is not a “false alarm,” because “false alarm suggests that we can all relax again and get back to our real work” [5]. In summary, the question of primary aldosteronism prevalence remains open. It seems reasonable to assert that PA can be present in up to 15–20% of hypertensive patients, depending on the population and methods of diagnosis used, as hereafter reported.

5. Primary Aldosteronism and Resistant Hypertension

Are there subgroups of essential hypertensive patients that more frequently can be diagnosed as affected by primary aldosteronism? The study of Mosso and coworkers [32] reports that the prevalence of PA confirmed with suppression test was diagnosed in 6.1% of 609 patients treated in primary care centers. Dividing all patients into groups based on blood pressure values and relating them to a control group, primary aldosteronism prevalence was 1.55% in normal subjects, 1.99% in Stage 1 hypertension JCN IV (SBP 140 to 159 mmHg, DBP 90 to 99 mmHg), 8.02% in Stage 2 (SBP 160 to 179 mmHg, DBP 100 to 109 mmHg), and 13.2% in Stage 3 (SBP > 180 mmHg, DBP > 110 mmHg) hypertension. Those having PA were younger and took a larger number of drugs for BP control. Of interest is the fact that only 1 out of 29 PA patients had mild hypokalemia, and the researchers explained the low frequency of reduced serum potassium levels as the result of screening and referral of these patients to secondary centers. Estimating the prevalence of hypokalemia PA close to 1.5%, they reported a total prevalence of 7.5%. But the point is that 13.2% of patients at hypertension Stage 3 JNC IV had PA. Calhoun and coworkers have studied 88 patients referred to a university clinic for resistant hypertension (hypertensive subjects requiring 3 or more different antihypertensive medications at pharmacologically effective doses) [24]. 20% of them had primary aldosteronism on the basis of suppressed plasma renin activity (PRA < 1.0 ng/mL/h) and high urinary aldosterone (>12 pg/24 h), in the presence of a high-sodium diet (>200 mEq/24 h).

They were treated with spironolactone with a consistent and significant reduction of BP (−26 ± 15.7/−12 ± 12.6 mmHg). Gallay in Seattle reported a prevalence of PA in 17% of patients with resistant hypertension [25]; similarly, Strauch et al. in Europe [26] and Eide and colleagues have reported primary aldosteronism in 23% of patients with RH [35].

Although cause-and-effect has not been confirmed, it appears that the increased occurrence of primary aldosteronism may be linked to the increasing incidence of sleep apnea syndrome and obesity.

Di Murro and colleagues [27] reported a prevalence of 33.9% of primary aldosteronism in hypertensive patients with sleep apnea syndrome. Pratt-Ubunama and coworkers reported 85% prevalence of obstructive apnea syndrome (OSA) in resistant hypertensive patients, and serum aldosterone levels were higher than in patients with OSA without resistant hypertension [36]. Patients with upper body or
visceral obesity frequently have elevated plasma aldosterone levels, but the mechanism is unknown. An increased aldosterone secretion could be secondary to a decreased secretion of atrial natriuretic peptide, which seems to be reduced in the case of obesity [37].

6. Primary Aldosteronism and Diabetes

Type 2 diabetic patients are frequently affected by hypertension, and approximately 50–75% fail to achieve satisfactory blood pressure control [38]. This is one cause of the high incidence of cardiovascular complications, such as heart failure, stroke, and kidney disease. A close relationship between aldosterone and insulin resistance has been demonstrated: hyperinsulinemia stimulates the production of aldosterone, and an excess of mineralocorticoids can cause the resistant hypertension observed in diabetic patients. Mukherjee and coworkers [28] have studied prospectively 100 Asian type 2 diabetic patients with uncontrolled hypertension and have analyzed ARR ratio. Those with a ratio >550 pmol/L/ng/mL/h underwent a confirmatory saline test, and, in the case of high aldosterone levels, imaging investigations and adrenal vein sampling were performed. Thirteen patients (13%) were diagnosed with primary aldosteronism; their blood pressure was significantly higher, 46% had plasma potassium levels lower than 3.5 mmol/L, and 62% of them had a surgically correctable form of PA. The limitation of this study was linked to the difficulties in safely withdrawing antihypertensive medications; therefore, a false negative ratio could be present and the saline test to indentify these was not performed on all patients. Consequently, a higher prevalence of PA may have been present in this population. Another report by Umprierrez and colleagues [29] screened 100 patients with type 2 diabetes and resistant hypertension, measuring ARR and performing confirmatory salt load tests in subjects with a ratio >30 ng/dL/ng/mL/h. They observed an increased ARR in 34% of patients, and 14% of them had primary aldosteronism. These results have a potentially great impact, because, for each 10 mmHg decrease of systolic BP, there is a 13% reduction of microvascular complications, a 12% decreased risk of fatal and nonfatal myocardial infarction, and a 17% decreased risk of death [39]. From these data arises the recommendation to investigate primary aldosteronism in all patients with type 2 diabetes and resistant hypertension, because its identification could have a tremendous impact on achieving BP control and consequently on decreasing cardiovascular complications and mortality.

7. Primary Aldosteronism and Target Organ Damage

The detection of primary aldosteronism is central in the study of essential hypertension for at least two reasons: the first is linked to therapeutic strategies, such as the indication for surgical procedures in the presence of adenoma or the use of mineralocorticoid antagonists. The second is the observation that cardiovascular and cerebrovascular complications may be more common in the case of PA.

Milliez and colleagues reported that the stroke rate was 12.9% in PA subjects, compared to 3.4% observed in a control group matched for age, gender, and blood pressure levels [40]. They also observed a higher incidence of myocardial infarction and atrial fibrillation in PA subjects. Catena and coworkers [41] have studied 54 patients with PA and compared left ventricular mass (LVMi) and function before and after treatment with a group of 274 patients with essential hypertension. At baseline, the groups were similar in clinical characteristics and blood pressure control, but significantly higher LVMi were observed in patients with aldosteronism. Decreased diastolic function was also reported. After one year of treatment, significant reductions of blood pressure and LVMi were present, and after an average period of 6.4 years of followup, LV mass further decreased, but not BP. The percentage reduction of LVMi was higher in patients with idiopathic hyperaldosteronism who underwent medical therapy than in the adenoma-producing aldosterone group, who were surgically treated. The cardiac changes observed in the period between one year and the end of study lead us to suppose that factors other than volume stress, which can result from the renal effects of aldosterone, or blood pressure are responsible for these changes. The activation of cardiac receptors might play a role in left ventricle hypertrophy and remodeling. It is known that interactions of aldosterone with angiotensin, endothelin, or bradykinin activate inflammatory cells and fibroblast proliferation, leading to collagen synthesis. Independently of blood pressure, aldosterone exerts detrimental effects on small vessels, such as pronounced fibrosis, and on heart geometry and function. The result of an increased fibrosis [42] explains the failure in diastolic function.

Clinical outcome in terms of myocardial infarction, stroke, revascularization procedures, and sustained arrhythmias was analyzed by the same authors after 7.4 years [43]. Before the beginning of treatment, at basal time, a history of cardiovascular events was present in 34% of patients with PA, significantly higher than the 11% registered in essential hypertension group. After treatment, at the end of followup, endpoint was reached in 19% of patients with PA, and 18% of essential hypertensives, demonstrating the importance of correction of hyperaldosteronism.

Of interest is the study of the German Conn’s Registry [44]: a population of 553 patients with PA was investigated, of which 56.1% had hypokalemia. They differed from normokalemic patients because of higher BP levels, but therapeutic strategies were not different between the groups. Aldosterone was significantly higher in patients with low potassium levels, and a correlation with the prevalence of vascular comorbidities was observed. The prevalence rate for cardiovascular events, such as angina or cardiac insufficiency, was higher in the hypokalemic group.

A larger work [45], the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, analyzes comorbidity and survival in a group of 3153 patients with ischemic heart disease who underwent coronary angiography. The study evaluated ARR, and 3.1% of patients had a ratio >50. After the division in quartiles on the basis of plasma aldosterone concentration, hazard ratio (HR) of all-cause death was higher
for quartiles with higher ARR. In fully adjusted analysis, patients of the fourth quartile had an increased risk of fatal stroke (HR = 7.02). Again, this study addresses the question of primary aldosteronism or elevated levels of aldosterone and points out the need to consider mineralocorticoid antagonists in medical treatment strategies. Some populations benefit from aldosterone antagonist therapy: this is true not only for hypertensive patients with primary aldosteronism, but also in patients with heart failure and chronic kidney disease. However, patients in these last two groups must be carefully observed for the development of potentially fatal hyperkalemia. The RALES trial demonstrates that, when added to ACEi, aldosterone receptor antagonists decreased mortality by 30% in NYHA class III and IV over a period of 24 months [46]. The addition of eplerenone or spironolactone in diabetic patients with proteinuria to ACEi or angiotensin receptor antagonists seems to reduce protein excretion, which is a causative factor of kidney disease progression [47].

8. Summary

The prevalence of primary aldosteronism cannot be precisely determined at this time. It is significantly more common than previously thought, representing probably the most common cause of secondary hypertension. Changes in the perceived epidemiology of PA are the consequence of increased investigations in normokalemic hypertensive patients, and this represents an evolution from the historical definition of the disease. Using plasma aldosterone to plasma renin activity ratio followed by aldosterone suppression tests, the prevalence in hypertensive patients can be estimated in the range of 5–12%. A higher prevalence up to 15–20% is highly probable in selected patients, such as those with type 2 diabetes and refractory high blood pressure or sleep apnea syndrome. In these populations, the study of aldosterone in diabetic patients with proteinuria to ACEi or angiotensin receptor antagonists seems to reduce protein excretion, which is a causative factor of kidney disease progression.

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