Long-Term Cardio- and Cerebrovascular Events in Patients With Primary Aldosteronism

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Background: Aldosterone plays a detrimental role on the cardiovascular system and PA patients display a higher risk of events compared with EH.

Objectives: The objectives of the study were to compare cardio- and cerebrovascular events in patients with primary aldosteronism (PA) and matched essential hypertension (EH).

Methods: We retrospectively compared the percentage of patients experiencing events at baseline and during a median follow-up of 12 years in 270 PA patients case-control matched 1:3 with EH patients and in PA subtypes [aldosterone-producing adenoma (n = 57); bilateral adrenal hyperplasia (n = 213)] vs matched EH.

Results: A significantly higher number of PA patients experienced cardiovascular events over the entire period of the study (22.6% vs 12.7%, $P < .001$). At the diagnosis of PA, a higher number of patients had experienced total events (14.1% vs 8.4% EH, $P = .007$); furthermore, during the follow-up period, PA patients had a higher rate of events (8.5% vs 4.3% EH, $P = .008$). In particular, stroke and arrhythmias were more frequent in PA patients. During the follow-up, a higher percentage of PA patients developed type 2 diabetes. Parameters that were independently associated with the occurrence of all events were age, duration of hypertension, systolic blood pressure, presence of diabetes mellitus, and PA diagnosis. After division into PA subtypes, patients with either aldosterone-producing adenoma or bilateral adrenal hyperplasia displayed a higher rate of events compared with the matched EH patients.

Conclusions: This study demonstrates in a large population of patients the pathogenetic role of aldosterone excess in the cardiovascular system and thus the importance of early diagnosis and targeted PA treatment. **(*J Clin Endocrinol Metab* 98: 4826–4833, 2013)**

Over the last 15 years, a wealth of studies has shed new light on the detrimental role of aldosterone in the cardiovascular system (1–3). These studies have shown that aldosterone per se, independent from its effects on blood pressure (BP) levels, can cause an increase in cardiovascular damage in different animal models and in humans (1–4). Primary aldosteronism (PA) is the most frequent cause of secondary hypertension, and patients display an increased risk of target organ damage compared with essential hypertension (EH) with similar BP and risk profiles (5, 6). However, few studies have investigated the rate of cardiovascular events in PA patients

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Abbreviations: A/C, aldosterone to cortisol ratio value; AF, atrial fibrillation; APA, aldosterone-producing adenoma; ARR, aldosterone to PRA ratio; AVS, adrenal vein sampling; BAH, bilateral adrenal hyperplasia; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; DBP, diastolic BP; EH, essential hypertension; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein; MI, myocardial infarction; MRA, mineralocorticoid receptor-antagonist; OR, odds ratio; PA, primary aldosteronism; PRA, plasma renin activity; SBP, systolic BP.

with matched EH. Milliez et al in 2005 (5) demonstrated an increased risk of events at diagnosis [stroke, myocardial infarction (MI) and atrial fibrillation (AF)] in 124 PA patients compared with 456 matched EH. In a subsequent study, Catena et al (6) compared 54 PA patients with 323 EH at diagnosis and with 108 EH during a 7-year follow-up study. They demonstrated an increased risk of events (stroke, MI, and sustained arrhythmias) in PA patients at diagnosis but no difference in the follow-up after adrenalectomy or therapy with a mineralocorticoid receptor-antagonist (MRA). Recently Savard et al (7) demonstrated an increased prevalence of cardiovascular complications [coronary artery disease (CAD), nonfatal MI, heart failure, and AF] in a large population of PA patients (defined on the basis of high aldosterone to plasma renin activity ratio (ARR) and aldosterone levels but without performing confirmatory/exclusion tests), compared with controls. Unfortunately, PA subtype differentiation was not available (7). Finally, Born-Frontsberg et al (8) described the prevalence of cardiovascular events in a large population of 553 PA patients but a comparison with a matched population of EH was not performed. In these three studies, subtype differentiation was not performed by adrenal vein sampling (AVS) in most cases, a technique that is considered the only reliable means to distinguish patients with unilateral [aldosterone producing adenoma (APA) or unilateral adrenal hyperplasia from bilateral adrenal disease (bilateral adrenal hyperplasia (BAH)]. Furthermore, only in the study by Catena et al (6) did patients have a long-term follow-up.

In the present retrospective study, we have investigated the rate of cardio- and cerebrovascular events in a large population of 270 PA patients compared with a matched (1:3) population of 810 EH during long-term follow-up (median 12 years), and we evaluate the most important predictors of events. Moreover, we evaluate the rate of events in PA subtypes compared with matched EH. Of note, 88% of PA patients underwent AVS, thus receiving the most accurate available subtype diagnosis.

Materials and Methods

Patient selection

All PA patients diagnosed in our unit between January 1992 and December 2009 who had the last follow-up visit between January 2008 and December 2010 were included in this retrospective study.

The follow-up period was considered from the diagnosis of PA until the last visit in our unit. For BAH patients, MRA therapy was initiated immediately after subtype diagnosis, and the dose was targeted to obtain normal potassium and BP levels in absence of side effects (eplerenone was not available in our country at the time of the study); for APA patients adrenalectomy was performed within 3 months from the AVS diagnosis. Three matched EH patients were included as controls for each PA patient. PA and EH patients were matched 1:3 for sex, age, systolic and diastolic BP (SBP and DBP) levels at the first visit in our unit, duration of hypertension, body mass index (BMI), smoking habits, and comorbidity for type 2 diabetes mellitus. EH patients were selected randomly from our database (software Hypermacondo) using the above-described criteria.

Diagnosis of PA was performed as previously described. Briefly, the cutoff level considered as a positive ARR was 40 (nanograms per deciliter per nanogram per milliliter per 1 hour^{-1}) (50 before 2001) together with an aldosterone level greater than 15 ng/dL. All antihypertensive drugs were stopped at least 3 weeks before the aldosterone and plasma renin activity (PRA) measurements; diuretics and spironolactone were stopped at least 6 and 8 weeks before measurements, respectively. Patients who could not remain untreated received an α-blocker (doxazosin) and/or a calcium channel blocker (verapamil or amlodipine) during the screening, until the final diagnosis. The confirmatory saline infusion test consisted of an iv saline load (2 L of 0.9% NaCl infused over 4 h) that was considered positive if posttest aldosterone levels were greater than 5 ng/dL (9).

Subtype diagnosis was performed by computed tomography scanning with contrast and fine cuts of the adrenal and subsequent AVS. Sampling was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 3 (at least 2 before 2008) (10), and lateralization was defined as an aldosterone to cortisol ratio value (A/C) from one adrenal at least 4 times the ratio from the other adrenal gland or 3 times the A/C of the contralateral with the A/C in the contralateral less than the A/C in the peripheral vein. Two hundred thirty-seven PA patients (88%) underwent successful AVS (57 APA, 180 BAH), whereas 33 remained with an undetermined subtype for different reasons (they did not undergo AVS because of age/high risk for surgery, personal choice, or they underwent unsuccessful AVS). Most of these patients (n = 30) had bilaterally normal appearance of the adrenal glands on computed tomography scanning, which in our hands was associated with a very high probability of BAH (95%) (11) and were treated with medical therapy. For this reason during the analysis of PA subtypes vs EH, these patients were included in the BAH group, whereas in the subtype comparison (APA vs BAH), they were excluded. A final diagnosis of APA was considered proven, providing that all the following conditions were satisfied: 1) histological demonstration of adenoma, 2) normalization of hypokalemia if present, 3) cure or improvement of hypertension, and 4) normalization of ARR and suppressibility of aldosterone levels less than 5 ng/dL under saline load (12). Finally, all patients with PA were screened for glucocorticoid-remediable aldosteronism using a long-PCR technique (13) and GRA patients were excluded from the present study.

We considered the following cardiovascular events: MI and unstable angina requiring angioplasty (in the text grouped together under CAD), stroke or transient ischemic attack (in the text together under stroke), sustained arrhythmias (AF, atrial flutter, sustained ventricular tachycardia, and ventricular fibrillation) demonstrated by electrocardiogram, and heart failure (HF) requiring hospitalization. Hormonal parameters were determined as previously described (8–10). Medical records of patients were reviewed independently by two investigators (F.R., F.V.) who were blinded to patients' identification and diagnosis and who evaluated whether any of the major clinical events listed

above had occurred. The study was approved by our local ethics committee.

Statistical analysis

Patients and controls were selected as described above. All data are expressed as mean ± SD for normally distributed variables and as median (25th to 75th percentile) for nonnormally distributed variables. The Student *t* test or the Kruskal-Wallis test was used for quantitative variables and the χ^2 test of the Fisher exact test for qualitative variables. The risk of events was expressed as odds ratio (OR) ± 95% confidence interval (CI). In the logistic regression analysis for factors associated with events, we included all variables significantly associated with the events in the univariate analysis. Sex, smoke habits, diagnosis of PA, and presence of diabetes were considered as dummy variables, whereas age, duration of hypertension, serum glucose, total and high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, potassium and aldosterone levels, and ARR were considered as quantitative variables. Events analysis over time was performed using Kaplan-Meier curves and the Mantel test (log rank) was used for comparisons between curves. Analyses were performed with the IBM SPSS software version 19 and with the SAS version 8 software.

Results

Comparison between EH and PA patients

Principal clinical and biochemical characteristics of the two patients' groups are summarized in Table 1. No differences were observed between the two groups for age, sex, duration of hypertension, SBP and DBP levels, smoking habits, BMI, and presence of type 2 diabetes as expected from the design of the study. Interestingly, EH patients displayed an increased prevalence of hypercholesterolemia and higher levels of total and low-density lipoprotein (LDL) cholesterol. PA patients displayed higher prevalence of hypokalemia, lower potassium and PRA levels and higher aldosterone and ARR, as expected.

During the total period between the diagnosis of hypertension and the end of follow-up (median 12 y for both groups), a significantly higher number of PA patients experienced a cardiovascular event (22.6% vs 12.7%, $P < .001$; OR 2.0; 95% CI 1.4–2.8), and PA patients had higher number of events per patient compared with EH patients (0.30 vs 0.15) (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org, and Figure 1). At diagnosis of PA, a higher number of patients had experienced events compared with EH (14.1% vs 8.4%, $P = .007$, OR 1.8; 95% CI 1.2–2.7), and also during the follow-up period, PA patients had a higher rate of events compared with EH patients (8.5% vs 4.3%, $P = .008$, OR 2.1; 95% CI 1.2–3.6) (Supplemental Table 1 and Figure 1). Kaplan-Meier estimates showing the incidence of the combined cardio- and cerebrovascular events in PA and EH patients ($\chi^2 = 14.45$; $P < .0001$) between the diagnosis of hypertension and the end of the study are available as Supplemental Material (Supplemental Figure 1). The analysis of event subtypes showed an increased prevalence of arrhythmias

Table 1. Clinical and Biochemical Parameters of EH and PA Patients

Parameters	PA	EH	*P* Value
Patients, n	270	810	
Age, y	44 ± 8.5	44 ± 11.4	0.98
Sex, M/F, %	161/109 (59.6/40.4)	483/327 (59.6/40.4)	1.00
Smoke, yes, no, ex, %	17/74/9	18/71/11	.77
SBP, mm Hg	155 ± 21	154 ± 19	.47
DBP, mm Hg	96 ± 12	95 ± 11	.21
Duration of hypertension, y	5 (2–10)	5 (2–11)	.68
Type 2 diabetes mellitus, %	4.1	4.1	1.00
BMI, kg/m^2	26.8 ± 4	26.7 ± 4.2	.8
Hypercholesterolemia, %	45.7	75.6	.0001
Hypertriglyceridemia, %	27.3	29.7	.46
Hypokalemia at diagnosis, %	31.5	5.9	.0001
Creatinine, mg/dL	0.95 ± 0.3	0.94 ± 0.2	.43
Potassium, mEq/L	3.7 ± 0.5	4.3 ± 0.5	.0001
Glucose, mg/dL	98 ± 20	97 ± 19	.42
Total cholesterol, mg/dL	209 ± 40	218 ± 40	.005
HDL cholesterol, mg/dL	54 ± 15	55 ± 14	.64
LDL cholesterol, mg/dL	125 ± 48	137 ± 37	.001
Triglycerides, mg/dL	128 ± 74	133 ± 77	.37
PRA, ng/mL·h	0.2 (0.1–0.3)	1.7 (0.6–5.2)	.0001
Aldosterone, ng/dL	29 (21–40.2)	17.5 (11.3–25.9)	.0001
ARR	135 (88–232)	9.7 (3.6–26.8)	.0001

Abbreviations: F, female; M, male. Hypercholesterolemia included LDL greater than 110 and/or total cholesterol greater than 190 mg/dL; hypertriglyceridemia included triglycerides greater than 150 mg/dL.

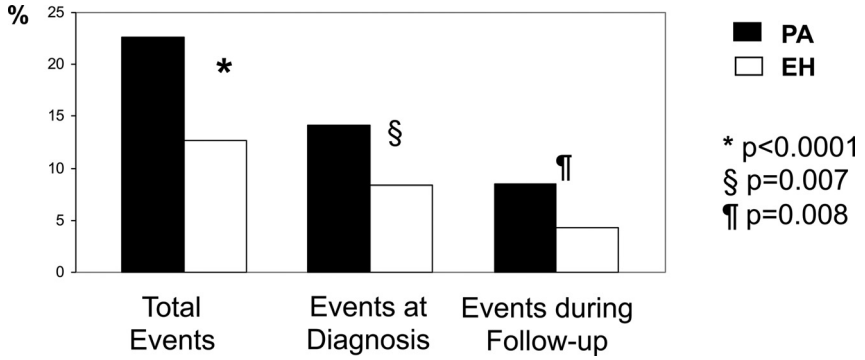

Figure 1. Comparison of cardiovascular events between PA and EH during the entire period from the diagnosis of hypertension to the end of the follow-up study, at diagnosis of PA, and during the follow-up from the diagnosis of PA to the end of the study.

(OR 1.9; 95% CI 1.1–3.3), stroke (OR 2.2; 95% CI 1.3–3.7), and HF (OR 10.3; 95% CI 2.8–37.9) (Table 2) during the total period of the study and an increased prevalence of stroke (OR 2.2; 95% CI 1.2–4.0) and arrhythmias (OR 2.2; 95% CI 1.1–4.6) at diagnosis of PA compared with EH (Table 2). Interestingly, during the follow-up after diagnosis of PA, only HF was more frequent in PA compared with EH (2.96% vs 0.12%), whereas the other cardiovascular events occurred with similar frequency (data not shown).

We also compared the principal hormonal and biochemical parameters between groups at the end of the study (Table 3). Of note, a higher percentage of PA patients developed type 2 diabetes (OR 1.5; 95% CI 1.0–2.3) compared with matched EH (and PA patients displayed a higher glucose levels compared with EH at the end of the follow-up period). Interestingly, potassium levels were no longer different between the two groups due to the specific therapy of PA patients (adrenalectomy or MRA).

Comparison between patients with and without events

Subsequently we compared patients (PA and EH combined) with and without events during the study. Patients with events displayed significantly higher age, SBP and DBP levels, and longer duration of hypertension; were more frequently males, hypokalemic, and with type 2 diabetes; and had higher creatinine, triglycerides, glucose, aldosterone, and ARR and lower HDL cholesterol and PRA (Supplemental Table 1). Multivariate analysis showed that the parameters that were independently associated with the occurrence of all events were age ($P < .001$), duration of hypertension ($P < .001$), SBP ($P = .01$), presence of diabetes mellitus ($P = .03$), aldosterone levels ($P = .04$), and the diagnosis of PA ($P < .001$). The multivariate analysis of variables associated with sustained arrhythmias were age ($P < .001$), duration of hypertension ($P < .001$), male sex ($P = .04$), and diagnosis of PA ($P = .02$); variables associated with stroke were age, duration of hypertension, and diagnosis of PA (all $P < .001$); variables associated with HF were duration of hypertension ($P = .004$) and diagnosis of PA ($P < .001$); and variables associated with CAD were duration of hypertension ($P = .007$), age ($P = .04$), aldosterone levels ($P = .009$), and glucose levels ($P < .001$).

Comparison between PA subtypes and EH

We compared patients with APA with matched patients with EH: a significantly higher number of APA patients

Table 2. Events in PA and PA Subtypes and Matched EH Patients During the Study Period

Events	PA (n = 270)	EH (n = 810)	*P* Value	APA (n = 57)	EH (n = 171)	*P* Value	BAH (n = 213)	EH (n = 639)	*P* Value
CAD									
Patients with CAD at diagnosis, %	2.6	3.1	.6	5.3	2.3	.2	1.9	3.3	.3
Patients with CAD during follow-up, %	2.6	1.5	.2	1.7	1.8	.6	2.8	1.4	.2
Patients with CAD in total, %	5.2	4.6	.6	7	4.1	.4	4.7	4.7	1.00
Stroke									
Patients with stroke at diagnosis, %	7.4	3.5	.006	12.3	2.9	.01	6.1	3.6	.1
Patients with stroke during follow-up, %	3	1.4	.1	5.2	1.2	.1	2.4	1.6	.5
Patients with stroke in total, %	10.4	4.9	.002	17.5	4.1	.004	8.5	5.2	.1
Arrhythmias									
Patients with arrhythmias at diagnosis, %	4.8	2.2	.03	8.8	0.6	.03	3.8	2.7	.4
Patients with arrhythmias during follow-up, %	3	2.1	.4	1.7	1.7	.4	3.2	2.2	.4
Patients with arrhythmias in total, %	7.8	4.3	.02	10.5	2.3	.02	7	4.9	.2
HF									
Patients with HF at diagnosis, %	0.7	0.25	.2	1.7	0.6	.4	0.5	0.2	.4
Patients with HF during follow-up, %	3	0.12	.001	3.5	0	.06	2.8	0.1	.001
Patients with HF in total, %	3.7	0.37	.001	5.2	0.6	.051	3.3	0.3	.001

CAD category grouped patients with MI and unstable angina.

Table 3. Clinical and Biochemical Parameters of EH and PA Patients at the end of the Follow-Up Period

Parameters	PA	EH	*P* Value
Patients, n	270	810	
SBP, mm Hg	137 ± 17	139 ± 15	.06
DBP, mm Hg	84 ± 10	84 ± 9	.6
Type 2 diabetes mellitus, %	13.5	8,5	.04
Hypercholesterolemia, %	45.7	74.4	.001
Hypertriglyceridemia, %	17.6	26.1	.01
Creatinine, mg/dL	0.98 ± 0.3	0.95 ± 0.2	.22
Potassium, mEq/L	4.3 ± 0.5	4.3 ± 0.4	.7
Glucose, mg/dL	106 ± 42	99 ± 22	.01
Total cholesterol, mg/dL	201 ± 38	207 ± 39	.1
HDL cholesterol, mg/dL	54 ± 15	55 ± 15	.64
LDL cholesterol, mg/dL	101 ± 58	128 ± 35	.001
Triglycerides, mg/dL	130 ± 87	125 ± 66	.6

Hypercholesterolemia included an LDL greater than 110 and/or total cholesterol greater than 190 mg/dL; hypertriglyceridemia included triglycerides greater than 150 mg/dL.

had a cardiovascular event during the study (OR 4.0; 95% CI 1.9–8.3) and at diagnosis of PA (OR 5.2; 95% CI 2.2–12.6) (Table 2 and Figure 2A) but not during the follow-up period subsequent to PA diagnosis (Supplemental Table 2). In particular, APA patients experienced a higher rate of arrhythmias and stroke compared with matched EH both in the total period of the study (OR 4.9; 95% CI 1.3–18.0, $P = .009$, and OR 5.0; 95% CI 1.8–13.8, $P = .0008$, respectively) and at diagnosis of PA (Figure 2A).

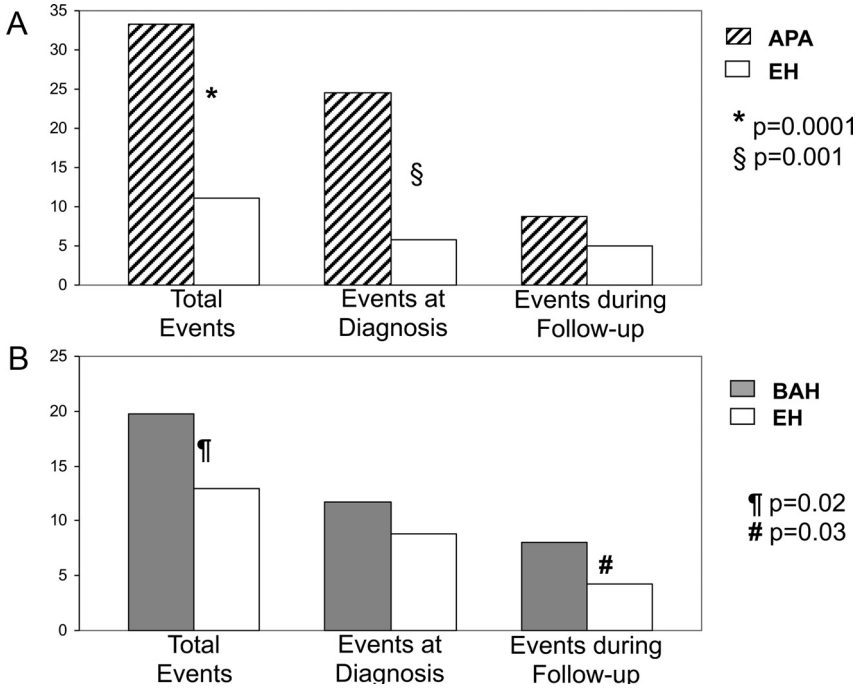

Figure 2. Comparison of cardiovascular events between APA and matched EH (A) and between BAH and matched EH (B) during the entire period from the diagnosis of hypertension to the end of the follow-up study, at diagnosis of PA, and during the follow-up from the diagnosis of PA to the end of the study.

We also analyzed the rate of events in BAH patients compared with matched EH patients. BAH patients displayed a higher rate of events during the study period compared with EH (OR 1.6; 95% CI 1.1–2.5): this difference was predominantly due to an increased rate of events during the follow-up after the diagnosis of PA (OR 2.0; 95% CI 1.05–3.7) compared with the rate of events at diagnosis (Table 2). This result was not affected by the removal of the PA patients of undetermined subtype from the BAH group. Analysis of event type revealed a nonsignificant trend for more frequent arrhythmias and stroke and a significantly higher rate of HF in the BAH group compared with EH (Table 2). Interestingly, BAH patients experienced a higher rate of events compared with EH patients despite similar BP levels and despite displaying lower LDL cholesterol levels (Supplemental Table 3). It should be noted, however, that the BAH patients displayed significantly higher glucose levels than the EH patients at the end of the study (Supplemental Table 3).

Comparison between APA and BAH patients

Finally, we compared PA subtypes, APA and BAH. It should be underlined that in this comparison patients were not matched for any variables. Clinical and biochemical parameters of APA and BAH patients are summarized in Supplemental Table 4. APA patients displayed lower potassium and higher aldosterone and ARR levels as expected. Patients with APA displayed a higher rate of events compared with BAH patients both in the total period of the study (OR 3.6; 95% CI 1.7–7.3) and at the diagnosis of PA (OR 5.2; 95% CI 2.2–12.6) but not during the follow-up after diagnosis. The evaluation of the type of events showed that APA patients more frequently experienced CAD (OR 9.9; 95% CI 1.01–97.5), stroke (OR 4.9; 95% CI 1.5–16.1), and arrhythmias (OR 4.1; 95% CI 1.2–14.0) before the diagnosis of PA compared with BAH patients and CAD and stroke during the total time of the study. Interestingly, among the total PA group, hypokalemic patients displayed an increased rate of events ($P = .03$) and had higher SBP, DBP, and aldosterone levels (data not shown). Finally, we observed a greater SBP and DBP reduction after adrenalectomy in APA patients compared with BAH patients after pharmacological therapy with MRA ($P =$

.03). In the total PA group, we also compared patients with events and without: PA patients with cardiovascular events were older, with a longer duration of hypertension and higher SBP and were more frequently males and hypokalemic.

Discussion

In the present study, we demonstrate an increased rate of cardio- and cerebrovascular events in a large population of primary aldosteronism patients compared with matched essential hypertensive patients.

We carefully matched of 270 PA with 810 EH patients for the most important variables to reduce the effect of factors that have been shown to increase the rate of cardiovascular events in hypertensive patients. In particular, our PA patients were matched 1:3 with EH for sex, age, and SBP and DBP levels at the first visit to our unit, duration of hypertension, BMI, smoking habits, and comorbidity for type 2 diabetes mellitus. Importantly, most the PA patients underwent subtype diagnosis using AVS, thus allowing the subdivision of the PA patients into APA and BAH: the comparison of the rate of cardiovascular events in APA and BAH compared with matched EH has not been performed in previous studies.

We showed that PA patients experienced cardiovascular events (MI or unstable angina requiring angioplasty, stroke or transient ischemic attack, sustained arrhythmias including AF, atrial flutter, sustained ventricular tachycardia and ventricular fibrillation, and heart failure requiring hospitalization) more frequently than those with EH, both at PA diagnosis, during the follow-up and in the overall period of the study. This confirms and extends previous findings of increased cardiovascular morbidity in PA patients (5–7, 14). Interestingly, PA patients displayed a higher number of events compared with EH despite showing significantly lower total and LDL cholesterol levels. This difference in cholesterol levels was also observed in the study by Milliez et al (5). The event analysis shows that arrhythmias and stroke were more frequent both during the total period of the study and at diagnosis, whereas HF was also more frequent during the follow-up. The increased frequency of stroke in PA patients has been observed both in sporadic (5, 6) and familial forms (15) and has been attributed at least in part to the direct effect of aldosterone on the vessel wall inducing inflammation, fibrosis, and remodeling (16, 17). Interestingly, in spontaneously hypertensive stroke-prone rats, an animal model of secondary aldosterone excess, therapy with MRA reduces the rate of stroke despite having no effect on BP levels (1, 18). The increased rate of sustained arrhythmias could be determined both by hypokalemia, increased QT interval in the electrocardiogram, increased in the myocardial fibrosis and ion channel remodeling (19–21). Consistently, a pivotal role of aldosterone and mineralocorticoid receptor activation in the determination of AF and ventricular arrhythmias has been shown in animal models (21, 22). Finally, the detrimental effect of aldosterone in the pathogenesis of heart failure is supported not only by the direct effects on cardiomyocytes (23) but also by the protective effects of mineralocorticoid receptor antagonist on patients with reduced ventricular function (24).

Intriguingly, PA patients developed type 2 diabetes more frequently during the study period compared with EH. This is consistent with previous findings indicating a higher prevalence of diabetes in PA patients compared with EH patients (25) and a role of aldosterone in glucose metabolism alterations, insulin resistance, and metabolic syndrome (26, 27).

It should be noted that in the multivariate analysis, together with the expected determinants associated with cardiovascular events such as age, SBP, and duration of hypertension, the PA status was independently associated with an increased risk of experience total events, stroke, arrhythmias, and heart failure.

The comparison of patients with APA with matched EH patients demonstrated that APA patients experience a higher rate of total events, arrhythmias, and stroke, both in the total period of the study and until diagnosis of PA but not during the follow-up period after adrenalectomy. Most of the difference in the event rate between APA and matched EH was due to events before the diagnosis of PA and subsequent adrenalectomy, highlighting the importance of early diagnosis and treatment of these patients. Also the comparison between BAH and matched EH patients showed an increased rate of total events in BAH; among the events, despite a trend for stroke and arrhythmias, only heart failure displayed a significantly higher rate in BAH compared with EH patients, but this may have been due to the relatively small numbers of events. Interestingly, the rate of total events during the follow-up was greater in BAH compared with EH despite showing no differences in BP levels (or even a tendency toward lower levels) and lower cholesterol levels. This suggests that aldosterone plays a detrimental role independent of its effect on BP: in fact, the only parameter that was significantly altered in BAH patients was the glucose levels. It is therefore conceivable that PA patients should be considered at an increased risk based on the higher aldosterone production and thus a lower BP target (for example, $< 130/80$ mm Hg) may be appropriate as in patients with previous cardiovascular events.

The comparative analysis of patients with APA vs those with BAH (not matched for any variables) yielded further observations of interest. APA patients experienced cardiovascular events (and particularly coronary events, strokes, and arrhythmias) more frequently than BAH patients. Given that cholesterol levels were not different between the two groups, other factors (including higher aldosterone levels) presumably accounted for the higher rate of coronary disease in APA patients. During the follow-up period, by contrast, the rate of cardiovascular events was similar in APA and BAH, suggesting a greater beneficial response of APA to adrenalectomy vs that of BAH to MRA. The reduction in BP levels was significantly greater in APA patients who underwent adrenalectomy compared with BAH patients treated with MRA. These observations support the importance of adrenalectomy in APA patients as the optimal approach to reducing cardiovascular risk and hence the necessity of careful subtype differentiation during the diagnostic workup of PA. In addition, BAH patients also displayed an increased rate of events, highlighting that even mild forms of aldosterone excess determine detrimental effects on the cardiovascular system and therefore should be carefully investigated and specifically treated.

The present study and those published previously in PA subjects (5–8) are coherent with previous studies on animal models showing that aldosterone is responsible for increased left ventricular hypertrophy, fibrosis, and necrosis (1–4); perivascular inflammation, fibrosis, and endothelial dysfunction (1–4); and glomerular ischemia and sclerosis and for mesangial fibrosis (1–4). Furthermore, aldosterone has been involved in the pathogenesis of the metabolic syndrome by reducing insulin sensitivity by activating oxidative stress and inflammation by impairing insulin receptor signaling and inhibiting glucose transport (28).

Strengths of our study include the fact that it is the largest in terms of the number of PA patients evaluated in this fashion, the careful approach to matching 1:3 with EH for a large number of confounding variables, and the careful PA subtype differentiation.

This study has some potential limitations: 1) the retrospective nature of the study; 2) we cannot exclude the possibility of having missed some mild forms of PA and/or having considered some forms of low-renin essential hypertension as PA due to the overlapping of these conditions (some units use different cutoffs for screening and confirmatory tests); 3) we paid particular attention to the detection and definition of the events, but, due to the nature of the study, we cannot completely rule out the possibility of having missed a minority of events; and 4) even if BP levels were similar between BAH and EH patients, even at the end of the study, we cannot rule out the possibility of incomplete therapeutic compliance for BAH patients (or insufficient MR blockade), especially for males, due to sex-related side effects.

Taken together, the results of the present study further confirm in a large population of patients the pathogenetic role of aldosterone in the cardiovascular system and thus the importance of early diagnosis of this condition. In fact, at PA diagnosis patients had a median duration of hypertension of 5 years and already displayed a higher rate of cardiovascular events compared with matched EH. Furthermore, this study indicates that APA patients display a poorer prognosis compared with those with BAH, probably determined by a more florid condition of hyperaldosteronism but with abrogation of this excess morbidity after adrenalectomy, thereby emphasizing the importance of differentiating PA subtypes in these patients.

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