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Adrenalectomy Lowers Incident Atrial Fibrillation in Primary Aldosteronism Patients at Long Term

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ABSTRACT

Primary aldosteronism (PA) causes cardiovascular damage in excess to the blood pressure elevation, but there are no prospective studies proving a worse long-term prognosis in adrenalectomized and medically treated patients. We have, therefore, assessed the outcome of PA patients according to treatment mode in the PAPY study (Primary Aldosteronism Prevalence in Hypertension) patients, 88.8% of whom were optimally treated patients with primary (essential) hypertension (PH), and the rest had PA and were assigned to medical therapy (6.4%) or adrenalectomy (4.8%). Total mortality was the primary end point; secondary end points were cardiovascular death, major adverse cardiovascular events, including atrial fibrillation, and total cardiovascular events. Kaplan–Meier and Cox analysis were used to compare survival between PA and its subtypes and PH patients. After a median of 11.8 years, complete follow-up data were obtained in 89% of the 1125 patients in the original cohort. Only a trend ($P=0.07$) toward a worse death-free survival in PA than in PH patients was observed. However, at both univariate (90.0% versus 97.8%; $P=0.002$) and multivariate analyses (hazard ratio, 1.82; 95% confidence interval, 1.08–3.08; $P=0.025$), medically treated PA patients showed a lower atrial fibrillation-free survival than PH patients. By showing that during a long-term follow-up adrenalectomized aldosterone-producing adenoma patients have a similar long-term outcome of optimally treated PH patients, whereas, at variance, medically treated PA patients remain at a higher risk of atrial fibrillation, this large prospective study emphasizes the importance of an early identification of PA patients who need adrenalectomy as a key measure to prevent incident atrial fibrillation.

Primary aldosteronism (PA), the most common cause of endocrine arterial hypertension, has been associated with a cardiovascular damage(1), including left ventricular hypertrophy(2), fibrosis(3), vascular remodeling(4), arterial stiffening, endothelial dysfunction(5), and microalbuminuria(6), which exceeded that expected by the degree of blood pressure (BP) elevation. Moreover, PA is common in patients with drug-resistant hypertension(7), which implies a more prominent cardiovascular damage and a worse prognosis(8). The detrimental role of aldosterone is also indicated by the finding of left ventricular hypertrophy in patients with aldosteronism and a hyperdynamic circulation even in the lack of elevated BP(9,10). Experimental data also support the

view that in the setting of normal- to high-sodium intake, excess aldosterone can damage the left ventricle and the left atrium(11).

It was, therefore, suggested that for the same degree of BP elevation, PA would carry a worse outcome than primary hypertension (PH), but this contention stands on retrospective surveys(12–14), the first of which reported a marked increase of relative risk of myocardial infarction (6.5-fold), stroke (4.2-fold), and atrial fibrillation (12.1-fold), in PA compared with PH patients(15). A meta-analysis of few small-sized studies also suggested that target treatment of PA can induce regression of left ventricular hypertrophy, a surrogate for hard cardiovascular outcomes(16), thus further supporting a causal relationship between hyperaldosteronism and cardiovascular risk. Whether the specific treatment delivered to PA patients, for example, medical therapy or adrenalectomy, has a different impact on prognosis remains, however, to be shown in prospective long-term outcome trials.

The PAPY study (Primary Aldosteronism Prevalence in Hypertension) prospectively recruited a sizable cohort of consecutively referred hypertensive patients nationwide in Italy between 2000 and 2005. This study was conceived to establish the high prevalence of PA and its subtypes in referred hypertensive patients(17) and to provide long-term follow-up data on the impact of specific treatment of PA on prognosis. Specifically, we wished to determine the cardiovascular event-free survival of medically and surgically treated PA patients, compared with demographically similar optimally treated patients with PH(18), but randomization to either treatment was ethically unacceptable because adrenalectomy was held to be the best available treatment for patients with unilateral PA. Therefore, following available guidelines(19), PA patients were assigned to adrenalectomy or medical treatment based on demonstration of lateralized aldosterone excess. We herein report on the main results of the longitudinal part of the study regarding the effects of specific treatments on long-term prognosis.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

We prospectively recruited between 2000 and 2005 consecutive hypertensive patients referred nationwide to specialized centers for hypertension. Briefly, they underwent a protocol approved by the Ethics Committee of the University of Padua,17 which entailed measurement of the aldosterone–renin ratio (ARR) at baseline and after captopril challenge after the same predefined work-up. The only exclusion criterion comprised a prior diagnosis of secondary hypertension and patient's refusal to participate in the study.

Treatment-naive patients were investigated with no antihypertensive drugs; those already treated underwent screening after switching to calcium channel blockers or doxazosin, or a combination of the two agents(19,20). Mineralocorticoid receptor antagonists (spironolactone, canrenone, or potassium canrenoate) and other agents affecting the renin–angiotensin–aldosterone system (diuretics, β -blockers, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor antagonists) were withdrawn at least 6 and 2 weeks before, respectively.

The screening test was performed in the sitting position after 1-hour rest and again 60 minutes after 50-mg oral captopril administration. Several variables, including measurement of plasma aldosterone concentration (PAC), plasma renin activity (PRA), Na⁺ and K⁺ in serum and in 24-

hour urine, and estimated glomerular filtration rate (by the CKD-EPI [Chronic Kidney Disease–Epidemiology Collaboration] equation) were measured. The aldosterone (PAC, in ng/dL):renin (PRA, in ng/mL/h) ratio at baseline and after captopril was calculated(21). Further work-up followed the recommendations available at that time, which basically anticipated those thereafter released by the Endocrine Society.19 Briefly, it comprised a saline infusion test and a high-resolution computed tomographic scan and magnetic resonance imaging, which were performed in all patients with an ARR ≥ 40 at baseline and ≥ 30 postcaptopril administration. Subtyping was performed in those fulfilling the aforementioned biochemical criteria, who showed a positive saline infusion test. Adrenal vein sampling was available at one third of the centers, which recruited 67% of the whole cohort. When bilaterally selective, which means with a selectivity index > 2.0 , it was used for allocating PA patients to adrenalectomy if the lateralization index exceeded a cutoff of 2.0 under unstimulated conditions(22). At centers where adrenal vein sampling was unfeasible, lateralized aldosterone excess production was ascertained by dexamethasone-suppressed adrenocortical ^{131}I -norcholesterol scintigraphy.

After subtyping, PA patients with lateralized aldosterone secretion were adrenalectomized(23); those with no evidence for lateralized aldosterone excess were medically treated with a mineralocorticoid receptor antagonist, mostly spironolactone, canrenone, or potassium canrenoate (median daily dose of 50 mg; range, 25–200 mg), plus additional antihypertensive drugs as needed to achieve a BP $< 140/90$ mmHg. After the baseline evaluation and diagnosis, the patients were invited for regular follow-up visits at each center, where the attending physicians were instructed to prescribe all antihypertensive medications that were needed to achieve the target BP values of $140/90$ mmHg defined by the 2003 European Society of Cardiology/ European Society of Hypertension guidelines(24).

PRA was measured by radioimmunoassay with commercial kits (Ren CTK; Sorin Biomedica, Saluggia, Italy, in 10 centers; or Angiotensin I RIA CT; Radim, Pomezia, Italy, in the others); intraassay and interassay coefficient of variation was within 8% and 10%, respectively. PAC was measured with a commercial kit (Aldosterone Mirya; Technogenetics, Cassina de Pecchi, Italy; normal range between 1.0–15.0 ng/dL supine and 3.0–32.0 ng/dL upright on a normal Na^+ diet; intra-assay and interassay coefficients of variation $< 5.6\%$). For the ARR calculation, PRA values < 0.20 ng/mL per hour were fixed at this value to avoid overinflation of the ARR.

Diagnostic Criteria

By protocol, PA was diagnosed if the ARR was ≥ 40 at baseline and ≥ 30 post captopril administration, and a previously validated logistic discriminant function score was ≥ 0.50 (21,25). The diagnosis of APA was confirmed in all adrenalectomized patients by a centralized Adjudication Committee based on the following (4 corners) criteria: (1) a biochemical diagnosis of PA; (2) lateralization of aldosterone secretion either at adrenal vein sampling or at NP59 dexamethasone suppressed adrenocortical scintigraphy; (3) adenoma demonstration at pathology assessment; and (4) evidence of normokalemia and cure or improvement of hypertension at follow-up at least 120 days after adrenalectomy. Cure was defined as a BP $< 140/90$ mmHg, for systolic and diastolic, respectively, without antihypertensive medications; improvement was defined as systolic and diastolic BP $< 140/90$ mmHg on the same or a decreased number of defined daily doses of medications(26). These criteria are endorsed by a large international study on how to assess outcome in PA(27). Patients with biochemical PA without lateralized aldosterone excess were held to have idiopathic hyperaldosteronism (IHA), also known as bilateral adrenal hyperplasia.

Follow-Up Evaluation

The study flow chart is illustrated in Figure S1 in the online-only Data Supplement. Long-term outcome data were gathered using a predefined form from medical records for the patients who underwent regular follow-up visits or through phone interviews with patients, and relatives and their general practitioner when the patient was unavailable. The death/alive status was also verified by means of the National Health Care System Database, and each event was validated by the Adjudication Committee blind to the diagnosis.

End Points

The predetermined end points were total death (primary), cardiovascular deaths, major adverse cardiovascular events, and total cardiovascular events (all secondary). Cardiovascular death comprised sudden death, death because of congestive heart failure, acute coronary syndrome, or stroke, according to the Syst-Eur trial (Systolic Hypertension in (Europe) criteria(28). Major adverse cardiovascular events entailed cardiovascular death and nonfatal acute coronary syndrome, stroke, ventricular tachycardia, and ventricular fibrillation. Total cardiovascular events comprised major adverse cardiovascular event plus hospital admission for heart failure, atrial fibrillation, other arrhythmias, and myocardial revascularization (either surgical or percutaneous). Definitions and the end points, which followed the guidelines(28–31). are reported in detail in the online-only Data Supplement. Detection of arrhythmias, including atrial fibrillation, was performed by standard 12-lead electrocardiogram, followed, if necessary in the cases where paroxysmal atrial fibrillation was suspected, by 24-hour Holter monitoring.

Statistical Analysis

Log or square-root transformation of skewed variables was used to achieve a gaussian distribution, as appropriate. Comparison of quantitative variables across groups was done by ANOVA followed by Bonferroni post hoc test; χ^2 analysis was used to compare categorical data. The assumption that cases lost and available at follow-up did not differ was verified with multivariate regression analysis. Event rate (total and cardiovascular deaths, major adverse cardiovascular event, atrial fibrillation, and total cardiovascular events) was estimated with Kaplan–Meier analysis (log-rank test). Cox stepwise (Wald) regression analysis with the inclusion and exclusion criteria of 0.05 and 0.10, respectively, was used to identify predictors of events. By protocol and given the low-risk features of the patients at baseline, a small number of events was expected, which limited the number of variables that could be included in a regression model. Accordingly, it was planned beforehand to use the procedure strategy described by Tabachnick and Fidell(32), in which the variables were entered in blocks: the first block comprised age and sex; the second, the diagnosis of hypertension, that is, PH and APA and IHA. We also tested interactions of age, sex, and hypertension diagnosis. Statistical significance was defined as $P < 0.05$ for the primary end point and $P < 0.01$ for secondary end points. SPSS Statistics, version 24 for MAC (IBM Corporation) was used for all analyses.

RESULTS

After a median follow-up of 11.8 years (interquartile range, 11.6–12.0 years), data were gathered in 89.0% of the 1125 consecutive newly diagnosed hypertensive patients recruited in the whole cohort. In both PA subtypes, the baseline characteristics of the patients available at follow-up (Table 1) showed the expected biochemical phenotype, for example, lower serum K^+ , lower PRA, and higher PAC than the PH patients. The APA patients had a more florid PA phenotype, which means, lower serum K^+ and PRA, and higher PAC, than the IHA patients; they were also older and showed a

higher systolic BP than the PH patients, suggesting that they were at somewhat higher cardiovascular risk. No patients had experienced any cardiovascular events; however, 5 had a history of paroxysmal atrial fibrillation at recruitment (2 APA, 1 IHA, and 2 PH patients). Among PA patients with paroxysmal AF at baseline, 1 APA and 1 IHA patients had a recurrence of the arrhythmia. The other 6 AF detected at follow-up in PA were de novo arrhythmias. The rate of cases lost to follow-up was similar across the 3 diagnosis groups; moreover, cases lost and cases available at follow-up did not differ significantly at multivariate regression analysis (Table S1). Overall, the features of the PA and the PH groups are representative of those commonly seen in referred hypertensive patients, thus making a selection bias unlikely.

All patients were reported to have a good long-term BP control, and none required sympathetic renal denervation during follow-up in any groups. The BP control achieved during follow-up, although optimal by protocol in all 3 diagnosis groups, theoretically could have influenced outcome. Hence, we examined the BP values during follow-up (median 11.8 years) in 688 patients (61.1% of the cohort) distributed in all diagnosis groups. This analysis confirmed the good control of both systolic and diastolic BP values expected by protocol and, moreover, allowed to rule out differences across groups (PA adrenalectomized $128\pm 10/80\pm 7$ mmHg, PA medically treated $132\pm 10/81$

Events at Follow-Up and Survival Analysis

All adrenalectomized patients were biochemically cured from PA, and no cases of recurrence of PA were recorded; $\approx 45\%$ were also cured from hypertension, for example, were free from high BP with no drug treatment. Table 2 shows the incident events recorded, which were few as expected, given the low-risk of the population and the optimal management of hypertension at these specialized centers.

For the primary end point at univariate analysis, we found a trend ($P=0.07$) toward worse survival in PA than in PH patients (Figure 1, top), which was accounted for by the medically treated PA cohort. With regard to the secondary end points, we found that the medically treated PA patients had a higher incidence of atrial fibrillation, compared with both the adrenalectomized APA patients and the PH group (Figure 2). Notably, this was highly significant even though some cases might have been missed because of our strict criteria for identifying this arrhythmia, and information on incident atrial fibrillation was available in fewer patients than for the primary event.

At Cox multivariate analysis in a regression model with age, the diagnosis group was identified as an independent predictor of atrial fibrillation (hazard ratio, 1.06; 95% confidence interval, 1.02–1.11; $P=0.002$): the medical treatment of PA patients was associated with an 82% increase of relative risk of atrial fibrillation compared with both APA and PH (hazard ratio, 1.82; 95% confidence interval, 1.08–3.08; $P=0.025$). An even greater relative risk of atrial fibrillation (hazard ratio, 2.29; 95% confidence interval, 1.31–4.00; $P=0.004$) was confirmed at a sensitivity analysis performed by adding estimated glomerular filtration rate to the Cox regression model.

DISCUSSION

The longitudinal phase of the PAPY study provided a unique opportunity to prospectively assess the long-term outcome of PA patients assigned to target treatment based on demonstration of lateralized aldosterone excess, compared with optimally treated PH patients. To date, available outcome data on PA patients only came from retrospective surveys that documented an adverse

prognostic effect of hyperaldosteronism in a rather consistent manner(12–14). In one such studies, PA patients were reported to be at higher cardiovascular risk than PH patients regardless of them being surgically or medically treated(12); at variance, in another larger study that examined PA patients by assignment to surgery or medical therapy, albeit in an insurance company database, there was a stronger effect of adrenalectomy on lowering mortality in spite of a relatively short (5.75 years) follow-up(14). The question on whether adrenalectomy or medical treatment of PA subtypes have the same long-term outcome, when studied prospectively with careful assignment to either treatment based on a predefined protocol, remained, therefore, unsettled.

We filled this gap of knowledge by examining the survival of PA patients in a large-scale prospective observational cohort study with long follow-up by treatment mode. This is, in our view, of much interest from the pathophysiological standpoint, because by protocol, patients diagnosed as APA had to be biochemically cured from the hyperaldosteronism after adrenalectomy, whereas, in contrast, the medically treated PA patients remained exposed to excess aldosterone because they received a mineralocorticoid receptor antagonist and all the additional drugs that were necessary to achieve an optimal long-term control of their high BP values, but the cause of aldosteronism was not eliminated.

By protocol, all patients had to achieve optimal control of BP values, which was confirmed by a sensitivity analysis, during the 11.8 years (median) of follow-up. This explains why our cohort overall showed a relatively low rate of deaths (4.0%) and major cardiovascular events (7.8%). These rates are similar to those found in cohort of similar age in the Framingham Heart Study(33) and agree with the notion that uncomplicated hypertensive patients, who achieve a good control of BP values, are at low risk of events. Perhaps because of this low event rate, we could observe no significant differences in the primary end point (total death), between PA and PH at univariate (Figure 2A) and multivariate analyses, at variance with previous(12,13,34), but not all, studies(14).

Given the accurate subtyping of PA patients accomplished in the PAPY study, we could examine the event-free survival by the PA subtype and related mode of treatment. We found that for all end points adrenalectomy translated into an event-free survival of PA patients similar to that of the optimally treated PH patients (Figure 2). These results supports the finding of a large survey performed in Taiwan(14), but differ from the decreased cardiovascular events-free survival in PA patients found in retrospective survey(12,13,34). In fact, with the strength of its prospective design and careful assignment to surgery or long-term medical therapy based on PA subtyping, the present study provides compelling evidence for the superiority of surgery over medical treatment, thus extending to white the data in an Asian population(14).

The significantly worse atrial fibrillation-free survival found in the medically treated PA patients, in whom lifelong medical treatment was needed because of the persistent hyperaldosteronism, in both univariate (Figure 2) and multivariate analyses is a novel finding that agrees with a bulk of evidences coming from both experimental studies and clinical observations(35). This higher rate of incident atrial fibrillation can be explained considering that [1] in PA patients, the relative risk for atrial fibrillation is much higher (≈ 7 - to 12-fold) than that for other major cardiovascular end points in both retrospective¹⁵ and observational studies(36) and [2] available knowledge from experimental and clinical studies implicate aldosteronism in causing atrial fibrillation in hypertensive patients(35).

Additionally, it is worth noting that medically treated PA require not only treatment with multiple antihypertensive drugs but also an increased number (from 2.3 to 2.7) and doses of these drugs needed to warrant BP control over time(36). By contrast, even when not experiencing cure of the

hypertension, which occurs in about half of the cases, in the adrenalectomized PA patients, the daily drug requirement commonly decreases (on average from 2.7 to 1.8)(36). Hence, in the adrenalectomized PA patients, the improved atrial fibrillation-free survival occurred notwithstanding a tapering of the medical therapy, whereas, conversely, in the medically treated PA patients, it arose in spite of an intensified drug treatment.

Limitations and Strengths

Some limitations are to be acknowledged in this study: first, as mentioned above, the PA patients were not randomly assigned to medical or surgical treatment because this was unacceptable ethically given that adrenalectomy is the best treatment that can be offered to PA patients with a lateralized form of PA. Second, the multicenter nature of the PAPY study reflects the management of hypertension at referral centers in a country with a relatively high standard of medical care and a capillary distribution of specialized hypertension centers, which suggests that generalization of its findings to countries/municipalities with a different level of medical care should be made with caution. Third, our low-risk cohort developed a small number of events, which could have hindered detection of differences between PH and PA patients in the rate of end points including cardiovascular death. On the contrary, it might also be argued that a selection bias occurred, because from the original cohort 11% of the patients were lost to follow-up, possibly those more likely to experience events than those harvested at follow-up(37). However, formal testing with regression analysis of patients lost and available to follow-up showed similar baseline features, including hypertension diagnosis (Table S1), suggesting that if this bias did occur, it probably marginally affected our conclusions. It might be claimed that another limitation, common to observational and even to randomized studies with mineralocorticoid receptor antagonists(38), regards to the knowledge of the intensity of and adherence to drug treatment and degree of BP control during follow-up, 2 pieces of information notoriously difficult to harvest in long-term studies. However, by protocol, attending physicians at participating centers, mostly ESH Center of Excellence, were well instructed to reach BP control through yearly meetings throughout the entire duration of the study. Moreover, available data in the majority of the patients confirmed the excellent BP control achieved and, alongside the low number of events recorded, this makes major differences in long-term BP control across groups during follow-up altogether unlikely. Finally, as atrial fibrillation was diagnosed by strict criteria but can be asymptomatic, particularly if paroxysmal, it could be that some cases were overlooked, particularly in the group showing a higher incidence of the arrhythmia. However, if it did occur, this potential bias might have blunted differences between groups, rather than the opposite, thus emphasizing our conclusions.

Conclusions

This study shows that the PA patients treated medically, because of a failure to achieve a diagnosis of unilateral disease, have significantly higher incidence of atrial fibrillation than primary hypertensive patients with similar demographic features and similar BP values. This worse outcome was abrogated when the hyperaldosteronism was cured by adrenalectomy, because an aldosterone-producing adenoma could be identified.

Perspectives

With the strength of a prospective study and a painstaking assessment of events during an 11.8-year (median) follow-up, this study provides compelling evidence that the long-term prognosis can be substantively improved in PA patients with a potentially surgically curable subtype. Thus, a timely screening of PA followed by subtyping is a key step for the prevention of atrial fibrillation in hypertensive patients.

Appendix

List of participating centers and PAPY study investigators: G.P. Rossi, A. Semplicini, C. Ganzaroli A.C. Pessina (Padova DMCS Internal Medicine 4); Franco Mantero (Padova, Endocrinology); Gilberta Giacchetti, Vanessa Ronconi, Marco Boscaro (Ancona, Endocrinology); Ermanno Rossi, Aurelio Negro (Reggio Emilia, Internal Medicine); Giampaolo Bernini, Angelica Moretti (Pisa, Internal Medicine); Claudio Ferri, Giovambattista Desideri (L'Aquila, Department of Internal Medicine and Public Health); Giuseppe Andronico (Palermo, Internal Medicine); Maria Lorenza Muiesan, Damiano Rizzoni, Enzo Porteri (Brescia, Internal Medicine); Gaetana Palumbo (Legnano, Internal Medicine); Claudio Letizia, Chiara Caliumi (Roma, Internal Medicine); Bruno Fabris (Trieste, Internal Medicine); Massimo Mannelli, Gabriele Parenti (Firenze, Endocrinology); Mauro Maccario, Ezio Ghigo (Torino, Endocrinology); Francesca Mallamaci, Carmine Zoccali (Reggio Calabria, Nefrology); Anna Belfiore (Bari, Internal Medicine).

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