Atrial fibrillation as presenting sign of primary aldosteronism: results of the Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive (PAPPHY) Study

Teresa M. Seccia[a], Claudio Letizia[b], Maria L. Muiesan[c], Silvia Lerco[a], Maurizio Cesari[a], Valeria Bisogni[a], Luigi Petramala[b], Giuseppe Maiolino[a], Roberta Volpin[a], and Gian Paolo Rossi[a]

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Background: Despite hyperaldosteronism being suggested as predisposing to arrhythmias, the relationship between atrial fibrillation and primary aldosteronism remains uncertain. Therefore, we tested the hypothesis that atrial fibrillation is a presentation of primary aldosteronism in hypertensive patients with unexplained atrial fibrillation.

Design and methods: The Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive (PAPPHY) Study recruited consecutive patients with atrial fibrillation and an unambiguous diagnosis of arterial hypertension at three referral centers for hypertension.

Results: In a cohort entailing 411 atrial fibrillation patients, we identified 18% (age 61 ± 11 years; 32% women), who showed no known cause of the arrhythmia. A thorough diagnostic work-up allowed us to identify primary aldosteronism in 73 of these patients, i.e. 42% [95% confidence interval (CI) 31.8–53.9]. Subtyping of primary aldosteronism demonstrated that surgically curable forms of primary aldosteronism accounted for 48% of the cases (95% CI 31.9–65.2). The high prevalence of primary aldosteronism was confirmed at sensitivity analyses.

Conclusion: These results provided compelling evidence that primary aldosteronism is highly prevalent in hypertensive patients with unexplained atrial fibrillation. Accordingly, they suggest that patients with no identifiable cause of the arrhythmia should be screened for primary aldosteronism to identify those who can be cured or markedly improved with target treatment.

Clinical Trial Registration: https://clinicaltrials.gov, Identifier: NCT01267747.

Keywords: aldosterone, atrial fibrillation, blood pressure, hypertension

Abbreviations: ANP, atrial natriuretic peptide; APA, aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; BP, blood pressure; LV, left ventricular; LVH, left ventricular hypertrophy; PAC, plasma aldosterone concentration; PAPPHY, Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive; PAPY, Prevalence of Primary Aldosteronism in hYpertension; PRA, plasma renin activity

INTRODUCTION

Atrial fibrillation is the most commonly sustained cardiac arrhythmia with a prevalence raising with age to exceeds 10% above age 80 years [1]. It imposes a huge burden on the healthcare systems, not only just because of its high prevalence rate but also because of increased mortality and morbidity due to cardioembolic stroke and heart failure [2], and need for long-term anticoagulation, heart rate control, medical care, and hospitalization [1].

Arterial hypertension is common among patients with atrial fibrillation as shown by results of four large-scale randomized clinical trials where the proportion of hypertensive patients ranged from 78.9% in RELY to 93.7% in ENGAGE-atrial fibrillation [3,4]. Moreover, although the annual risk of incident atrial fibrillation is low in women recruited in the Women's Health Study who were prospectively followed at long-term, the 14-year risk was found to increase by five-fold with SBP raising from 120 mmHg to more than 160 mmHg [5].

In arterial hypertension, inappropriate aldosterone levels can be a key factor predisposing atrial fibrillation [6,7]. In the Prevalence of Primary Aldosteronism in hYpertension (PAPY) Study, patients exposed long-term to aldosteronism exhibited a risk of atrial fibrillation higher than those whose primary aldosteronism was cured with adrenalectomy [8]. Experimental studies [7], anecdotal reports [9,10] and retrospective studies [11–13] also suggest a higher risk of atrial fibrillation in patients with hyperaldosteronism. Thus, the PAPPHY (Prospective Appraisal of the

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[a]Department of Medicine-DIMED, University Hospital, University of Padua, Padua, [b]Department of Department of Translational and Precision Medicine, University 'La Sapienza' Rome, Rome and [c]Internal Medicine, University of Brescia, Brescia, Italy

Correspondence to Gian Paolo Rossi, MD, FACC, FAHA, Clinica dell'Ipertensione Arteriosa, Department of Medicine-DIMED, University Hospital, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy. Tel: +39 49 821 7821; e-mail: gianpaolo.rossi@unipd.it

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Prevalence of Primary aldosteronism in HYpertensive patients presenting with atrial flutter or fibrillation) Study was set out as an investigator-initiated unsponsored prospective research project to test the hypothesis that atrial fibrillation can be a presentation of primary aldosteronism in hypertensive patients [14].

METHODS

The PAPPHY Study protocol (Identifier: NCT01267747 at clinicaltrials.gov) has already been reported [14] and is only recapitulated here (see Supplemental Data, http://links.lww.com/HJH/B148). We prospectively recruited consecutive patients with arterial hypertension who presented with ECG-confirmed atrial fibrillation, entailing new-onset paroxysmal, persistent or long-standing atrial fibrillation, or a history of it. Patients were screened at the Arterial Hypertension Unit of the University of Padua, the Arterial Hypertension Center of the University 'La Sapienza' in Rome and the Unit of Internal Medicine of the University of Brescia. The patients with known atrial fibrillation causes other than aldosteronism (Supplemental Table 1, http://links.lww.com/HJH/B148) at initial screening were excluded from further work-up to avoid potential confounders. Criteria for selecting the patients to undergo case detection of primary aldosteronism followed the Endocrine Society guidelines published in 2008 [15] and revised in 2016 [16].

Primary aldosteronism was diagnosed following the last available guidelines for case detection and management of primary aldosteronism [16] and of atrial fibrillation [1,16] in all enrolled patients. However, a simplified diagnostic work-up, which skipped the confirmatory test, was adopted in patients with a florid primary aldosteronism phenotype as identified by a high aldosterone-to-renin ratio (ARR), for example, more than 100 [ng/dl * (ng/ml/h)$^{-1}$], based on the findings of the largest study on use of the quantitative information conveyed by the ARR (AQUARR) [17], which showed that in these patients specificity approaches 100%, the false negative rate tends to 0% and two prevalence independent indexes of accuracy, the diagnostic odds ratio (DOR) and the positive likelihood ratio (PLR), both tended to infinity [17]. Primary aldosteronism was excluded when ARR less than 26 and plasma aldosterone concentration (PAC) less than 15 ng/dl at the first or a repeated test [8]. In all primary aldosteronism patients presenting with an ARR value in a grey area (i.e. between 26 and 100, and a PAC >15 ng/dl) at the first and a repeated test after a further 1 month wash-out, a confirmatory (captopril challenge) test was performed to rule out false positive results [16]. At the end of this work-up, patients with biochemically confirmed primary aldosteronism underwent subtyping by computed subtyping by computed tomography and adrenal vein sampling [18]. The diagnosis of aldosterone-producing adenoma (APA) was eventually confirmed by accepted criteria, which require biochemical cure, i.e. normalization of plasma renin activity (PRA) and aldosterone, after adrenalectomy (Table 1) [8,19].

Left ventricular (LV) hypertrophy (LVH), LV geometry and LV end diastolic volume were determined at echocardiography by expert cardiologists, as detailed in the Supplemental Methods, http://links.lww.com/HJH/B148. A control group of 61 healthy individuals from the same ethnic group was examined in the same period of time by the same expert cardiologist (M.C.) unblinded to the diagnosis [20].

The study complies with the Declaration of Helsinki; the local IRB approved the research protocol; an informed consent was obtained from the participants.

Statistical analysis

Normal distribution was assessed with Kolmogorov–Smirnov test, and quantitative variables that showed a skewed distribution underwent appropriate transformation to achieve a normal distribution, as required. One-way ANOVA followed by Bonferroni's posthoc test, or *t* test, were used to compare quantitative variables among/between groups. The distribution of categorical variables was compared by chi-square analysis.

TABLE 1. Clinical and biochemical features of the patients presenting with atrial fibrillation who had primary aldosteronism or primary (essential) hypertension

	PA ($n=31$)		
	APA ($n=15$)	Non-APA ($n=16$)	Primary hypertension ($n=42$)
Age (years)	59 ± 11	62 ± 9	63 ± 12
Sex (M/F)	66/34	75/25	66/34
BMI (kg/m^2)	28.9 ± 6.3	28.2 ± 4.9	28.6 ± 4.4
SBP (mmHg)	154 ± 21	149 ± 16	143 ± 15
DBP (mmHg)	88 ± 9	90 ± 9	84 ± 13
eGFR (ml/min)	77 ± 28	88 ± 16	80 ± 17
Pulse pressure (mmHg)	67 ± 6	59 ± 2	59 ± 5
Arterial compliance (ml/mmHg)	1.92 ± 0.19	1.83 ± 0.17	2.00 ± 0.11
Systemic vascular resistance index (dynes s/cm^5 m^2)	2490 (2070–2920)	2280 (1960–2590)	2150 (1920–2370)
Serum K^+ (mmol/l)	3.6 ± 0.3	3.8 ± 0.5	3.9 ± 0.4
Urinary Na^+ excretion (mmol/24 h)	149 ± 58	117 ± 43	156 ± 76
Treatment (%)			
CCB	67	56	17
α-adrenergic blockers	27	62	29
ARB/ACE-I	20/56	31/6	21/14

Mean ± standard deviation, or percentage (*n*/*N*), or median (95% CI), as appropriate. No difference between groups (APA vs. non-APA, APA vs. primary hypertension, non-APA vs. primary hypertension) reached statistical significance. ACE-I, angiotensin-converting enzyme-inhibitor; APA, aldosterone-producing adenoma; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate. Normal values: arterial compliance: 1.56 ± 0.41 ml/mmHg; systemic vascular resistance index: 3059 (2921–3236) dynes s/cm^5 m^2.

Rate of primary aldosteronism and its subtypes was estimated with 95% confidence interval using the equations reported in the Supplemental data, http://links.lww.com/HJH/B148. Significance was set at two-tailed $P < 0.05$.

RESULTS

Participating centers

Of the 21 European centers that initially agreed to participate in the study, only 3 (16%) eventually actively recruited patients: at Padua (88% of the patients), Rome (8%) and Brescia (4%). Alleged reasons for centers' withdrawal were the following: work-up considered as time-consuming (60%), shortage of clinical scientists (20%), local referral of the hypertensive patients with atrial fibrillation to units other than the hypertension unit/center (10%), and lack of local financial support (10%). Nothwithstanding a long enrolment period (from 2015 to 2018), we were unable to reach the calculated sample size and, therefore, the study was smaller than the size calculated when the PAPPHY study was conceived. In order not to introduce a time-dependent bias associated with an unduly long recruitment with associated changes in practice, it was decided to stop the study 411 patients were screened.

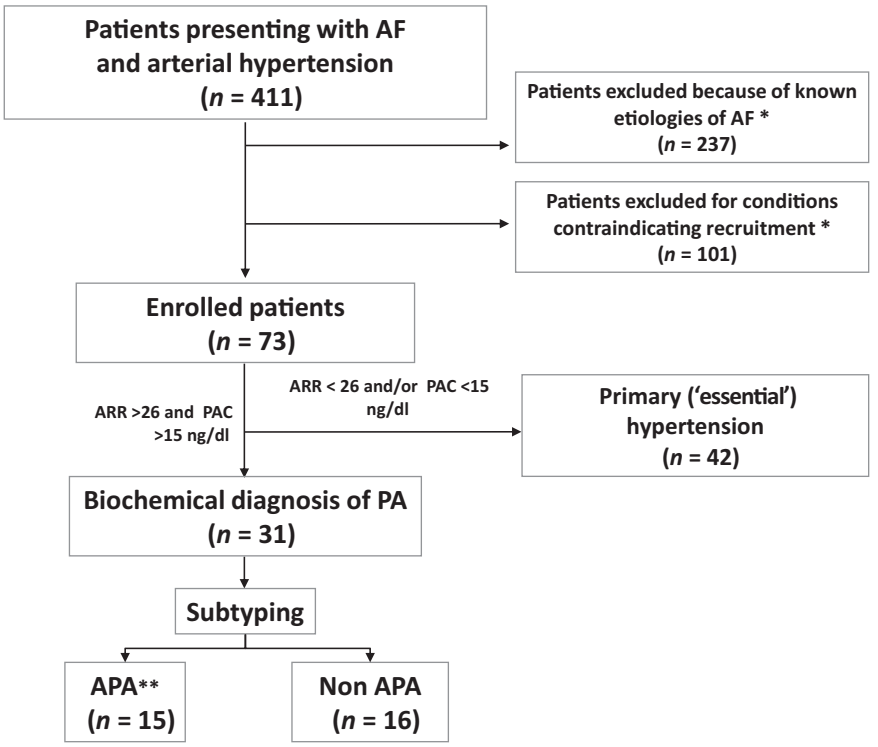
Patients eligible and excluded

The patients screened and enrolled were equally split between men and women (51 and 49%); their main demographic features are shown in Supplemental Table 2, http://links.lww.com/HJH/B148. Seventy-three of the patients screened (18% of 411 the whole cohort) met the inclusion criteria (Fig. 1 and Supplemental Figure 1, http://links.lww.com/HJH/B148). Major exclusion reasons were valvular and/or coronary heart disease, chronic kidney disease, poor clinical status or advanced age, cancer, current abnormal thyroid function, heart failure, patient's refusal, acute stroke and/or coronary syndrome, known secondary form of hypertension other than primary aldosteronism, myocardiopathy associated with alcohol abuse, and pericarditis, as defined in Fig. 2.

Enrolled patients had a mean eGFR of 81 ± 19 ml/min, were younger, mostly men, and with higher SBP and DBP, than excluded patients (Supplemental Table 2, http://links.lww.com/HJH/B148). They had only minor differences and overall similar demographic and clinical characteristics across centers (Supplemental Table 3, http://links.lww.com/HJH/B148). Of note, no patients with atrial flutter could be enrolled [21].

Rate of primary aldosteronism in enrolled patients

By exploiting a thorough diagnostic work-up [16] in the 73 eligible patients, we could unambiguously identify primary aldosteronism in 42% [95% confidence interval (CI): 31.8–53.9), who were split between those who had a surgically cured APA and those with a bilateral form (48 vs. 52%): thus, 20% (95% CI: 12.8–31.3) and 22% (95% CI: 13.9–32.8) of all the hypertensive patients with unexplained atrial



** See Supplemental Figure 1 for exclusion criteria; ** Confirmed by the 'four corner criteria' at follow-up*

FIGURE 1 The flow chart of the study shows the numbers of patients with atrial fibrillation and arterial hypertension screened for the PAPPHY Study, and those included and excluded. The diagnosis of aldosterone-producing adenoma (APA) followed the four corner criteria [8]. PAPPHY, Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive Study.

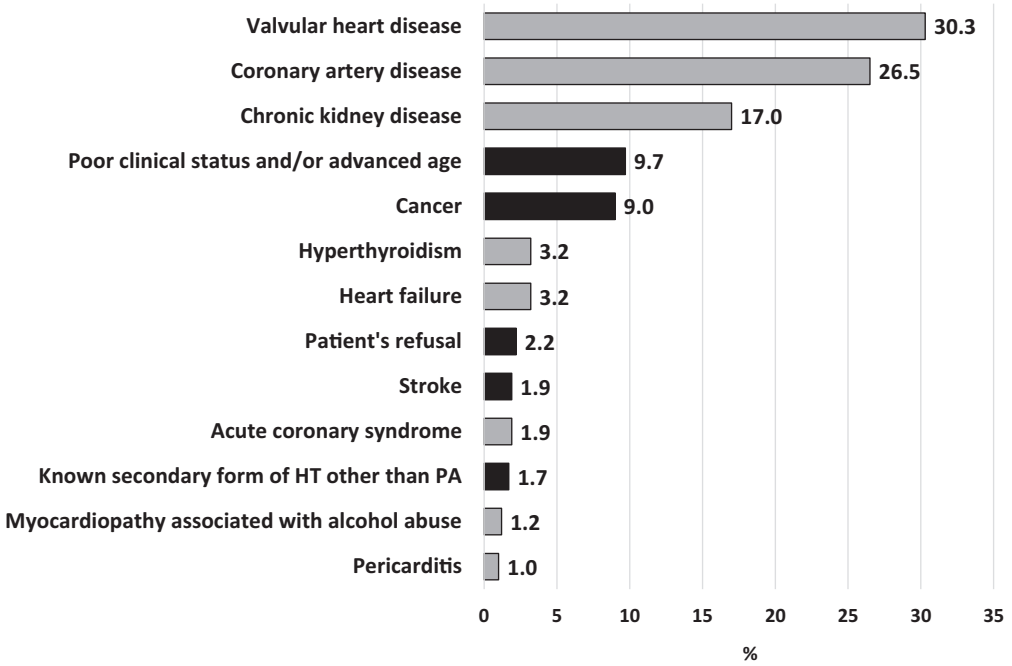


FIGURE 2 Conditions associated with arterial hypertension and atrial fibrillation that precluded enrolment of the screened patients in the PAPPHY Study. Bars indicate the percentage values of each condition in the overall excluded patients: grey bars indicate known causes of atrial fibrillation, whereas black bars stand for conditions contraindicating enrolment. Some conditions were associated in the same patients. PA: primary aldosteronism. PAPPHY, Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive Study.

fibrillation had a surgically curable and nonsurgically curable form of the disease, respectively (Fig. 3).

The primary aldosteronism patients had all the hallmarks of this condition, entailing elevated PAC and ARR, whereas duration of atrial fibrillation and arterial hypertension did not differ significantly from the primary hypertensive patients.

We explored the rate of primary aldosteronism in different scenarios in sensitivity analyses by excluding patients with obstructive sleep apnea ($n = 4$), type 2 diabetes mellitus ($n = 10$), obesity (defined as BMI $\geq$30; $n = 23$), and patients with any of these conditions ($n = 47$). We found that the rate of primary aldosteronism decreased slightly to 36% after excluding all with at least one of them, and to 39% with

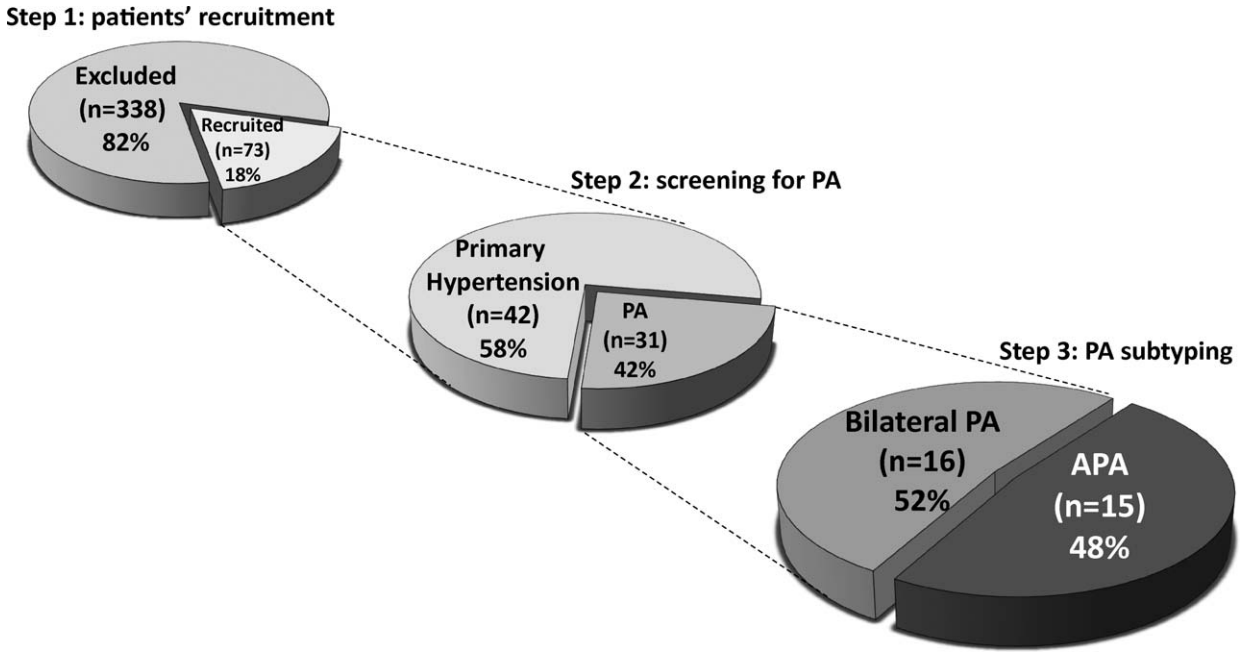


FIGURE 3 In the PAPPHY Study, 42% of the hypertensive patients presenting with unexplained atrial fibrillation were found to have primary aldosteronism, with 48% of them discovering a surgically correctable form, that is, an aldosterone-producing adenoma (APA). PAPPHY, Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive Study.

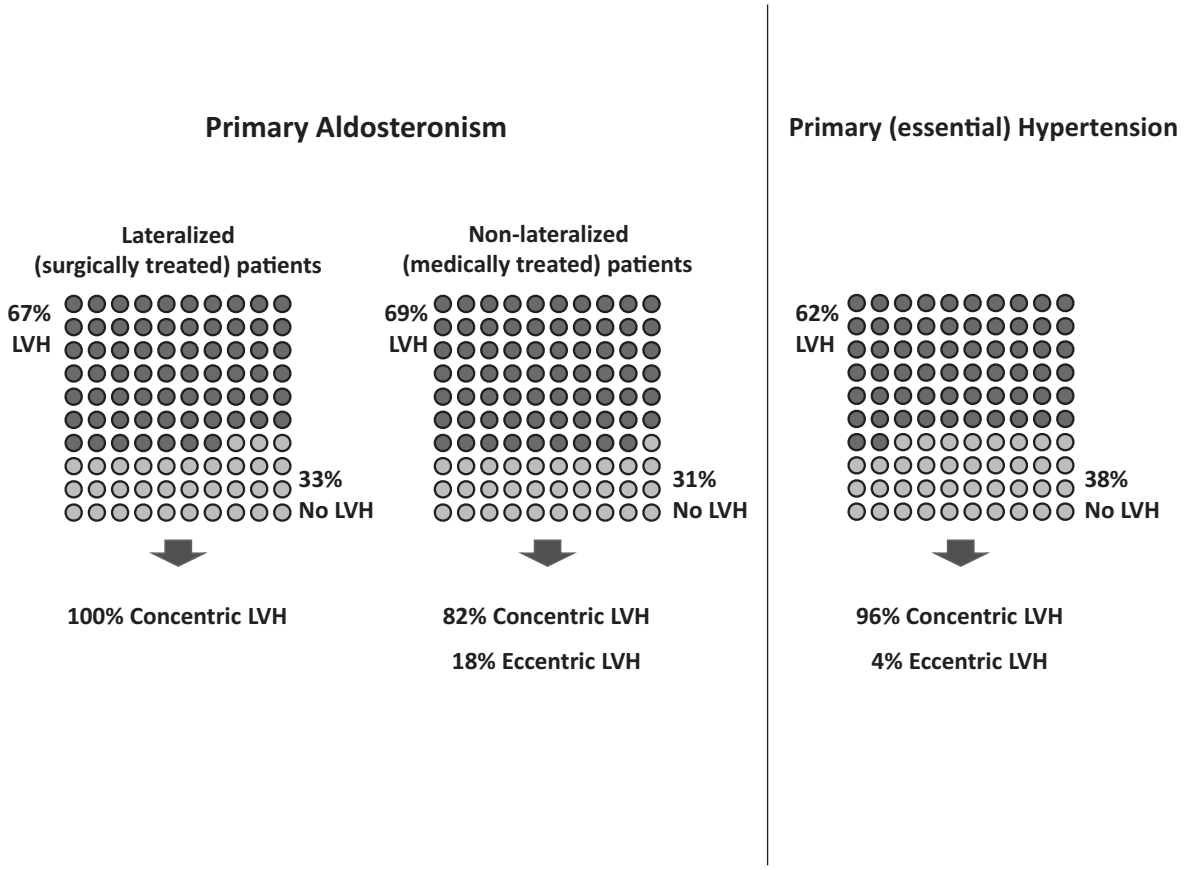


FIGURE 4 Rate of left ventricular hypertrophy and its subtypes in the patients presenting with atrial fibrillation recruited in the PAPPHY Study. The rate of patients presenting with LVH did not differ between APA, or non-APA, and primary hypertension ($X^2 = 1.16$). Most patients had concentric LVH in all groups, however, with difference between APA and non-APA, and between non-APA and primary hypertension groups ($X^2 = 26.29$, $P = 0.001$). Normal geometry was assessed as normal RWT ($\leq$0.42) and normal LV mass; concentric remodeling as normal LV mass with relative wall thickness (RWT) greater than 0.42; in the presence of increased LV mass, concentric or eccentric hypertrophy were diagnosed if RWT was 0.42 or less or greater than 0.42. APA, aldosterone-producing adenoma; PAPPHY, Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive Study.

exclusion of the patients with each of the aforementioned conditions; some patients had more than one conditions.

Echocardiography

Both cohorts of primary aldosteronism and primary hypertension patients showed increased LV dimensions and volumes compared with healthy individuals, indicating prominent hypertension-mediated LV changes and a very high rate of LVH by far of the concentric type (Fig. 4).

Overall, in spite of significantly higher index of systemic vascular resistance in the APA patients, the primary aldosteronism did not differ significantly from the primary hypertension patients for LV end diastolic and systolic diameters (Supplemental Table 4, http://links.lww.com/HJH/B148). The ascending aorta diameter, LV posterior wall, interventricular septal wall thickness, and LV relative wall thickness did not differ significantly between groups (Supplemental Table 4, http://links.lww.com/HJH/B148; Table 2). However, there was left atrium dilatation in primary aldosteronism patients, as shown by the increased left atrial diameter/aorta root ratio, in line with the presence of concentric LVH and atrial fibrillation, without difference across groups. LV ejection fraction, cardiac index, stroke volume, and stroke work, did not differ across all groups of hypertensive patients (Table 2).

DISCUSSION

To the best of our knowledge this study is the first that prospectively investigated with a rigorous design and protocol, the rate of primary aldosteronism in hypertensive patients presenting with atrial fibrillation that was not attributable to known concomitant conditions. After conceivement of this protocol, owing to the rigorous recruitment criteria, it took considerable efforts to complete this study, which led most of the centers that initially agreed to participate to drop out. Nonetheless, the findings were rewarding in that they evidenced a high rate of primary aldosteronism, thus supporting our initial hypothesis. Among hypertensive patients presenting with atrial fibrillation, who had no obvious causes for the arrhythmia, when carefully investigated, two out of five were eventually discovered to have primary aldosteronism. This rate is much higher than that found in hypertensive patients seen by general practitioners (seven-fold higher) [22], in those referred to specialized hypertensive centers (four-fold

TABLE 2. Echocardiographic data of the patients presenting with or without primary aldosteronism

	PA (n = 31)		
	APA ($n = 15$)	Non-APA ($n = 16$)	Primary hypertension ($n = 42$)
Left atrial diameter (mm)	43 ± 2	42 ± 2	42 ± 1
Left atrial diameter/aorta (mm)	1.21 ± 0.06	1.20 ± 0.06	1.22 ± 0.03
Aortic root (mm)	36 ± 1	36 ± 1	35 ± 1
LV end-diastolic diameter (mm)	50 ± 2	49 ± 2	50 ± 1
LV end-systolic diameter (mm)	29 ± 2	29 ± 1	28 ± 1
Posterior wall thickness diastole (mm)	12 ± 1	13 ± 1	13 ± 1
Interventricular septal wall thickness diastole (mm)	13 ± 1	13 ± 1	13 ± 1
LV mass index ($g/m^{2.7}$)[a]	58 ± 6	54 ± 3	59 ± 4
LV relative wall thickness	0.51 ± 0.02	0.51 ± 0.02	0.51 ± 0.02
LV midwall fractional shortening (%)	16.2 ± 0.6	15.6 ± 0.7	15.9 ± 0.4
LV end-diastolic volume (ml)	172 ± 13	160 ± 9	167 ± 5
LV end-systolic volume (ml)	55 ± 6	55 ± 4	55 ± 2
LV ejection fraction (%)	68 ± 2	65 ± 2	65 ± 1
Cardiac index ($l/min/m^2$)	3.80 ± 0.26	4.12 ± 0.30	4.43 ± 0.32
LV stroke volume (ml)	117 ± 10	105 ± 8	111 ± 5
LV stroke work (g-m)	262 ± 23	225 ± 10	168 ± 4

Mean ± standard deviation, or percentage (*n/N*), or median (95% CI), as appropriate. APA, aldosterone-producing adenoma; LV, left ventricle.
[a]Normal values: less than 50 $g/g/m^{2.7}$ in men, less than 47 $g/g/m^{2.7}$ in women. No difference between groups (APA vs. non-APA, APA vs. primary hypertension, non-APA vs. primary hypertension) reached statistical significance.

higher) [8], and in patients with drug-resistant hypertension (two-fold to three-fold higher) [16,23].

It must be acknowledged that in order to generate unbiased information on the rate of primary aldosteronism, which is the most common cause of secondary hypertension and through hyperaldosteronism can cause atrial fibrillation (reviewed in [7]), we carefully excluded from this study all patients with obvious causes of atrial fibrillation (Fig. 2). Accordingly, it might be that we over-estimated the rate of primary aldosteronism because the likelihood that the patient has primary aldosteronism might be lowered if there was an obvious underlying cause of atrial fibrillation. However, it might also be argued that we have under-estimated the rate of primary aldosteronism because the conditions (excluded in this study) that *per se* cause atrial fibrillation do not preclude the possibility that hyperaldosteronism may be involved in causing atrial fibrillation.

To challenge the robustness of these results, we performed sensitivity analyses by excluding the patients with conditions as sleep apnea, type 2 diabetes mellitus, and obesity, that could favor atrial fibrillation. We found that even after these prior exclusions, the rate of primary aldosteronism remained consistently higher than 35%, thus providing unambiguous evidence that hyperaldosteronism is commonly associated with atrial fibrillation in hypertensive patients.

A wealth of experimental studies indicating that inappropriate aldosterone levels lead to oxidative stress, subclinical inflammation and electric remodeling of the atria, all changes predisposing to atrial fibrillation, support this conclusion (reviewed in [7]).

At a stage when the practice guidelines on case detection of primary aldosteronism [16], albeit clearly acknowledging the excess cardiovascular damage associated with primary aldosteronism, did not list atrial fibrillation among the features that should alert physicians to screen their hypertensive patients for primary aldosteronism, these results are important and fill a gap of knowledge in this field, which might call for a change of practical recommendations in the future.

Of note, the mineralocorticoid receptor antagonist eplerenone was shown to reduce the incidence of new-onset atrial fibrillation in a randomized clinical trial in mild systolic heart failure patients [24]; moreover, two recent meta-analyses showed a reduction of atrial fibrillation risk in mineralocorticoid receptor antagonists-treated patients, as compared with nontreated patients. However, both considered patients with a variety of cardiovascular diseases, ranging from heart failure to cardiac surgery and radiofrequency catheter ablation, thus confounding the identification of the causative role of hyperaldosteronism [25,26].

At variance with these findings, unilateral laparoscopic adrenalectomy, but not medical treatment, lowered incident atrial fibrillation in a 12-year-long long-term prospective study of hypertensive patients undergoing target treatment for primary aldosteronism [27], thus confirming results of a long-term observational study [28]. Therefore, collectively the present and the published results strongly support a role of inappropriate aldosterone levels in the development of atrial fibrillation.

It has to be noted that this cohort had entailed patients older than in previous studies on primary aldosteronism [27,28], which can be readily explained by the fact that atrial fibrillation prevalence increases with age, particularly in patients with arterial hypertension [6]. As aging implies a rise of the ARR, the increased rate of primary aldosteronism found in this study could result from an accumulation of aldosterone-producing cell clusters within the adrenal glands, which seem to be age-dependent and may represent an early stage of APA formation [29,30]. Our cohort of hypertensive patients with atrial fibrillation showed a very high rate of LVH, but no differences of LV mass index and rate of LVH between primary aldosteronism and nonprimary aldosteronism patients (Supplemental Table 4, http://links.lww.com/HJH/B148). This is only seemingly in

contrast with the previously reported excess of LVH of primary aldosteronism patients [31] because, by protocol, only selected hypertensive patients with atrial fibrillation, that is, those with hypertension-mediated cardiac organ damage complicated by the arrhythmia, were recruited in this study. Given the presence of the arrhythmia, we could not undertake an accurate assessment of diastolic dysfunction in these patients, and therefore whether the patients with atrial fibrillation and primary aldosteronism had more diastolic dysfunction than those without primary aldosteronism remains unsettled. However, of clinical relevance, the lack of overt differences of LV changes between primary aldosteronism and essential hypertensive patients indicates that by itself echocardiography cannot provide clues on the presence of undetected primary aldosteronism in such patients and, therefore, does not entail a proxy of primary aldosteronism replacing the biochemical screening.

Further important clinical implications of the present results are as follows: as primary aldosteronism is common among hypertensive patients with atrial fibrillation, all such hypertensive patients should be regarded as possible carriers of primary aldosteronism and screened for this condition. Moreover, as atrial natriuretic peptide (ANP), which is known to be released during atrial fibrillation [32,33], blunts aldosterone secretion [34] and thus the ARR, the atrial fibrillation patients with primary aldosteronism can show false-negative ARR results at screening. As with aging, both plasma renin and aldosterone secretion decrease, thus affecting the ARR, further specific research will be needed to determine the optimal ARR cutoff for screening of primary aldosteronism in elderly patients with hypertension and atrial fibrillation. For these reasons, we might have failed to detect primary aldosteronism in some patients with falsely 'normal' ARR values owing to raised ANP and atrial dilatation [35].

Limitations and strengths

Although this study had major strengths, including its prospective design, predefined protocol, and thorough diagnostic work-up, both at screening and at subtyping, some limitations need to be acknowledged. Only a minority of the centers that initially agreed to participate recruited patients, which may suggest a selection bias in that only centers with a high interest in the study and a high degree of alertness toward primary aldosteronism research might have participated. At variance with this contention, we discovered that a major reason for centers' withdrawal, was the heterogeneous management of atrial fibrillation patients across Europe with hypertension specialists only rarely being involved. It could also be argued that patients with atrial flutter and some totally asymptomatic atrial fibrillation [36–38] were missed because the protocol required atrial fibrillation had to be ECG-confirmed before recruiting the patients. Moreover, the rate of primary aldosteronism could be under-estimated because chronic kidney disease was an exclusion criterion, whilst hyperaldosteronism is known to cause kidney damage [38]. Finally, we cannot comment on primary aldosteronism association with the type of atrial fibrillation, for example, paroxysmal, persistent or long-standing, because of the relatively small sample size of this study [6].

In conclusion, along with the demonstration that adrenalectomy outperformed medical treatment with mineralocorticoid receptor antagonists in preventing incident atrial fibrillation in primary aldosteronism patients, our results suggest the need to screen for primary aldosteronism in all hypertensive patients with unexplained atrial fibrillation, at least in those who are plausible candidates for unilateral laparoscopic adrenalectomy [27]. Adrenal vein sampling will then allow to pinpoint those who can benefit from unilateral laparoscopic adrenalectomy.

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Conflicts of interest

There are no conflicts of interest.

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