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Review Article

Atrial Fibrillation and Primary Aldosteronism: A Meta-Analysis

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Abstract

Primary Aldosteronism (PA) is a condition notoriously causing serious damage to cardiovascular system. It is reported that regardless of high blood pressure high level of long exposition of aldosterone determine target organ damage and predisposes to atrial fibrillation. Arterial hypertension is a major risk factor for atrial fibrillation (AF) and between 50% and 90% of AF patients have hypertension [22]. PA patients were reported to have a highly significant 12-fold higher risk of AF than essential hypertensive patients [23]. We searched on PubMed, Cochrane library and Web of science for clinical studies on the prevalence of arrhythmias such as atrial fibrillation and cerebrovascular events among PA patients. In this meta-analysis we want to evaluate the risk of AF associated to hyperaldosteronism because there are results not always clear that deserve a further investigation. The results show us that AF is a prevalence risk associated with PA vs EH. As for the stroke events, the results show that AF as prevalence is not associated with PA vs EH.

Keywords: Atrial Fibrillation; Cardiovascular System; Meta Analysis; Primary Aldosteronism.

Abbreviations: AF: Atrial Fibrillation; PA: Primary Aldosteronism; EH: Essential Hypertension.

Introduction

Primary aldosteronism (PA) is an endocrine disorder defined by an excessive autonomous aldosterone production unresponsive to renin regulation, leading to hypertension and electrolytes imbalance. It has a prevalence of 4.3% to 9.5% in all patients with hypertension, 13% of patients with stage 3 hypertension, and 17% to 23% of patients with resistant hypertension [1].

Higher rates of long-term mortality and comorbidity have been reported in patients with PA compared with patients with essential hypertension (EH) [2-3]. Long-term exposure to elevated aldosterone levels might result in substantial cardiovascular damage independent of blood pressure [2]. It has been associated with cardiovascular damage and with marked target organ damage affecting the heart, the carotid artery, or the kidney [4-5].

The destructive 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 blood pressure [6-7].

Worldwide, AF is the most common sustained cardiac arrhythmia in adults (9,10). AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy [9]. The currently estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF [10-12].

Increasing age is a prominent AF risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD),

chronic kidney disease (CKD), obesity, and obstructive sleep apnoea (OSA) is also important [13-17].

It has been shown to increase the risk of all-cause mortality and major cardiac and cerebrovascular complications. The prevalence of arrhythmias and cardiovascular and cerebrovascular complications in PA have been investigated in several studies till now.

The aim of this meta-analyses is to test the hypothesis that the rate of Atrial fibrillation is increased in PA patients comparing to Essential hypertension patients.

Materials and Methods

We searched on PubMed, Cochrane library and Web of science for clinical studies on the prevalence of arrhythmias such as atrial fibrillation and cerebrovascular events among PA patients. We found 110 articles and after the title and abstract reading, we selected 17 studies related to inclusion criteria. For the selection process of suitable articles, we followed the PRISMA guidelines for reviews and meta-analyses [24]. After the final assessment of the articles, 5 of them were chosen as final studies to be included in the meta-analyses. As follows are reported the inclusion and exclusion criteria:

The inclusion criteria

- Age above 18 years old
- Studies of atrial fibrillation and stroke prevalence in PA and comparison with EH patients.

The Exclusion criteria

- Studies on animals
- Studies without a control cohort
- Studies not in English
- Reviews, letters and meta-analysis

Data extraction

We worked using a standardized sheet to extract information on the first author, year of publication, country of the study group, retrospective or prospective design, sample size, primary and secondary outcomes for the presence of atrial fibrillation and stroke in both groups. Then proceeded with statistical analyses.

Studies included

The electronic search for atrial fibrillation and cerebrovascular events among PA patients revealed 110 articles. After the title and abstract reading, we found 17 studies related to the inclusion criteria. After the final assessment of the articles, 5 of them were chosen as final studies to be included in the meta-analyses. The characteristics of the final studies are shown in the (Table 1).

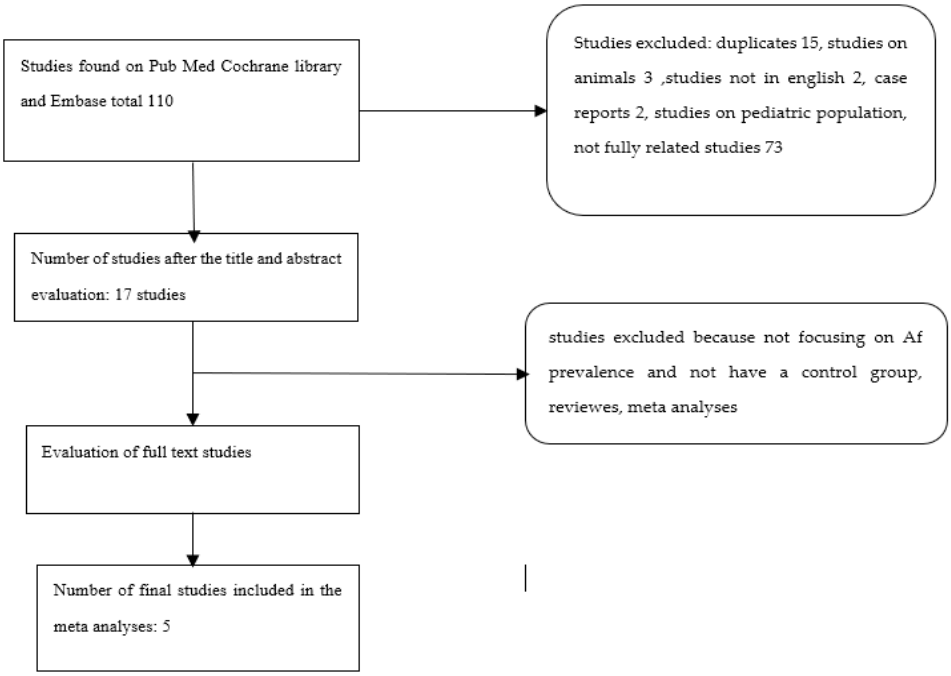

Figure 1: Meta-analysis flow chart

Results

Statistical analysis

Statistical analyses were performed with STATA (version BE 17; Stata Corporation, College Station, TX, USA) for studying the prevalence of AF and STROKE in PA. The pooled frequency with calculation of relative ratio (RR) and 95% confidence interval (CI) of RR were assessed using a fixed and random-effect model. The between-study heterogeneity was assessed by the I2 statistic.

First author	Publication year	country	setting	study design	sample size	PA	EH	AF PA	AF EH	Stroke PA	Stroke EH
Cristiana Catena	2008	Italy	1	1	377	54	323	11	8	6	9
Paul Milliez	2005	France	1	2	589	124	465	10	3	16	16
Gian Paolo Rossi	2018	Italy	1	1	1001	107	894	5	10	3	7
Chien Ting Pan	2020	Taiwan	1	2	11010	2202	8808	59	238	320	962
Sebastien Savard	2013	France	1	1	1749	459	1290	18	14		

Table 1: Characteristics of the studies included in the meta-analysis.

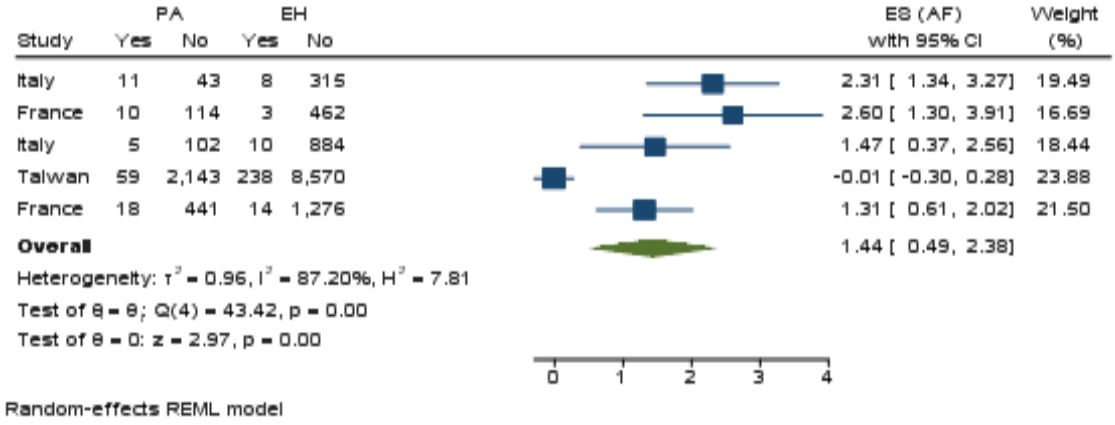

Figure 2: Forest plot of AF in PA patient's vs EH patients. Test of I^2 is used to assess heterogeneity among studies. A Random effects model is used to perform the meta-analyses

Study outcomes

Primary Outcome

Risk of AF in the PA patients compared to the EH patients

Primary hyperaldosteronism was associated with a higher prevalence of AF compared to Essential hypertension in the random effects model (RR: 1,44, 95% CI: 0,49-2,38) (Figure 1). Since the heterogeneity of the included studies was high (I2=87), the method we used for the meta-analyses was the random effects model. The funnel plot was generally symmetric.

Secondary outcome

Risk of Stroke in the PA patients compared to the EH patients

Primary hyperaldosteronism was not associated with a higher prevalence of AF compared to Essential hypertension in the random effects model (RR: 1,00, 95% CI: 0,31-1,69) (Figure 4). Since the heterogeneity of the included studies was high (I2=72,24), the method we used for the meta-analyses was the random effects model.

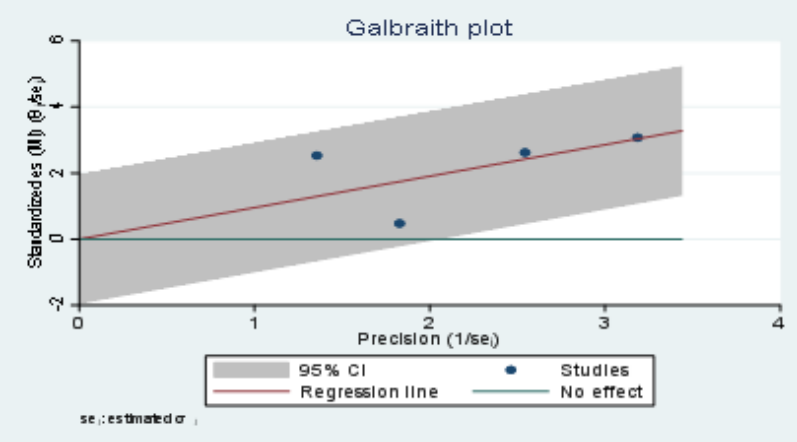

Figure 3: Galbraith plot of AF in PA

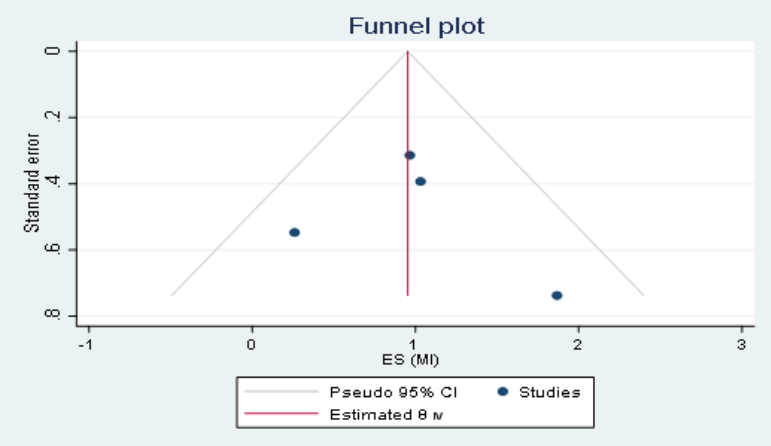

Figure 4: Funnel plot of AF in PA.

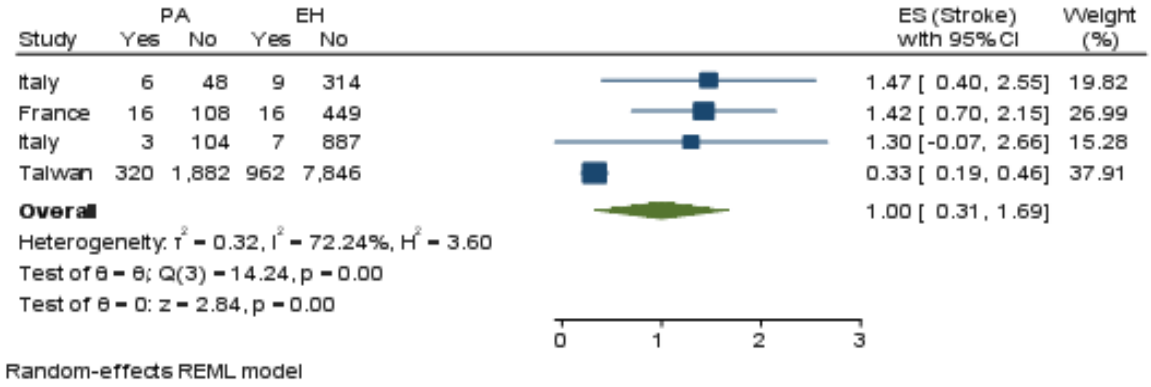

Figure 5: Forest plot of Stroke in PA patient's vs EH patients. Test of I2 is used to assess heterogeneity among studies. A Random effects model is used to perform the meta-analysis

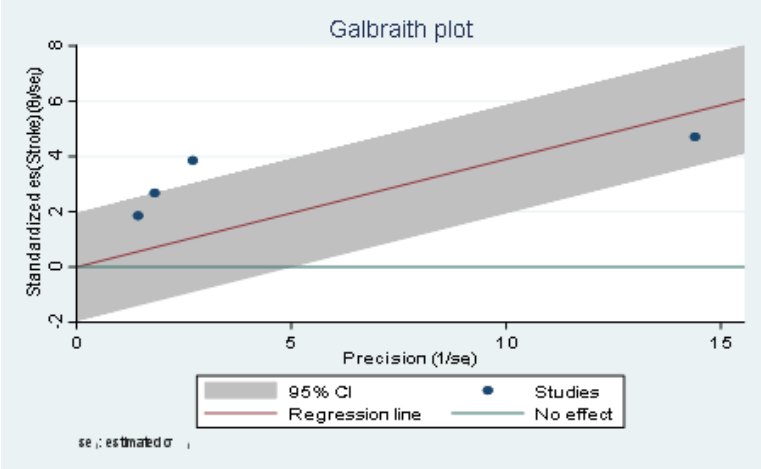

Figure 6: Galbraith plot of Stroke in PA

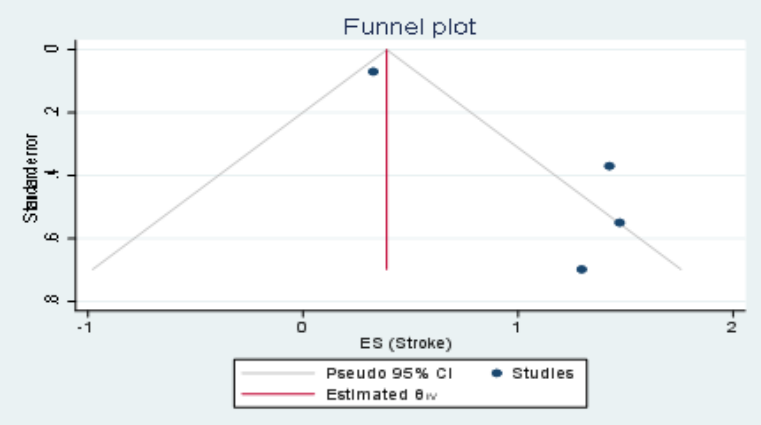

Figure 7: Funnel plot of Stroke in PA

Discussion and Results

In Table 1, are reported the studies included in the meta-analysis after the process of exclusion, according to the flow chart diagram. The results obtained show us that AF is a prevalence risk associated with PA vs EH. As for the stroke events, the results show that AF as prevalence is not associated with PA vs EH. One strength of this study, is the accuracy in choosing the studies considering the criteria of inclusion and exclusion.

One weakness is the high dis-homogeneity of the study for both forest plot as reported in the funnel plot although less sharp in the first case without stroke. The second disadvantage of the study is the number of studies selected is very low and so, in the meta-analysis, not only it is important the quality of the study but also the quantity of the studies in order to have a robust statistical meaning. In the Galbraith plot (Figure 2 and Figure 5 respectively) it is evident the outlier of one study reducing more to the homogeneity of the meta-analysis (Figure 5). In Figure 3 and Figure 4 is not reported a study because was out of scale. In the case and above all of stroke prevalence, it is necessary to deep investigation, such as the importance of the study. Anyway, high value of aldosterone is reported and accepted as a devastating effect on the cardiovascular system, especially in a long period. A recent meta-analysis by Monticone et al. [18] indicated that patients with PA have a 2.56-fold higher risk for ictus, 1.77-fold for coronary disease, and 3.4-fold for heart failure than EH patients. Hypokalaemia may facilitate the development of AF [20], since hypokalaemia is a direct inducer of arrhythmias. It is known that some genetic mutations are not correlated with hyperkaliaemic effects and so PA is not always associated with AF [21]. In a recently completed prospective study that recruited consecutive hypertensive patients referred for evaluation of AF, 42% had PA [25]. Several studies report an increased risk of developing left ventricular hypertrophy, early diastolic disfunction and ventricular

fibrosis in PA patients [26-27]. PA patients exhibit significant changes of myocardial texture compared with demographically and hemodynamically similar EH patients, which may be due to CF and occur before the development of overt LVH and diastolic dysfunction. These changes correlated with a prolongation of the PQ interval, a decrease of LV early filling, and an increase of ACLVF, thus indicating that LV filling occurs predominantly during atrial contraction in PA patients [28]. In a meta-analysis conducted by Wu et. al demonstrated that PA was associated with significantly increased risk of stroke, coronary artery disease, and LVH when compared with EH group. Moreover, PA resulted in significantly higher levels of SBP, DBP, and urinary potassium [29].

It is clear that complexity of PA remains a relevant factor and each case deserve accurate investigation. Furthermore, a complete abolition of the PA-related increased risk for new-onset AF has been documented in PA patients cured by unilateral adrenalectomy [19]. Due to several factors of atrial fibrillation and not related to hyperaldosteronism, the physicians need caution both in diagnosis and in therapy suggestions.

Conclusions

The meta-analysis shows us a good association of AF with PA and confirms several hypotheses that the cardiovascular system is tremendously influenced by high levels of aldosterone. Further research is necessary to understand the statistical weight in other variables like genetic factors and other forms of hypertension. So it is clear that PA can induce atrial fibrillation (AF), and hypertension patients with multiple factors should also be screened for PA. The early diagnosis and surgical treatment of PA caused by aldosterone producing adenoma, improves hypertension, reduces the need for medication and can prevent cardiovascular complications. We encourage physicians to take in account the AF effect in any case and not rule out PA in patients presenting with even moderate hypertension, resistant hyper-tension, or developing hypertension or stroke before 40 years of age, and consider the type of genetic mutation to have more clear vision into the diagnosis of PA, and its deleterious effects.

Conflicts of Interest: "The authors declare no conflict of interest."

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