

## Endocrine Surgery Review

### **Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis.**

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#### **In Brief**

Primary aldosteronism is a frequent cause of secondary hypertension, affecting roughly 5-12% of patients with hypertension (1). It is characterized by hypertension, suppressed plasma renin levels, hypokalemia and inappropriate secretion of aldosterone as a result of an adrenal adenoma or bilateral adrenal hyperplasia. Traditionally it was thought this form of hypertension was benign with very low incidence of cardiovascular events (2). More recently, however, long-term exposure to elevated plasma aldosterone level has been shown to be detrimental and result in significant cardiovascular events (3). The identification of those conflicting results, require further analysis to assess the association between primary aldosteronism and adverse cardiovascular events.

In this study, Monticone and colleagues performed a meta-analysis of prospective and retrospective observational studies, comparing patients with primary aldosteronism and essential hypertension (as a control group). Co-primary endpoints of their study were to determine and compare the incidence of stroke and coronary heart disease between these two groups. Secondary endpoints comprised the comparison of atrial fibrillation, heart failure, target organ damage, metabolic syndrome and diabetes in both groups.

A total of 31 studies were included in this analysis, with 3838 patients with primary aldosteronism and 9284 patients with essential hypertension. Clinical and biochemical characteristics were similar between primary aldosteronism and essential hypertension patients. Ten studies were prospective, 13 were retrospective and 8 were not specified. With a median duration of 8.8 years the clinical endpoints were assessed.

Of note, subjects included in this meta-analysis were mostly white males, with females comprising 28% of the population in the primary aldosteronism and 32% in the essential hypertension group. Due to this disparity the authors performed a random risk analysis which showed no significant difference in the proportion of female with primary aldosteronism and essential hypertension (OR 0.98, 95% CI 0.84-1.130).

***Primary study endpoints:*** Six studies with 4956 patients showed significant association between primary aldosteronism and stroke (OR 2.58, 95% CI 1.93-3.45) relative to individuals with essential hypertension. This result was consistent across matched and un-matched studies. When investigating the association between primary aldosteronism and the risk of coronary artery disease, there were 8 studies with 7267 patients, that showed an increased risk of coronary heart disease (OR 1.77, 95% CI 1.1-2.83) in the primary aldosteronism group when compared to the essential hypertension group.

**Secondary study endpoints:** Patients with primary aldosteronism had an increased risk of atrial fibrillation (OR 3.52, 95% CI 2.06-5.99; seven studies with 6580 patients) heart failure (2.05, 95% CI 1.11-3.78; five studies with 5739 patients) diabetes (OR 1.33, 95% CI 1.01-1.74; 9 studies 7348 patients) and metabolic syndrome (OR 1.53, 95% CI 1.22-1.91; 8 studies 3162 patients).

Of note, primary aldosteronism still increased the risk of stroke, coronary heart disease, atrial fibrillation, diabetes and metabolic syndrome when only prospective studies were included in the analysis.

**Subgroup analysis:** When blood pressure was matched between the two groups, patients with primary aldosteronism had an increased risk of stroke (OR 2.63, 95% CI 1.76-3.94), atrial fibrillation (OR 4.00, 95% CI 1.83-8.76), and heart failure (3.39, 95% CI 1.79-6.41) when compared to those with essential hypertension.

The risk of left ventricular hypertrophy was investigated in 20 studies, included 5672 patients and showed higher rates in individuals with primary aldosteronism in comparison with patients with essential hypertension (OR 2.29 95% CI 1.65-3.17). Similarly, this association was confirmed in a subgroup analysis when match for blood pressure, and when only prospective studies were included in the analysis.

Finally, when comparing patients with aldosterone-producing adenomas to bilateral adrenal hyperplasia, the risk of stroke, coronary heart disease and atrial fibrillation was not different in these two groups.

### **Critique**

This meta-analysis shows robust evidence for a significant increase in cerebrovascular and cardiovascular events, target organ damage (left ventricular hypertrophy), metabolic syndrome, and diabetes, in patients with primary aldosteronism when compared to patients with essential hypertension. In a subgroup analysis of matched studies, this association was independent of blood pressure, sex and age, indicating that high aldosterone levels can result in adverse cardiovascular events.

Although there are multiple animal model studies that have previously demonstrated the detrimental role of aldosterone in the setting of sodium repletion on the cardiovascular system, human subject models are lacking. It has been demonstrated that excess aldosterone can promote vascular inflammation resulting in atherosclerosis (4-6).

Furthermore previous reports provide evidence that in primary aldosteronism abundance of glucocorticoids can further add to the adverse cardiovascular events and has a deleterious effect on insulin secretion and function through impairment of post-receptor signaling (7, 8)).

The evidence from this current meta-analysis, strongly supports the importance of early screening of hypertensive patients considered high risk for primary aldosteronism. The Endocrine Society has in 2016 updated their clinical practice guidelines regarding screening, diagnosing, and treatment of primary aldosteronism (9). As a result, screening tests are now recommended for almost half of the patients with essential hypertension (10). However, as demonstrated by Ruhle et al. in a study including nearly 37,000 patients with hypertension and hypokalemia, which are consider high risk, only 2.7% were ever screened for primary aldosteronism (1).

The present study has a few intrinsic limitations in our opinion. The study reviewers were unmasked, which has the potential to result in a selection bias. Fifteen studies included in this

meta-analysis compared patients with primary aldosteronism to patients with essential hypertension without correcting for confounding variables, which could potentially affect the internal validity of the analysis. Moreover, this study population was mainly comprised of white European patients (23/31 studies), which makes it difficult to draw conclusions for black or asian patients. Different socio-economic background and diet habits (sodium intake) may yield different results if conducted in those populations.

Finally a comparison between the two subtypes of primary aldosteronism is of limited value because patients were not matched for confounding variables and the number of the events in each subgroup was too small to draw definitive conclusions.

### **Future Directions**

This excellent meta-analysis supports the association between primary aldosteronism and adverse cardiovascular events, and highlights the importance of early detection and management of patients with primary aldosteronism. It also sheds light on the necessity of future studies to investigate if early detection and management of primary aldosteronism can reduce adverse cardiovascular events in this patient population.

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