Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Invited Review

J Hypertens Res (2019) 5(4):148–153

Cardiovascular, cerebrovascular and metabolic risk in primary aldosteronism – beyond hypertension

Raluca-Alexandra Trifanescu, Catalina Poiana

**"Carol Davila" University of Medicine and Pharmacy,
"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania**

Received: September 19, 2019, Accepted: November 6, 2019

Abstract

Primary aldosteronism is the most common cause of endocrine hypertension. 5 to 10% of hypertensive patients had primay aldosteronism. Excessive aldosterone production is associated with hypertension, sodium retention, increased potassium excretion that may lead in 9-37% of cases to hypokalemia. Patients with primary aldosteronism have higher cerebrovascular and cardiovascular morbidity and mortality, higher metabolic risk, higher prevalence of sleep apnea, chronic kidney disease, diabetes mellitus, osteoporotic fractures than matched patients with essential hypertension and similar blood pressure values. From the cardiovascular point of view, both normokalemic and hypokalemic primary aldosteronism patients had higher prevalence of left ventricular hypertrophy, angina pectoris, non fatal myocardial infarction, heart failure and atrial fibrillation. In patients with aldosterone producing adenoma (APA), surgical removal of the tumor was associated with improvement of cardiovascular outcome, with similar events to essential hypertension during follow-up. By contrary, patients with bilateral idiopathic primary aldosteronism treated with mineralocorticoid receptor antagonists (spinolactone, eplerenone) showed persistent increased cardiovascular risk during follow-up if plasma renin activity remained suppressed (<1 μg/L/h). In patients treated with higher mineralocorticoid receptor doses, leading to unsuppressed plasma renin activity (≥1 μg/L/h), cardiovascular outcomes were similar to essential hypertension patients. Due to increased prevalence, high cardiovascular, cerebrovascular and metabolic complications associated to primary aldosteronism, efforts should be made for a proper screening (especially in patients with resistant hypertension, sleep apnea), an early diagnosis, a proper lateralization and treatment, in order to improve the outcome of these patients.

Keywords: primary aldosteronism, secondary endocrine hypertension, renin, non fatal myocardial infarction, heart failure, atrial fibrillation.

Introduction

Primary aldosteronism (PA) is the most frequent cause of endocrine secondary hypertension [1]. It is characterized by autonomous aldosteron secretion, that is independent of renin, angiotensin II and sodium and potassium status. Excessive activation of the mineralocorticoid receptor lead to volume expansion, hypertension and in advanced stages to hypokalemia and metabolic alkalosis [2]. It affects about 10% of hypertensive patients (4-19%) and about 20% of patients with resistant hypertension [3].

Corresponding author: Raluca-Alexandra TRIFANESCU, „C.I. Parhon" National Institute of Endocrinology, Bucharest, 34-38 Aviatorilor Avenue, Sector 1, 011863, Bucharest, Romania,
E-mail address: raluca.trifanescu@umfcd.ro

Primary aldosteronism is associated with increased risk of cardiovascular and cerebrovascular events, with increased metabolic risk (including diabetes mellitus and metabolic syndrome), with increased risk for chronic kidney disease and sleep apnea, with increased risk for osteoporotic fractures. Target organ damage (heart, kidney, brain) is higher than in patients with essential hypertension [1]. This is due to inflammation, oxidative stress, insulin resistance, endothelial dysfuction and fibrosis associated with primary aldosteronism [4].

In PA cases submitted to selective adrenal venous sampling, lateralization of aldosterone hypersecretion permits the diagnosis of aldosterone producindg adenoma (APA). When there is no clear lateralization, the patients were considered having bilateral adrenal hyperplasia BAH). APA patients were submitted to surgical adrenaletomy, while patients with BAH receinved medical treatment with mineralocorticoid receptor antagonists (spironolactone or eplerenone) [5].

Complications in primary aldosteronism are more frequent than in essential hypertension with the same severity of increased blood pressure. Target organ damage, cardiovascular, cerebrovascular and renal complications more prevalent than in essential hypertension with same blood ressure values are a solid argument for screening for primary aldosteronism in risk population [5,6]. Both normokalemic and hypokalemic primary aldosteronism are associated with increased risk of comorbidities [7].

Cerebrovascular events

In a series of 533 patients with primary aldosteronism from the Conn syndrome registry, prevalence of cerebrovascular events was 12.6% in hypokalemic PA patients and 13.2% in normokalemic PA patients. Prevalence of stroke was higher in normokalemic PA patients than in hyokalemic ones (7.8% *vs.* 4.2%) [7].

A meta-analysis of 31 studies, 3838 patients with PA *vs.* 9248 patients with essential hypertension, followed-up for 8.8 years after hypertension diagnosis confirmed the results of previous study: PA patients showed an increased risk for stroke (OR= 2.58, 95% CI= 1.93-3.45) [8].

Cardiovascular events

Prevalence of all cardiac events is higher in patients with hypokalemic PA (35.2% *vs.* 20.2%). Both angina pectoris and chronic cardiac insufficiency were more prevalent in hypokalemic than in nomokalemic PA patients (9% *vs.* 2% and 5.5% *vs.* 2.1%, respectively). PA patients also showed increased prevalence of myocardial infarction (3.6-4.1%), atrial arrhythmias (7.8-12.3%). Interestingly, prevalence of ventricular arrhythmias was similar in hypokalemic and normokalemic PA (1.9% *vs.* 2.1%) [7].

Comparing 459 patients with primary aldosteronism and 1290 control patients with essential hypertension matched for gender, age (± 2 years) and office systolic blood presure (± 10 mm Hg) in a controlled cross-sectional study, Savard and co-authors found in PA increased risk of electrocardiographic and echocardiografic left ventricular hypertrophy (odds ratio= 2 after adjustement for hypertension duration), coronary artery disease (adjusted OR= 1.9), non fatal myocardial infarction (adjusted OR= 2.6), heart failure (adjusted OR= 2.9) and atrial fibrillation (adjusted OR=5). The increased cardiovascular risk was similar across plasma potassium levels and plasma aldosterone concentration [6].

A recently published meta-analysis of 31 studies (3838 patients with PA *vs.* 9248 patients with essential hypertension) confirmed the results of previous studies: PA patients showed an increased risk for left ventricular hypertrophy (OR= 2.29, 95% CI= 1.65-3.17, coronary artery disease (OR= 1.77, 95% CI= 1.1-2.83), atrial fibrillation (OR= 3.52, 95% CI= 2.06-5.99), heart failure (OR= 2.05, 95% CI= 1.1-3.78) [8].

Mechanisms by with aldosterone excess favors onset of atrial fibrillations and heart failure are multiple: effects on cardiomyocites (representing up to 75% of myocardial tissue) with left ventricular hypertrophy and left ventricule diastolis dyfumction; effect of macrophages, promoting inflammation, necrosis and reparative fibrosis; effects on myofibroblasts and vessel endocthelial cells enhancing extracellular matrix, promoting fibrosis, electrical heterogeneity and re-entry circuits; in hypokalemic PA patients, there is also and increased PQ interval, and increases A wave and decreased E wave duration leading to changes in left ventricule filling pattern [9].

Treatment influence on cardiometabolic outcomes

When comparing cardiovascular and cerebrovascular events (myocardial infarction, coronary

artery disease, stroke, transient ischaemic attack, arrhythmias, heart failure) in 270 patients with PA (57 aldosterone producing adenomas - APA and 213 bilateral adrenal hyperplasia- BAH), with a control group (n= 810 patients with essential hypertension), total events were more frequent in PA group (22.6% *vs.* 12.7%, p < 0.001). The events were more frequent in PA both at diagnosis (14.1% *vs.* 8.4%) and during follow-up (8.5% *vs.* 4.3%). Patients with APA treated by surgery showed increased prevalence of total events and increased prevalence of events at diagnosis, but after surgical removal of APA, the number of events was similar to essential hypertension. By contrary, patients with BAH medically treated with mineralocorticoid receptor (MR) antagonists showed higher prevalence of total events and higher prevalence of events during follow-up [10].

In a series of 602 patients with PA treated by mineralocorticoid antagonists (no lateralization or unsatisfactory or indeterminate lateralization in 84% of patients in whom adrenal vein sampling was performed) compared with 41853 age-matched patients with essential hypertension, the authors reported an increased prevalence of composite cardiovascular events (56.3 *vs.* 26.6 events/1000 person-years): myocardial infarction or coronary revascularization (multivariate ajusted hazar ratio= 1.81), hospital admission for congestive heart failure (HR= 1.61) and cerebrovascular accident or transient ischaemic attack or transient ischaemic attack (HR= 2.38). Also the incidence of atrial fibrillation (HR= 1.93), diabetes mellitus (HR= 1.26) and total mortality (HR= 1.34) were increased in medically treated PA patients as compared with essential hypertension ones. The excess risk for composite cardiovascular outcomes and mortality was limited to PA patients whose plasma renin activity remained suppressed (<1 μg/L/h) on medical treatment with mineralocorticoid receptor antagonists (adjusted HR= 2.83, 95% CI= 2.11-3.8 and adjusted HR= 1.79, 95% CI= 1.14-2.8, respectively), while PA patients treated with higher mineralocorticoid receptor antagonists doses, who had unsuppressed plasma renin activity (≥1 μg/L/h), had similar outcomes with essential hypertension patients [11].

Similar data were reported for atrial fibrilation: HR for atrial fibrillation is 2.55 for patients with medically treated PA patients whose plasma renin activity (PRA) was < 1 μg/L/h compared wtih essential hypertension and HR= 1.03 for PA patients whose PRA was ≥1 μg/L/h. Moreover, PA patients treated by sugery showed even lower incidence of atrial fibrillation (HR= 0.75) as copmpared with essential hypertension patients [12].

In the PAPY study population, atrial fibrillation free survival was significantly higher in patients with essential hypertension than in patients with PA and in patients with PA due to idiopathic hyperaldosteronism who were medically treated. However, atrial fibrillation free survival was similar in patients adrenalectomized for APA and in patients with essential hypertension. This was the first study to show that adrenalectomy lowered incident atrial fibrillation in primary aldosteronism patients [13].

Diabetes mellitus and metabolic syndrome

In PA there is an increased prevalence of glycaemic disordes as compared with essential hypertension (OR= 1.55). Meta-analysis of 16 studies found an increased prevalence of impaired fasting glucose (31.2%), impaired glucose tolerance (26.19%) and diabetes mellitus (15.2%). PA patients showed a lower level of insulin sensitivity in comparison with the normal group and an increased insulin resistance (presented by HOMA index) compared with normal controls, but weaker than in essential hypertension group [14].

Increased prevalence of both diabetes mellitus and impaired glucose tolerance was also reported in a series of 117 PA patients compared with 117 patients with essential hypertension (41.9% *vs.* 17.1%). Prevalence of metabolic syndrome was also higher in PA (51.3% *vs.* 24.8%). Basal insulin secretion index (HOMA β) was decreased in PA compared with essential hypertension, but ody mass index, triglycerides, LDL cholesterol were significantly increased in essential hypertension compared with PA [15].

In a recently published paper, prevalence of type 2 diabetes mellitus in PA patients was significantly higher than that in EH patients (22.8% *vs.* 12.2%, P<0.05), especially in middle-aged and old patients and in patients with hypokalemia. However, prevalence of metabolic syndrome was similar [16].

In a series of Romanian patients with PA, we found a positive correlation between fasting glycaemia and plasma aldosterone and a negative

correlation between fasting glycaemia and serum potassium levels [17].

In a series of 152 PA patients, Hanslik and co-authors found a negative correlation between serum potassium concentration and the 2 h oral glucose tolerance test glucose concentration [18].

Studying new onset diabetes mellitus risk in 2367 patients with PA (754 with aldosterone producing adenomas) and in 3016 control patients with essential, followed-up 5.2 years, patients who underwent adrenalectomy had reduced risk of diabetes mellitus vs. Essential hypertension patients, but patients receiving mineralocorticoid receptor antagonists had increased risk of diabetes mellitus [19].

A meta-analysis of 31 studies showed an increased risk for metabolic syndrome (OR= 1.53, 95% CI= 1.22-1.91) and diabetes mellitus (OR= 1.33, 95% CI= 1.01-1.74) in PA patients as compared with patients with primary essential hypertension [8].

In 2210 patients with PA, prevalence of diabetes mellitus defined as HbA1c ≥ 6.5% was higher than in genral population (21.6% *vs.* 12.1%). Higher prevalence of diabetes mellitus was reported in patients with PA associating subclinical hypercortisolism, defined as 8 a.m. serum cortisol ≥ 1.8 μg/dl after overnight dexamethasone suppression test (26.8%) than in patients with PA without subclinical hypercorisolim (16.9%, p= 0.001). Body mass index and HbA1c were significantly higher in bilateral PA (prevalence of HbA1c between 5.7-6.4% 41.3% *vs.* 30.5%). Odds ratio for prediabetes in bilateral *vs.* unilateral PA was 1.603 (95% CI 1.0038-2.477) [20].

Subclinical hypercortisolism is not rare in PA [21].

Mass spectrometry-based analysis of the 24-h urine steroid metabolome in 174 patients with newly diagnosed PA showed that a significant proportion of patients had mild glucocorticoid excess concurrently with excess production of aldosterone - Connshing's syndrome. Several surrogate parameters of metabolic risk correlated significantly with glucocorticoid, but not mineralocorticoid excess in Connshing's sydrome. Adrenalectomy removed both mineralocorticoid and glucocorticoid excess and up to 30% of patients undergoing surgery developed postoperative adrenal insufficiency. By contrary, patients with PA treated with mineralocorticoid antagonists might have persistent metabolic risk, due to persistant mild glucocorticoid excess [22].

Pathogeny of hyperglycemia in primary aldosteronism implied a direct negative effect of aldosterone excess on β cells function, direct negative effect of aldosterone excess on insulin receptor in dipose tissue and hepatocytes (insulin resistance), direct effect of aldoterone through collagn deposition and fibrosis in pacreas, liver, adipose tissue and muscles. Hypokalemia also lead to altered tissue insulin response at insulin and altered insulin secretion. After adrenalectomy, improvement of first phase of insulin secretion induced by glucose was reported. Both surgery and spironolactone treatment improved altered response to insulin [23].

Chronic kidney disease

There is an increased prevalnce of chonic kidney disease both in patient with normo and hypokalemic PA (6.6-6.8%) [7].

Patients with PA showed significantly higher 24- hour urinary albumin excretion (UAE) than in hypertensive controls and relative glomerular hyperfiltration. Glomerular hyperfiltration was considered to underestimate renal damage in PA. In 213 PA patients (102 APA and 111 cases with bilateral hyperaldosteronism, prevalence of chronic renal disease was 15.7% in APA and 8.1% in bilateral hyperaldosteronism at the first visit and significantly increase to 37.1% and 28.3% one year after treatment. Higher UAE and lower serum potassium levels were independent predictors of decreasing estimated glomerular filtration rare one year after treatment [24].

In a larger series of 505 PA patients, 202 submitted to adrenalectomy and 303 patients on MR antagonists from the Japan Primary Aldosteronism Study, the increased age, low serum potassium levels, high eGFR, and high plasma aldosterone levels were independent predictors for a large initial eGFR fall in both group. However, in patients on MR antagonists, cases with a small initial eGFR fall had a significantly steeper long-term eGFR slope than those with a large initial fall (tertile 1 versus 2, P=0.025; tertile 1 versus 3, P=0.017) [25].

Autoimmune diseases

There is an increased incidence of new onset autoimmune diseases in PA compared with matched EH (HR= 3.82), in APA compared with matched EH (HR= 2.96). The risk of incident new onset

autoimmune diseases remained increased in patients treated by adrenalectomy (HR=3.1) or MRA (HR= 4.04) compared with matched essential hypertension controls and followed-up for a mean of 8.9 years[26].

Conclusions

For similar blood pressure elevation, primary aldosteronism was associated with a worse cardiovascular, cerebrovascular, metabolic and renal outcome, as compared with essential hypertension. Adrenalectomy improved vascular outcome, so efforts should be make for an early diagnosis, for a correct lateralization and referral to adrenalectomy. In patients treated with mineralocorticoid receptor antagonists, the therapy goals should be serum potassium normalization, normalization of blood pressure and obtaining a plasma renin activity higher than 1 ng/ml/hour.

Abbreviations

PA= primary aldosteronism
APA= aldosterone producing adenoma
EH= essential hypertension
MRA= mineralocorticoid receptor antagonist
OR= odds ratio
HR= hazard ratio
UAE= urinary albumin excretion

Conflict of interest

The authors confirm that there are no conflicts of interest.

References

1. Williams TA and Reincke M. Diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. European Journal of Endocrinology. 2018;179:R19–R29. doi:org/10.1530/EJE-17-0990.
2. Vaidya A, Mulatero P, Baudrand R, Adler GK. The Expanding Spectrum of Primary Aldosteronism: Implications for Diagnosis, Pathogenesis, and Treatment. Endocr Rev. 2018;39(6):1057-88. doi:10.1210/er.2018-00139.
3. Morimoto R, Omata K, Ito S, Satoh F. Progress in the Management of Primary Aldosteronism. Am J Hypertens. 2018;31(5):522-31. doi:10.1093/ajh/hpy018.
4. Tirosh A, Garg R, Adler GK. Curr Hypertens Rep. 2010;12(4):252-7. Doi: 10.1007/s11906-010-0126-2.
5. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(5):1889-916. doi: 10.1210/jc.2015-4061
6. Savard S, Amar L, Plouin PF, Steichen O. Cardiovascular Complications Associated With Primary Aldosteronism: A Controlled Cross-Sectional Study. Hypertension. 2013;62(2):331-6. Doi: 10.1161/HYPERTENSIONAHA.113.01060
7. Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S et al, Participants of the German Conn's Registry. Cardiovascular and Cerebrovascular Comorbidities of Hypokalemic and Normokalemic Primary Aldosteronism: Results of the German Conn's Registry. J Clin Endocrinol Metab. 2009;94(4):1125-30. doi: 10.1210/jc.2008-2116.
8. Monticone S, D'Ascenzo F, Moretti C , Williams TA, Veglio F et al. Cardiovascular Events and Target Organ Damage in Primary Aldosteronism Compared With Essential Hypertension: A Systematic Review and Meta-Analysis. Lancet Diabetes Endocrinol. 2018;6 (1):41-50. doi: 10.1016/S2213-8587(17)30319-4.
9. Seccia TM, Caroccia B, Adler GK, Maiolino G, Cesari M et al. Arterial Hypertension, Atrial Fibrillation, and Hyperaldosteronism: The Triple Trouble. Hypertension. 2017;69(4):545-50. Doi: 10.1161/HYPERTENSIONAHA.116.08956.
10. Mulatero P, Monticone S, Bertello C, Viola A, Tizzani D et al. Long-term Cardio- And Cerebrovascular Events in Patients With Primary Aldosteronism. J Clin Endocrinol Metab. 2013;98(12):4826-33. doi: 10.1210/jc.2013-2805.
11. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A et al. Cardiometabolic Outcomes and Mortality in Medically Treated Primary Aldosteronism: A Retrospective Cohort Study. Lancet Diabetes Endocrinology. 2018;6(1):51-9. doi: 10.1016/S2213-8587(17)30367-4.
12. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A et al. Incidence of Atrial Fibrillation and

Mineralocorticoid Receptor Activity in Patients With Medically and Surgically Treated Primary Aldosteronism. JAMA Cardiol. 2018; 3(8):768-74. doi: 10.1001/jamacardio.2018.2003.

13. Rossi GP, Maiolino G, Flego A, Belfiore A, Bernini G et al, PAPY Study Investigators. Adrenalectomy Lowers Incident Atrial Fibrillation in Primary Aldosteronism Patients at Long Term. Hypertension. 2018;71:585-91. doi: 10.1161/HYPERTENSIONAHA.117.10596
14. Chen W, Li F, He C, Zhu Y, Tan W. Elevated Prevalence of Abnormal Glucose Metabolism in Patients With Primary Aldosteronism: A Meta-Analysis. Ir J Med Sci. 2014;183(2):283-91.doi: 10.1007/s11845-013-1007-x.
15. Deng YL, Zhang SL, Liu PM, Mai LF, Tang JY et al. [Comparison on Metabolic Disorders and Uric Acid Levels Between Patients With Primary Aldosteronism and Essential Hypertension]. Zhonghua Xin Xue Guan Bing Za Zhi. 2016; 44(9):743-9. Doi: 10.3760/cma.j.issn.0253-3758.2016.09.003.
16. Rong LW, Li NF, Luo Q, Wang MH, Zhang DL. Prevalence and characteristics of metabolic syndrome and its components in primary aldosteronism. Increased prevalence of type 2 diabetes mellitus in elderly patients. Journal of Hypertension. 2019; 37:p e279. doi: 10.1097/01.hjh.0000573560.66143.df.
17. Trifanescu RA, Popa C, Iordachescu C, Sava M, Popescu N et al. Increased Prevalence of Diabetes Mellitus in Primary Aldosteronism. Interdiab 2016 - Diabetes Mellitus as Cardiovascular Disease", Proceedings of INTERDIAB 2016 Conference.467-76. ISSN-L 2393-3488; ISSN 2393-3488, Niculescu Publishing House.
18. Hanslik G, Wallaschofski H, Dietz A, Riester A, Reincke M et al., participants of the German Conn's Registry. Increased Prevalence of Diabetes Mellitus and the Metabolic Syndrome in Patients With Primary Aldosteronism of the German Conn's Registry. Eur J Endocrinol. 2015;173(5):665-75. doi: 10.1530/EJE-15-0450.
19. Vin-Cent Wu, Shih-Chieh J Chueh, Likwang Chen, Chia-Hui Chang, Ya-Hui Hu et al, TAIPAI Study Group. Risk of New-Onset Diabetes Mellitus in Primary Aldosteronism: A Population Study Over 5 Years. J of Hypertension. 2017;35(8):1698-708. doi: 10.1097/HJH.0000000000001361.
20. Akehi Y, Yanase T, Motonaga R, Umakoshi H, Tsuiki M et al., Japan Primary Aldosteronism Study Group. High Prevalence of Diabetes in Patients With Primary Aldosteronism (PA) Associated With Subclinical Hypercortisolism and Prediabetes More Prevalent in Bilateral Than Unilateral PA: A Large, Multicenter Cohort Study in Japan. Diabetes Care. 2019;42:938-45. doi: 10.2337/dc18-1293.
21. Beuschlein F, Reincke M, Arlt W. The Impact of Connshing's Syndrome - Mild Cortisol Excess in Primary Aldosteronism Drives Diabetes Risk. J Hypertens. 2017;35(12):2548. Doi: 10.1097/HJH.0000000000001550.
22. Arlt W, Lang K, Sitch AJ, Dietz A, Rhayem Y et al. Steroid Metabolome Analysis Reveals Prevalent Glucocorticoid Excess in Primary Aldosteronism. JCI Insight. 2017;2(8): 93136. Doi: 10.1172/jci.insight.93136
23. Fischer E, Adolf C, Pallauf A, Then C, Bidlingmaier M et al. Aldosterone Excess Impairs First Phase Insulin Secretion in Primary Aldosteronism. J Clin Endocrinol Metab. 2013;98(6):2513-20. Doi: 10.1210/jc.2012-3934
24. Yoshitsugu Iwakura, Ryo Morimoto, Masataka Kudo, Yoshikiyo Ono, Kei Takase et al. Predictors of Decreasing Glomerular Filtration Rate and Prevalence of Chronic Kidney Disease After Treatment of Primary Aldosteronism: Renal Outcome of 213 Cases. J Clin Endocrinol Metab. 2014;99:1593–8. doi: 10.1210/jc.2013-2180
25. Hiroki Kobayashi, Masanori Abe, Yoshihiro Nakamura, Katsutoshi Takahashi, Megumi Fujita et al., JPAS/JRAS Study Group. Association Between Acute Fall in Estimated Glomerular Filtration Rate After Treatment for Primary Aldosteronism and Long-Term Decline in Renal Function. Hypertension. 2019;74(3):630-8. doi: 10.1161/HYPERTENSIONAHA.119.13131.
26. Leay Kiaw Er, Likwang Chen, Yao-Chou Tsai , Yen-Hung Lin, Wei-Chieh Huang et al. TAIPAI Study Group. Risk of New-Onset Autoimmune Diseases in Primary Aldosteronism: A Nation-Wide Population-Based Study. J Hypertens 2019 Nov 20[Online ahead of print].