Incidental Congestive Heart Failure in Patients With Aldosterone-Producing Adenomas

Wei-Chieh Huang, MD; Ying-Ying Chen, MD; Yen-Hung Lin, MD, PhD; Likwang Chen, PhD; Po-Chih Lin, MD; Yu-Feng Lin, MD; Yu-Chun Liu, MD; Che-Hsiung Wu, MD, PhD; Jeff S. Chueh, MD; Tzong-Shinn Chu, MD; Kwan Dun Wu, MD; Chun-Yao Huang, MD, PhD; Vin-Cent Wu, MD, PhD; TAIPAI Study Group*

Background—Previous studies show that patients with primary aldosteronism are associated with higher risk of congestive heart failure (CHF). However, the effect of target treatment to the incidental CHF has not been elucidated. We aimed to investigate the risk of new-onset CHF in patients with aldosterone-producing adenomas (APAs) and explore the effect of adrenalectomy on new onset of CHF.

Methods and Results—From 1997 to 2009, 688 APA were identified and matched with essential hypertension controls. The risks of developing incidental CHF (hazard ratio, 0.49; 95% CI, 0.31–0.75; $P=0.001$) and mortality (hazard ratio, 0.29; 95% CI, 0.20–0.44; $P<0.001$) were significantly lower in the APA group after targeted treatment. A total of 605 patients with APAs who underwent adrenalectomy lowered the risks of CHF (subdistribution hazard ratio, 0.55; 95% CI, 0.34–0.90; $P=0.017$) and mortality (adjusted hazard ratio, 0.27; 95% CI, 0.16–0.44; $P<0.001$) compared with essential hypertension controls.

Conclusions—In conclusion, for patients with APAs, adrenalectomy can be associated with lower risk of incidental CHF and all-cause mortality in a long-term follow-up. (*J Am Heart Assoc.* 2019;00:e012410. DOI: 10.1161/JAHA.119.012410.)

Key Words: adrenalectomy • aldosterone-producing adenomas • cardiovascular disease • congestive heart failure • essential hypertension • primary aldosteronism

Primary aldosteronism (PA) is a major cause of secondary hypertension caused by autonomous aldosterone secretion, which leads to hypertension and hypokalemia and is independent of renin.[1–3] It affects 5% to 13% of patients with hypertension, which consequently makes it the leading cause of secondary hypertension.[4] Previous studies have indicated that patients with PA have an increased prevalence of cardiovascular events,[5,6] cardiomegaly,[7] and left ventricular dimension index.[8] Moreover, long-term exposure to high aldosterone levels, in addition to high blood pressure, may eventually lead to cardiovascular and renal structural and functional damages,[9] including marked left ventricular (LV)

Clinical Perspective

What Is New?

- Patients with primary aldosteronism have a higher risk of congestive heart failure.
- Adrenalectomy is the treatment of choice for patients with aldosterone-producing adenomas, but its association with future congestive heart failure is unknown.
- We found that the risks of incident congestive heart failure and mortality were significantly lower in the group of patients with aldosterone-producing adenomas undergoing adrenalectomy compared with control patients with essential hypertension.

What Are the Clinical Implications?

- These findings highlight the importance of reaching an accurate diagnosis of primary aldosteronism and aldosterone-producing adenomas as adrenalectomy appears to be associated with improved outcomes in these patients.

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hypertrophy, increasing collagen deposition in myocardium, and renal hyperfiltration, and proteinuria.[6,10–13] In addition, aldosterone excess could produce a substantially increased risk of cardiovascular atherosclerosis via proinflammatory and profibrotic effects on the vascular wall and is associated more with metabolic syndrome.[14–19] PA traditionally can exist at least in 2 heterogeneous forms, that is, aldosterone-producing adenoma (APA; where excessive aldosterone secretion is associated with an unilateral adrenal mass [lateralized PA]), or idiopathic bilateral hyperaldosteronism (where excessive aldosterone secretion is associated with bilateral adrenal hyperplasia).[4]

Adrenalectomy has been advocated as the treatment of choice for APAs once the differential diagnosis is confirmed (with adrenal venous sampling, postural stimulation test, or NP59-SPECT), and the patient's anesthetic risk is acceptable. Adrenalectomy can significantly correct hypertension, hypokalemia, and biochemical abnormalities and even regress increased LV masses in patients with APAs. The treatment of idiopathic bilateral hyperaldosteronism is a mineralocorticoid receptor antagonist (MRA), plus other antihypertensives if and as indicated.[20]

Congestive heart failure (CHF) is a more concerning public health problem than is currently acknowledged.[21] However, clinical evidence to investigate an association between APAs and new-onset CHF is lacking, especially on a population scale, so exploring the CHF risk after the target treatment is warranted.

Therefore, we conducted this study to investigate the risks of CHF and mortality in patients with PA with APAs, as compared with their propensity score matched essential hypertension (EH) controls, thus to establish evidence of the benefits of adrenalectomy for a lower risk of incidental CHF.

Material and Methods

Data Availability Statement

We are unable to make our data, analytic methods, and study materials available to other researchers because of the following limitation: The Taiwanese Government allows researchers to analyze the National Health Insurance (NHI) data only from locations within Taiwan. Currently, the government owns 2 centers that store NHI data for academic use: the data science center of health and welfare (https://dep.mohw.gov.tw/DOS/np-2497-113.html) and the information integration and application service center of the NHI Administration (https://www.nhi.gov.tw/Content_List.aspx?n=468220093AFEB6DF&topn=CA428784F9ED78C9). Researchers in Taiwan are required to submit their research plans and institutional review board approvals for the proposed studies and to pay for using such data. The amount of payment depends on the volume of data retrieved.

Data Source

This population-based retrospective cohort study is based on data from the NHI Research Database dating between 1997 and 2009. The NHI Research Database has been implemented in Taiwan since 1995 and is one of the largest and most comprehensive population-based health insurance databases in the world; it has been used extensively in various studies.[22–24] The NHI covers almost all of the 23.7 million people living in Taiwan and contains medical information regarding ambulatory visits, hospital admissions, prescriptions, interventional procedures, disease profiles, and vital status.[25,26] The NHI Administration is the only healthcare costs payer of the NHI; it routinely checks for data accuracy and reliability.[27,28] To avoid rejection of claims reimbursement from NHI Administration, physicians in Taiwan usually follow clinical guidelines. Since diagnostic tests for PA are costly and intrusive, Taiwanese physicians follow the Aldosteronism Society's clinical practice guidelines—the Taiwan PA consensus[29]—and focus on performing lateralization tests on patients found to have a high possibility of PA after a confirmation test.

Study and Control Cohorts

This study included patients diagnosed as having PA (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] 255.1) (see Data S1, Tables S1 and S2).[22–28,30–33] The administrative data on diagnoses and MRA prescriptions for patients identified with PA in Taiwan had been well audited because of efficient NHI Administration reimbursement system.[22] PA was diagnosed by combining

ICD-9-CM 255.1 and the prescription of an MRA within 1 year before and after the diagnosis. The accuracy of PA diagnoses has been validated with a sensitivity of 0.89 and specificity of 0.8.[22] We also developed additional algorithms to ascertain comorbid conditions among patients with PA. Except for a couple of comorbid conditions, for which confirmation required more detailed *ICD-9-CM* coding, we used only the first 3 digits of the *ICD-9-CM* codes to identify comorbid conditions. This rule also tended to yield a lower rate of type II errors in identifying comorbidities.[34,35] While reviewing NHI data, the identification of a specific comorbid condition was based on the criterion that there was at least 1 inpatient NHI record or 3 outpatient records within 1 year before the initial PA diagnosis.[22,23,25,28,36]

In this nested propensity score–matched case, patients with EH were recruited from those with diagnoses of hypertension, and received antihypertensive agents (from the Anatomical Therapeutic Chemical Classification) after exclusion of patients with secondary hypertension. The Figure shows the flow diagram of selecting our study subjects.

Ethics Statement

Our study followed all applicable institutional and governmental regulations concerning the ethical use of data from human subjects. Informed consent was waived because patients were anonymous in the present analysis, and there was neither a breach of privacy nor interference with clinical decisions related to patient care. This study was exempt from a full ethical review by the Institutional Review Board of National Taiwan University Hospital (201301017RINC).

Outcome Measures

All 688 patients with PA and 2752 matched patients with EH were followed until the events, defined as either death of the study subjects or to the end of 2010. The diagnosis of CHF is compounded by the typical reliance on the first listed diagnosis, which was well validated using the *ICD-9* code from a population-based surveillance program.[21]

Statistical Analysis

Baseline characteristics of the study population were described using frequencies, with percentages for categorical variables. Given the differences in baseline characteristics and risks between study and control cohorts, we tried to match each patient in the APA cohort with 4 patients in the respective EH cohort with 2 sets of similar propensity scores based on nearest-neighbor matching without replacement, and using a caliper width equal to 0.1 of the SD from the

propensity score. We constructed the propensity score by all the factors listed in Table 1.

Cox regression models with time-varying covariates account for the influences on risk of CHF or death together with the matched set. Time-varying covariates took the value 0 before the start of an MRA or surgical treatment and could switch to 1 at the start of treatment for CHF, and mortalities occurring before the end of 2010 were properly identified. Date of censoring was defined as the earliest of the date of death of study subjects during follow-up, date of last withdrawal from NHI or date of follow-up termination, whichever comes the earliest. Because of higher mortality rates in male patients and elderly patients, a competing-risk regression, using the Fine and Gray model by considering the subdistribution hazard ratio (sHR), was also performed.[29,37] The incidence density rates of end points were calculated using rate per 1000 people-years. Cox proportional hazards regression, estimated hazard ratio, and 95% CI to plot hazards of PA to EH. All analyses were performed with R software, version 2.8.1 (Free Software Foundation, Inc., Boston, MA).

Results

Characteristics of the Study Population

Baseline characteristics are presented in Table 1, and there were 688 patients with newly diagnosed APAs. In both APA and EH groups, dyslipidemia was the most common underlying disease, followed by diabetes mellitus; in addition, calcium-channel blockers were the most commonly used antihypertension medication. (Data S1 also provides detailed information regarding comparison of PA and EH; see Tables S3 and S4.)

After an average of >5-year follow-up (5.2±3.5 years), 23 (3.34%) patients in the APA group and 172 (6.24%) patients in the EH group had new-onset (incidental) CHF. There is no statistical difference in onset of atrial fibrillation between nonmatched groups; however, after propensity score matching, the statistical difference of preexisting atrial fibrillation between matched groups was significant (0.65% versus 0.00%; *P*=0.034). Patients in APA group after matching had lower prevalence of atrial fibrillation.

The Comparative Incidence of Incidental CHF and All-Cause Mortality in Patients With APA Versus EH

After targeted treatment (including either adrenalectomy or MRA therapy), the incidence of incidental CHF was 5.3 per 1000 person-years in the APA group, whereas the incidence of incidental CHF in the EH controls (versus the APA group) was 11.1 per 1000 person-years.
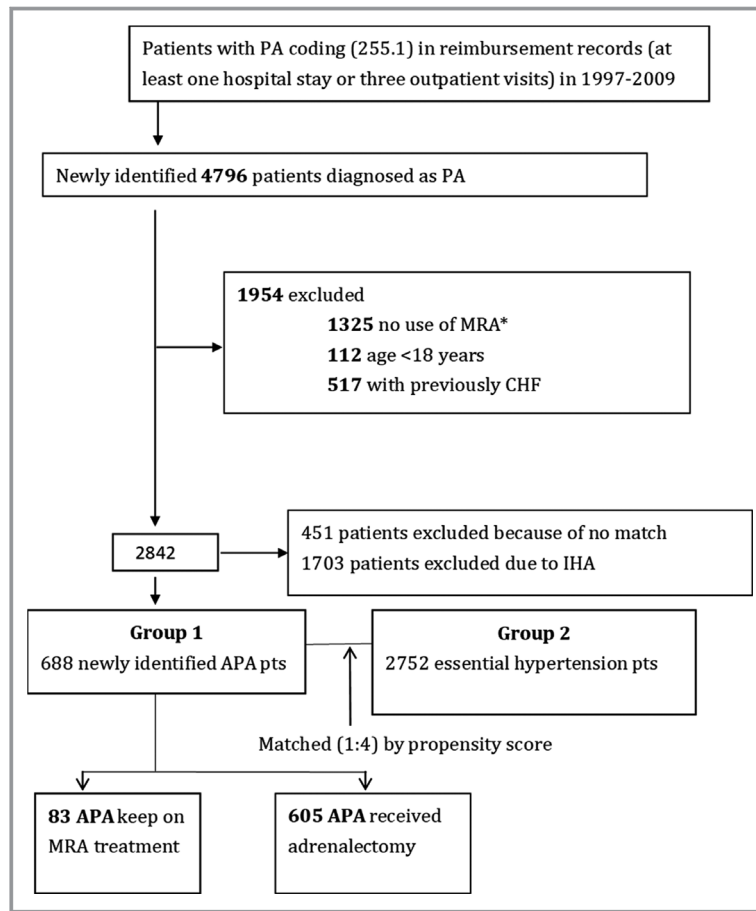
Figure. Flow diagram of selecting study subjects. Our study enrolled patients with PA, which was diagnosed by combining *ICD-9-CM* 255.1 and use of MRA 1 year before and after the diagnosis. We also excluded patients with documented congestive heart failure (CHF). APA indicates aldosterone-producing adenoma; IHA, Idiopathic bilateral hyperaldosteronism; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism.

The mortality incidence was 5.7 per 1000 person-years in the APA group, but 19.1 per 1000 person-years in the EH control group.

Regarding the comparison of the APA versus its propensity scored–matched EH controls (Table 2), as most patients underwent adrenalectomy (605/688=87.9%) in the APA group, the incidence of CHF and mortality was lower relative to the EH group: CHF (adjusted hazard ratio, 0.49; 95% CI; 0.31–0.75; *P*=0.001); mortality (adjusted hazard ratio, 0.29; 95% CI, 0.20–0.44; *P*<0.001; Table 2).

Risk of CHF and All-Cause Mortality After Adrenalectomy

Considering adrenalectomy as a time-varying factor, risks of developing CHF (sHR, 0.55; 95% CI; 0.34–0.90; *P*=0.017) or mortality (sHR, 0.27; 95% CI, 0.16–0.44; *P*<0.001) were significantly lower in the patients with APAs who underwent

adrenalectomy, as compared with their respective EH controls. After adjusting mortality as a competing risk, adrenalectomy was associated with the lower risk of incident CHF (sHR, 0.56; 95% CI, 0.34–0.91; *P*=0.019; Table 3) in the patients with APAs who underwent adrenalectomy. However, there was no statistically significant difference of the risks of developing CHF (sHR, 0.99; 95% CI, 0.82–1.19; *P*=0.903) or mortality (sHR, 1.08; 95% CI, 0.94–1.23; *P*=0.262) in the patients with APAs with an MRA and without adrenalectomy, as compared with their respective EH controls.

Discussion

Main Findings

This large, long-term, real-world study had several significant findings: The patients with APAs who underwent adrenalectomy were associated with lower risks of incidental CHF and

Table 1. Baseline Characteristics of Study Population With APA

Variables	Matched APA/EH			
	EH (n=2752)	APA (n=688)	*P* Value	SD
Propensity score	−2.52±0.46	−2.52±0.46	0.998	0.000
Sex				
Women, n (%)	1592 (57.85)	399 (57.99)	0.966	−0.003
Men, n (%)	1160 (42.15)	289 (42.01)		−0.003
Age	46.93±13.27	47.04±11.06	0.510	−0.009
Urbanization level				
Urban, n (%)	1281 (46.55)	326 (47.38)	0.287	−0.009
Suburban, n (%)	726 (26.38)	195 (28.34)		−0.032
Rural, n (%)	745 (27.07)	167 (24.27)		0.060
Monthly income, n (%)				
<NT$19 100, n (%)	1655 (60.14)	422 (61.34)	0.845	−0.012
NT$19 100–NT$41 999, n (%)	905 (32.89)	220 (31.98)		0.014
≥NT$42 000, n (%)	192 (6.98)	46 (6.69)		0.011
Preexisting comorbidity				
Cerebrovascular disease, n (%)	136 (4.94)	34 (4.94)	0.999	0.000
CKD, n (%)	21 (0.76)	5 (0.73)	0.999	−0.004
COPD, n (%)	57 (2.07)	14 (2.03)	0.999	−0.003
Coronary artery disease, n (%)	16 (0.58)	4 (0.58)	0.999	0.000
Dementia, n (%)	12 (0.44)	0 (0.00)	0.141	−0.094
Diabetes mellitus, n (%)	236 (8.58)	66 (9.59)	0.407	0.035
Hemiplegia, n (%)	15 (0.55)	5 (0.73)	0.576	0.023
Liver disease, n (%)	117 (4.25)	31 (4.51)	0.753	0.012
Peptic ulcer, n (%)	155 (5.63)	42 (6.10)	0.646	0.020
Peripheral vascular disease, n (%)	11 (0.40)	3 (0.44)	0.999	0.006
RA, n (%)	10 (0.36)	1 (0.15)	0.704	−0.043
Solid tumor, n (%)	55 (2.00)	14 (2.03)	0.999	0.003
SLE, n (%)	6 (0.22)	2 (0.29)	0.664	0.014
Atrial fibrillation, n (%)	18 (0.65)	0 (0.00)	0.034	−0.115
Dyslipidemia, n (%)	320 (11.63)	80 (11.63)	0.999	0.000
Parkinson disease, n (%)	8 (0.29)	1 (0.15)	0.698	−0.031
Medication for hypertension				
α-Blocker, n (%)	129 (4.69)	43 (6.25)	0.097	0.069
ACEI or ARB, n (%)	1087 (39.50)	274 (39.83)	0.896	0.007
β-Blocker, n (%)	1322 (48.04)	348 (50.58)	0.233	0.051
Calcium-channel blocker, n (%)	1857 (67.48)	465 (67.59)	0.999	0.002
Diuretic, n (%)	1005 (36.52)	250 (36.34)	0.965	−0.004
Other medication				
Aspirin, n (%)	135 (4.91)	41 (5.96)	0.287	0.047
Clopidogrel, n (%)	56 (2.03)	12 (1.74)	0.759	−0.021
Ticlopidine, n (%)	23 (0.84)	2 (0.29)	0.206	−0.073
Warfarin, n (%)	22 (0.80)	4 (0.58)	0.805	−0.026

Table 1. Continued

| Variables | Matched APA/EH | | | |
	EH (n=2752)	APA (n=688)	*P* Value	SD
PPI, n (%)	76 (2.76)	16 (2.33)	0.598	−0.028
H2 blocker, n (%)	198 (7.19)	53 (7.70)	0.624	0.019
Statin, n (%)	192 (6.98)	46 (6.69)	0.867	−0.012
NSAID, n (%)	1264 (45.93)	319 (46.37)	0.864	0.009
Steroid, n (%)	224 (8.14)	49 (7.12)	0.430	−0.038
SSRI, n (%)	45 (1.64)	10 (1.45)	0.866	−0.015
Nitrate, n (%)	5 (0.18)	0 (0.00)	0.590	−0.060
Outcome of interests				
CHF, n (%)	172 (6.25)	23 (3.34)	0.002	−0.136
Mortality, n (%)	312 (11.34)	25 (3.63)	<0.001	−0.296

ACEI indicates angiotensin-converting enzyme inhibitor; APA, aldosterone-producing adenoma; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EH, essential hypertension; H2 blocker, histamine-2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; NT$, New Taiwan dollar; PA, primary aldosteronism; PPI, proton pump inhibitor; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSRI, selective serotonin reuptake inhibitor.

mortality than EH controls after targeted treatment. However, there was no statistically significant difference in the risks of developing CHF in the patients with APAs with an MRA and without adrenalectomy, as compared with their respective EH controls. These results suggest that adrenalectomy was associated with a lower risk of incidental CHF as well as mortality in real-world practice.

Current Therapeutic Practice Among Patients With APA

Although a significant number of patients with PA with APAs can be cured by surgical adrenalectomy, many patients are treated medically with an MRA.[37,38]

The benefits of adrenalectomy on our patients are obvious and associated with a lower risk of CHF (sHR, 0.56) and mortality (adjusted hazard ratio, 0.27) in patients with APAs. Therefore, accurate diagnosis (confirmation of the PA

diagnosis, differential diagnosis of idiopathic bilateral hyperaldosteronism versus APA subtype, and lateralization of the APA lesion if any) and timely adrenalectomy is suggested in treating patients with lateralized PA, and individual therapeutic strategies could then be planned.

Lower Risk of New-Onset CHF and All-Causes Mortality in Patients With APAs Undergoing Adrenalectomy

In this study, we found that adrenalectomy was associated with the significantly lower risk of new-onset CHF and mortality in patients with APAs. Similar findings of lower rates of cardiovascular events have been reported in several previous studies[39–42]; however, there was no associated evidence of lower rates of new-onset CHF in those studies. Catena et al[39] followed 54 patients with PA for 12 years, 24 of whom received adrenalectomy. They found that rates of

Table 2. Incidence Rate of CHF, Mortality and HRs (APA and EH)

Variables	Events	Person-Years	Incidence Rate*	Events	Person-Years	Incidence Rate*
	EH			APA		
CHF	172	15 486	11.1	23	4327.9	5.3
Mortality	312	16 372	19.1	25	4423.3	5.7
Comparison of CHF and Mortality Risks in APA vs EH Patients						
	HR	*P* Value	Adjusted HR (95% CI)	*P* Value	HR Competing With Mortality (95% CI)	*P* Value
CHF	0.49 (0.32–0.76)	0.001	0.49 (0.31–0.75)	0.001	0.51 (0.33–0.79)	0.002
Mortality	0.30 (0.20–0.45)	<0.001	0.29 (0.20–0.44)	<0.001		

APA indicates aldosterone producing adenoma; CHF, congestive heart failure; EH, essential hypertension; HR, hazard ratio; PA, primary aldosteronism.
*Per 1000 person-years.

Table 3. Risk of CHF and Mortality of Patients With APA Undergoing Adrenalectomy

Variables	Crude		Adjust*		Compete†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
APA patients with adrenalectomy (N=605)						
CHF	0.55 (0.34–0.89)	0.016	0.55 (0.34–0.90)	0.017	0.56 (0.34–0.91)	0.019
Mortality	0.26 (0.16–0.44)	<0.001	0.27 (0.16–0.44)	<0.001	NA	NA
APA patients with MRA, without adrenalectomy (N=83)						
CHF	0.99 (0.82–1.19)	0.928	0.99 (0.82–1.19)	0.903	0.99 (0.82–1.20)	0.930
Mortality	1.00 (0.94–1.23)	0.266	1.08 (0.94–1.23)	0.262	NA	NA

APA indicates aldosterone producing adenoma; CHF, congestive heart failure; NA, not applicable.
*After adjusting propensity score matching, expressed as adjusted hazard ratio.
†Taking mortality as a competing risk and expressed as subdistribution hazard ratio.

myocardial infarction, stroke, revascularization procedures, and sustained arrhythmia were comparable with those of EH. Rossi et al[40] showed that the percentage of changes of LV mass index in short- and long-term follow-ups were more prominent in patients undergoing adrenalectomy. Another testament demonstrating the benefit of adrenalectomy is the work of Strauch et al[43]: surgical adrenalectomy in 29 patients with APAs/PA with 7.4 years follow-up, compared with conservative treatment of patients with PA, was associated with a significant reduction of blood pressure and improved arterial stiffness parameters. As a result, the regression of risk of cardiovascular complications after adrenalectomy could work to remedy the association between aldosterone and LV hypertrophy.

To our knowledge, our study is the first to show that adrenalectomy in patients with APAs was associated with not only a reduction of 73% chance of mortality but also a reduction of 45% chance of new-onset CHF. This significant effect of adrenalectomy on lowering all-cause mortality and new-onset CHF is important for urging clinicians to reach an accurate diagnosis of PA and prompt differential diagnosis of its APA versus an idiopathic bilateral hyperaldosteronism subdiagnosis, to provide the most effective individualized therapeutic options for the patients with PA.

Possible mechanisms of the superior effect of adrenalectomy in preventing CHF can be explained by the following factors:

1. Hypertension is one of the most important factors contributing to CHF. Not only could patients with APAs have improved or normalized blood pressure after adrenalectomy[44] but this reduction of blood pressure could last for a long time.[45,46] In contrast, the aldosterone level remains high in patients with APAs using an MRA, even though the mineralocorticoid has been blocked. The doses and kinds of antihypertensive agents used have also been shown to increase with time.[40,47]

2. Several studies have shown that the structural cardiac changes seen in patients with APAs without adrenalectomy, mostly LV hypertrophy/hyperplasia, are resolved or greatly improved after adrenalectomy.[48–52] LV mass and LV mass index are also shown to significantly decrease after adrenalectomy, as seen in a prospective study of 6.4 years.[48,52]

3. With medical and MRA treatment for APAs, the patient's drug compliance is vital, and poor medication compliance was associated with higher levels of aldosterone, which could lead to further deterioration of PA and associated complications.

4. Adrenalectomy in patients with APAs could lower the prevalence of new-onset atrial fibrillation, which is deeply related to CHF and mortality, and consequently was associated with a lower risk of new-onset CHF and mortality.

Our study showed the evidence that adrenalectomy is the treatment of choice for patients with APAs suitable for operation; the treatment goal is to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage, especially CHF.

Strengths and Limitations

This study has several strengths. First, we provided a large cohort of patients with APAs and a long-term follow-up by using a population-based database, which carries a low risk of selection bias. Second, our investigation analysis targeted patients in real-world practice and provided clinical support to previous echocardiography findings and smaller-scale clinical observational and in vitro studies.[22] Third, patients with APAs were compared with their respective EH control patients, via proper propensity score matching, and both groups had comparable baseline cardiovascular risk profiles.

However, there are also some weaknesses in our retrospective cohort analysis that should be acknowledged. First, the data retrieved and examined in this study were from population-based health insurance registration data, where the diagnostic results were not "controlled" as ideally as some single- or multicenter clinical studies could have achieved. These findings may shed light on some heterogeneity of findings in previous studies, as targeted treatment has not always been accounted for in the studies. It is unlikely that prospective randomized trials of adrenalectomy for prevention of CHF among patients with APAs will ever be undertaken because of the sheer number of patients that would require randomization to have adequate numbers of the patients with APAs. Second, as a claims-based analysis, we could not eliminate the possibility of selection bias and residual confounding. The propensity score matching prompted a rigorous adjustment, but the confounding inherent to unmeasured factors affecting treatment assignment still could not be fully accounted for. Third, it is possible that the diagnosis of PA on the basis of only the *ICD* code may not be correct. However, we located patients with PA using both diagnosis with 255.1x and existence of an MRA prescription, and this model has been examined in previous studies with meticulous sensitivity and specificity. Fourth, actual blood pressure control cannot be acquired in this registry. Fifth, because of patients' and treating physicians' choice, a few cases choose second-class medical care, and this choice is associated with poor clinical outcomes. Therefore, a prospective study is needed to investigate the risk of new-onset CHF in patients with APAs and explore the effect of adrenalectomy on new-onset CHF.

Conclusions

For patients with APAs, adrenalectomy can be associated with a lower risk of incidental CHF and all-cause mortality in a long-term follow-up.

Appendix

Membership of the Taiwan Primary Aldosteronism Investigation (TAIPAI) Study Group

Tai-Shuan Lai, Vin-Cent Wu, Shao-Yu Yang, Kao-Lang Liu, Chin-Chen Chang, Bo-Chiag Lee, Shuo-Meng Wang, Kuo-How Huang, Po-Chih Lin, Yen-Hung Lin, Lian-Yu Lin, Shih-Cheng Liao, Ruoh-Fang Yen, and Ching-Chu Lu (National Taiwan University Hospital, Taipei, Taiwan); Chieh-Kai Chan (NTUH Hsin-Chu branch); Leay-Kiaw Er, Ya-Hui Hu, Chia-Hui Chang, Che-Hsiung Wu, and Yao-Chou Tsai (Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taipei, Taiwan); Shih-Chieh Jeff Chueh (Cleveland Clinic Institute of Urology and Kidneys); Chen-Hsun Ho (Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare);

Wei-Chieh Huang (New Taipei City Hospital); Ying-Ying Chen (MacKay Memorial Hospital); and Kwan-Dun Wu (National Taiwan University Hospital, Taipei, Taiwan NTUH, Director of Coordinating Center).

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Supplemental Material

Data S1.

Identification of primary aldosteronism from the National Health Insurance Research Databases

<u>Material and Methods</u>

Our population-based retrospective cohort study is based on data from the National Health Insurance Research Databases (NHIRD) dating between 1997 and 2009. The NHIRD has been implemented in Taiwan since 1995 and is one of the largest and most comprehensive databases in the world, having been used extensively in various studies.[1-3] The National Health Insurance (NHI) covers almost all of the 23.7 million people living in Taiwan and contains medical information about outpatient visits, hospital admissions, prescriptions, interventional procedures, disease profiles, and vital status.[4, 5] The NHI Administration (NHIA) routinely checks for data accuracy and thus reliability.[6-8]

   We have proved the abovementioned hypothesis of such identification of PA diagnosis by using multi-center medical records as the "gold standard" and matched with the TNHI reimbursement records.[2] The diagnosis of PA is according to clinical judgment. In order to increase the diagnostic specificity, we used validated algorithm to enroll PA patients. Our strategy, based on a combination of PA ICD-9 codes, and spironolactone claim, had the highest positive predictive value (PPV) for the identification of patients with PA. Using 3 out-patient visits or one inpatient has higher PPVs than one outpatient or one inpatient record. PPVs varied with different algorithms with PA code: PPV for antihypertensive drugs in use (PPV= 66.9%, 95%CI = 63.0%-70.6%), claims with hypokalemia and antihypertensive drug in use (PPV= 89.4%, 95%CI = 85.4%-93.0%), and final decisions of clinical certainty of PA with spironolactone in use[2] (PPV= 93.4%, 95%CI = 89.4%-97.0%). By searching the procedure codes, we analyzed the ratio of image study, adrenal venous sampling (AVS), and postural stimulation tests among the PA patients in this study. Since the diagnostic and procedure codes were for insurance reimbursement, they were recorded with high accuracy, and it reflected the 'real-world practice' to identify aldosteronism in Taiwan during the past decade (Table S1). In order to validate the diagnostic tests from the NHI database, we scrutinized the database of TAIPAI (the patients in the database of TAIPAI are included as a fraction of the whole NHI database; but more detailed clinical parameters of the patients are available from TAIPAI than from NHI database, because the former is a multicenter quality-control data registry, while the latter is a population-base health insurance data registry). The TAIPAI study group included two medical centers (National Taiwan University

Hospital (NTUH), Taipei, Taiwan; Taipei University Hospital , Taipei, Taiwan), and five regional hospitals (Cardinal Tien Hospital, New Taipei City, Taiwan; Taipei Tzu Chi Hospital, New Taipei City, Taiwan; Yun- Lin Branch of NTUH, Douliou City, Taiwan; Hsin-Chu Branch of NTUH, Hsin-Chu City, Taiwan; Zhongxing Branch of Taipei City Hospital, Taipei, Taiwan). Because there is no specific ICD-9 diagnosis of aldosterone producing adenoma, PA patients with the diagnosis of adrenal tumor (ICD-9 code =227, 227.0, 239.7) were further analyzed as a specificity test.

Results

131I-6β-Iodomethyl-19-Norcholesterol SPECT/CT (NP-59 SPECT/CT) plays an important ancillary role, especially among those patients for whom AVS was unavailable and CT showed a unilateral adrenal mass. Currently iodocholesterol scintigraphy is no longer used in some countries, like the United States (U.S.), but remains available in Taiwan, Japan and other countries. It has the ability similar to conventional visual scale (VS) in differentiating APA from IAH, and yet an excellent ability to predict postsurgical outcomes of adrenalectomy[9].

CT scan, postural stimulation and AVS were the leading procedures to identify APA from our two datasets[3] (the NHI dataset of the current article and the TAIPAI dataset) (Table S2). Salt loading test is the most commonly used diagnostic procedure to identify PA form the TAIPAI database. From TAIPAI cohort, we notice that the diagnostic utility of AVS and posture stimulation tests was almost the same as that from the NHI database. Most of the hospitals form the TAIPAI group were equipped with the capacity of NP-59 SPECT/CT, and therefore the diagnostic utility of NP-59 SPECT/CT was higher than that from the NHI database.

In Taiwan, patients who received captopril tests showed a sensitivity of 66.2% and a specificity of 89.1%.[10] According to our previous validation, the NP-59 for Primary Aldosteronism patients showed an accuracy of 77.4% for predicting pathological change of aldosteronism[11]; However NP-59 semi-quantification in differentiating APA could reach the accuracy of 85.7%.[9]

The result of our AVS among the TAIPAI dataset showed that 44.7% of PA patients were found to have lateralized hypersecretion of aldosterone (i.e.: APA; including 32.7% with lateralization towards the right and 12% with lateralization towards the left), and no lateralization could be identified among the other 55.3% PA patient; i.e.: idiopathic adrenal hyperplasia).

For the comparison between patients with aldosterone producing adenoma who were treated with surgery versus MRA, PA patients with the diagnosis of adrenal tumor (ICD-9 code =227, 227.0, 239.7) were further analyzed as a specificity test

from TAIPAI cohort. In our dataset, among the patients who underwent adrenalectomy and had the ICD-9 record of an adrenal tumor, there was a very high positive predictive value (96%) of APA. Furthermore, in the specificity test of this study we chose- only to include those confirmed APA patients to run the test, which although sacrificed some sensitivity, increased the positive predictive rate. In such a conservative way, we are confident to report the beneficial effects of adrenalectomy on the all-cause mortality among these APA patients.

Among the patients who underwent AVS we further identified those patients with incidentaloma (not APA) and contralateral adrenal aldosteronism, and compared them with the previously mentioned combo coding of PA and adrenal tumor. The result showed a high incidence of such discrepancy (99.2%) and indirectly confirmed the high specificity of coding about adrenal adenoma among PA patients as APA.[8]

Table S1. The details of diagnostic procedures from national health insurance data[12]

	Before Match			After Match*		
	No Operation	Operation	*p*	No Operation	Operation (n=822)	*p*
	(n=2516)	(n=846)		(n=822)		
Male sex	1188 (47.2%)	369 (43.6%)	0.073	358 (43.6%)	360 (43.8%)	0.960
Age (year)	52.91 ± 15.44	46.6 ± 10.85	<0.001	46.9± 13.7	46.9 ± 10.8	0.447
Age < 35 y/o	292 (11.6%)	114(13.5%)	0.161	140(17.0%)	107(13.0%)	0.027
Age < 40 y/o	521(20.7%)	226(26.7%)	<0.001	256(31.1%)	208(25.3%)	0.010
Subtype						
CT	1481(58.9%)	539(63.7%)	0.017	529(64.4%)	520(63.3%)	0.692
MRI	808(32.1%)	283(33.5%)	0.391	267(32.5%)	278(33.8%)	0.289
AVS	471(18.7%)	190(22.5%)	0.023	151(18.4%)	195(23.7%)	0.020
NP-59	304(12.1%)	113(13.4%)	0.186	99(12.0%)	129(12.9%)	0.343
Posture	1085(43.1%)	413(48.8%)	0.336	379(46.1%)	399(48.5%)	0.421

AVS, adrenal venous sampling, CT, computer tomography, MRI, Magnetic Resonance Imaging, NP-59, 131I-6β-Iodomethyl-19-Norcholesterol SPECT/CT

Table S2. Details of diagnostic procedures from TAIPAI database[12].

Total 563 patients	No Operation (n=330)	Operation (n=233)	P
Male sex	159(48.2%)	111(47.6%)	0.932
Age (in year)year)	56.1 ± 12.5	52.2 ± 11.8	<0.001
Age <35 year old	24 (7.2%)	28 (12.0%)	0.096
Age <40 year old	52(15.8%)	56(24.0%)	0.026
Confirmation test			
Capoten test	109(33.0%)	55(23.6%)	0.018
Salt loading test	205(62.1%)	134(57.5%)	0.294
Subtype			
CT	307(93.0%)	212(91%)	0.426
MRI	63(19.1%)	46(19.7%)	0.914
AVS	82(24.8%)	61(26.2%)	0.423
NP-59	66(20.0%)	52(22.3%)	0.256
Posture	158 (47.9%)	105 (45.1%)	0.398

Detailed information regarding to comparison of PA and EH

Table S3 showed baseline characteristics of all study population. Of the 2,391 newly diagnosed PA patients enrolled in this study, 1,307 (54.7%) were female. 151 (6.3%) patients in the PA group had new-onset CHF and 279 patients (11.7%) in the PA group died. After targeted treatment, the incidence of new onset CHF was of 11.8 per 1000-person year in the PA group. The incidence of mortality and CHF were lower among the PA group after targeted treatment than that of the EH group (Incidence rate of CHF, EH vs. PA = 13.7 vs. 11.8; incidence rate of Mortality, EH vs. PA = 24.1 vs. 20.8, Table S2). Regarding to comparison of PA/EH (Table S4), in the comparison of PA and EH group, the risk of CHF was not significantly different between both groups (adjusted hazard ratio (HR)=0.87, CI: 0.73-1.03, p = 0.109, Table S2), but the risk of all-causes mortality was lower in PA group (adjusted hazard ratio (HR)=0.87, CI: 0.76-0.099, p = 0.35, Table S2).

Table S3. Baseline Characteristics of all Study Population.

Variables	Matched PA/EH			
	EH (n = 9564)	PA (n = 2391)	p	StD
Propensity score	-4.04 ± 1.58	-4.04 ± 1.58	0.997	0.000
Sex				
Women	5013 (52.42%)	1307 (54.66%)	0.050	-0.045
Men	4551 (47.58%)	1084 (45.34%)		-0.045
Age	49.98 ± 13.98	49.98 ± 13.98	0.999	0.000
Urbanization level				

Urban	4428 (46.30%)	1124 (47.01%)		-0.008
Suburban	2543 (26.59%)	644 (26.93%)	0.581	-0.006
Rural	2593 (27.11%)	623 (26.06%)		0.022
Monthly income, n (%)				
<NT$19100	5637 (58.94%)	1443 (60.35%)		-0.014
NT$19100–NT$41999	3240 (33.88%)	789 (33.00%)	0.397	0.013
≥NT$42000	687 (7.18%)	159 (6.65%)		0.021
Comorbidity				
Cerebrovascular disease	630 (6.59%)	178 (7.44%)	0.145	0.034
CKD	175 (1.83%)	54 (2.26%)	0.182	0.030
COPD	445 (4.65%)	123 (5.14%)	0.308	0.023
Coronary artery disease	51 (0.53%)	14 (0.59%)	0.756	0.007
Dementia	55 (0.58%)	10 (0.42%)	0.437	-0.022
Diabetes Mellitus	1140 (11.92%)	307 (12.84%)	0.220	0.028
Hemiplegia	52 (0.54%)	18 (0.75%)	0.231	0.026
Liver disease	566 (5.92%)	127 (5.31%)	0.282	-0.026
Peptic Ulcer	715 (7.48%)	182 (7.61%)	0.828	0.005
Peripheral vascular disease	59 (0.62%)	9 (0.38%)	0.222	-0.034
RA	50 (0.52%)	7 (0.29%)	0.183	-0.036
Solid tumor	236 (2.47%)	60 (2.51%)	0.883	0.003
SLE	20 (0.21%)	6 (0.25%)	0.629	0.009
Atrial fibrillation	69 (0.72%)	17 (0.71%)	0.999	-0.001
Dyslipidemia	1376 (14.39%)	336 (14.05%)	0.695	-0.010
Parkinson disease	48 (0.50%)	15 (0.63%)	0.432	0.017
Medication for hypertension				
Alpha-Blocker	566 (5.92%)	155 (6.48%)	0.313	0.023
ACEI or ARB	3723 (38.93%)	918 (38.39%)	0.639	-0.011
Beta-Blocker	4495 (47.00%)	1080 (45.17%)	0.114	-0.037
Calcium-Channel Blocker	5793 (60.57%)	1439 (60.18%)	0.743	-0.008
Diuretic	3934 (41.13%)	992 (41.49%)	0.763	0.007
Other Medication				
Aspirin	527 (5.51%)	140 (5.86%)	0.517	0.015
Clopidogrel	120 (1.25%)	29 (1.21%)	0.918	-0.004
Ticlopidine	85 (0.89%)	24 (1.00%)	0.630	0.012
Warfarin	60 (0.63%)	16 (0.67%)	0.775	0.005

PPI	343 (3.59%)	90 (3.76%)	0.669	0.009
H2 blocker	854 (8.93%)	214 (8.95%)	0.968	0.001
Statin	801 (8.38%)	205 (8.57%)	0.742	0.007
NSAID	4566 (47.74%)	1151 (48.14%)	0.731	0.008
Steroid	874 (9.14%)	224 (9.37%)	0.722	0.008
SSRI	244 (2.55%)	55 (2.30%)	0.511	-0.016
Nitrate	17 (0.18%)	7 (0.29%)	0.303	0.024
Outcome of interests				
CHF	671 (7.02%)	151 (6.32%)	0.240	-0.028
Mortality	1257 (13.14%)	279 (11.67%)	0.056	-0.045

ACEI: Angiotensin-Converting-Enzyme Inhibitor; APA: Aldosterone Producing Adenoma; ARB: Angiotensin Receptor Blocker; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; EH: Essential Hypertension; H2 blocker: Histamine-2 receptor antagonist; NT$: New Taiwan dollar; NSAID: NonSteroidal Anti-Inflammatory Drug; PA: Primary Aldosteronism; PPI: Proton-Pump Inhibitor; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematous; SSRI: Selective Serotonin Reuptake Inhibitors

Table S4. Incidence rate of CHF, Mortality and HRs (PA and EH).

Variables	Events	Person-Years	Incidence Rate*	Events	Person-Years	Incidence Rate*
	EH			**PA**		
CHF	671	49133	13.7	151	12830	11.8
Mortality	1257	52191	24.1	279	13408	20.8
Comparison of PA and EH						
	HR	p	Adjusted HR	p	HR Competing with mortality	p
PA/EH						
CHF	0.87 [0.73,1.04]	0.136	0.87 [0.73,1.03]	0.109	0.88 [0.74,1.05]	0.150
Mortality	0.87 [0.76,0.99]	<0.031	0.87 [0.76,0.99]	0.035		

*: Per 1000 Person-Years

APA: aldosterone producing adenoma; CHF, congestive heart failure; EH, essential hypertension; HR, hazard ratio; PA, primary aldosteronism

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