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ORIGINAL RESEARCH

Major Adverse Cardiovascular Events in Primary Aldosteronism After Adrenalectomy or Mineralocorticoid Receptor Antagonist Treatment: A Systematic Review and Meta-Analysis

Chien-Wei Huang, MD; Tse-Ying Huang, MD; Ya-Fei Yang, MD; Li-Yang Chang, MBBS; Yu-Kang Tu, PhD; Vin-Cent Wu, MD, PhD; Jui-Yi Chen, MD

BACKGROUND: The object of this study was to investigate the incidence rate of major adverse cardiovascular event (MACE) among patients with primary aldosteronism (PA) after adrenalectomy or mineralocorticoid receptor antagonist (MRA) treatment.

METHODS AND RESULTS: A systematic review and meta-analysis was conducted by searching PubMed, Embase, Cochrane Library, Web of Science, CINAHL, and Scopus through April 15, 2024. Studies reporting the MACE incidence rate in patients with PA after treatment were included. We adapted the random-effects model and performed subgroup and meta-regression analyses. A total of 20 studies involving 16 927 patients with PA were included. There were 5939 patients with PA who underwent adrenalectomy. A total of 10 474 patients received MRA treatment. Additionally, 546 patients received either adrenalectomy or MRA treatment. The pooled incidence rate of MACE among patients with PA after treatment was 2.20/100 patient-years (95% CI, 1.70–2.80), higher than that of non-PA hypertension (1.20/100 patient-years [95% CI, 0.70–2.10]). Patients with PA after adrenalectomy had a lower MACE incidence rate (2.00/100 patient-years [95% CI, 1.40–2.60]) compared with those undergoing MRA treatment (3.30/100 patient-years [95% CI, 2.40–4.10], P=0.017). Advanced age (coefficient: 0.071, P<0.001) and diabetes (coefficient: 0.070, P=0.001) increased the risk of posttreatment MACE. A curvilinear dose–response relationship between the posttreatment plasma renin activity and the MACE incidence was observed, with the lowest risks at plasma renin activity of 1.0 to 2.0 ng/mL per hour ($P_{nonlinearity}$<0.001).

CONCLUSIONS: The MACE incidence in treated patients with PA was 2.20 per 100 patient-years, higher than in patients with hypertension without PA. Maintaining posttreatment plasma renin activity between 1.0 and 2.0 ng/mL per hour appears crucial for minimizing cardiovascular risk. Adrenalectomy proved more effective than MRA treatment in reducing MACE risk. Advanced age and diabetes significantly increased the risk of posttreatment MACE.

Key Words: adrenalectomy ■ major adverse cardiovascular event ■ mineralocorticoid receptor antagonist ■ primary aldosteronism ■ renin

Correspondence to: Jui-Yi Chen, MD, Division of Nephrology, Department of Internal Medicine, Chi-Mei Medical Center, No.901, Zhonghua Rd. Yongkang Dist., Tainan 71004, Taiwan. Email: kwuilus0101@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- The current meta-analysis presents the latest information about the incidence of major adverse cardiovascular event (MACE) among patients with primary aldosteronism after treatment.
- It indicates that patients with primary aldosteronism have an increased risk of MACE after treatment compared with those with non-primary aldosteronism hypertension; furthermore, this study demonstrates a U-shaped relationship between the posttreatment plasma renin activity and the incidence of MACE and underscores the heightened risk of posttreatment MACE associated with advanced age and diabetes.

What Are the Clinical Implications?

- The study's findings highlight the critical role of primary aldosteronism-targeted treatment to mitigate MACE risks, but MACE incidence is still higher compared with those after treatment for non-primary aldosteronism hypertension.
- The discovery of a U-shaped correlation between posttreatment plasma renin activity levels and MACE occurrence suggests an optimal plasma renin activity range for minimizing MACE, which warrants further exploration.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
MRA	mineralocorticoid receptor antagonist
PA	primary aldosteronism
PRA	plasma renin activity

Primary aldosteronism (PA) is a common form of hypertension caused by the overproduction of aldosterone. Patients with PA commonly exhibit high blood pressure, various degrees of hypokalemia, and metabolic alkalosis.[1] Furthermore, excessive aldosterone is suggested to result in increased insulin resistance and mineralocorticoid receptor activity, which can lead to endothelial dysfunction, vascular remodeling, and cardiovascular and cerebrovascular complications in patients with PA.[2] There were several studies demonstrating that patients with PA have an increased risk of developing cardiovascular, cerebrovascular, and metabolic complications.[3,4] The prevalence rate of cardiovascular events such as ischemic heart disease, stroke, and heart failure (HF) among the 2582 patients with PA who participated in the JPAS (Japan Primary Aldosteronism Study) between 2006 and 2016 was 9.40%.[3] The study by Monticone et al. found that patients with PA had an increased risk of coronary artery disease (CAD), stroke, HF, and atrial fibrillation (AF) compared with those with non-PA hypertension.[4,5] Therefore, it is essential to promptly identify and treat patients with PA in order to mitigate the cardiovascular adverse effects.

Current guidelines recommend that adrenalectomy is suggested for unilateral PA, whereas a mineralocorticoid receptor antagonist (MRA) is indicated for bilateral PA.[6,7] The objective of targeted treatment for PA is to reduce the excessive production of aldosterone and mitigate the overactive function of the mineralocorticoid receptor.[1] Recently, several studies have reported the incidence of cardiovascular events following therapy, either adrenalectomy or MRA treatment, in patients with PA.[8–27] However, the results remain inconclusive, which could potentially be attributed to the relatively limited sample sizes and distinct characteristics of the cohorts. Furthermore, several studies have assessed the correlation between biomarkers, such as blood pressure, serum potassium level, and plasma renin, and the prognosis of patients with PA after treatment, specifically in relation to cardiovascular outcomes.[28–31] These findings are yet to be determined. Additionally, the impact of plasma renin activity (PRA) levels after PA treatment on the prognosis of major adverse cardiovascular events (MACE) is also unclear.

Until now there are no data concerning the incidence rate of MACE among patients with PA after treatment. Hence, this study aims to assess the incidence rate of MACE in patients with PA who had undergone adrenalectomy or MRA treatment, as well as to identify factors associated with the occurrence of MACE after treatment.

METHODS

Search Strategy

This study was prospectively registered at the International Prospective Register of Systematic Reviews (CRD42023481435) and was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses 2020 statement (Table S1).[32] Two reviewers (C.W.H. and T.Y.H.) comprehensively searched for studies published before April 15, 2024 in the databases of PubMed, Embase, Cochrane Library, Web of Science, CINAHL, and Scopus without any restrictions regarding language or publication date. The search was carried out using the following search terms: [(primary aldosteronism) OR hyperaldosteronism] AND [(major adverse cardiovascular event) OR (cardiovascular death) OR (myocardial infarction) OR stroke OR (heart

failure) OR (atrial fibrillation)] AND [adrenalectomy OR (mineralocorticoid receptor antagonist)]. The details of our search strategy are delineated in Table S2. This meta-analysis did not require informed consent as it was based on aggregated data from previously published studies. The authors declare that all supporting data are available within the article and its supplementary files.

Eligibility Criteria

The study aimed to clarify the incidence rate of MACE among patients with PA after adrenalectomy or MRA treatment. The definition of PA and the strategy for patient assignment to adrenalectomy or MRA treatment were based on that of each enrolled study (Table S3). The titles and abstracts of the studies retrieved from the search were assessed, and the entire texts of relevant articles were thoroughly examined to ascertain the eligibility of the studies for inclusion in this study. Additionally, scanning of the reference lists of relevant full-text papers was performed to identify crucial studies that might be overlooked.[33] The excluded studies consisted of duplicate records, studies unrelated to PA, studies not investigating adrenalectomy or MRA, absence of relevant outcomes or unavailable data, studies involving nonhuman subjects, and those with ineligible study designs. Furthermore, we calculated the incidence rate of MACE by extracting data on the number of events and the total observation time. Studies lacking these data were excluded. Prospective and retrospective cohort studies and case series were selected, and case reports, cross-sectional studies, conference abstracts, comments on other studies, and protocol were excluded. Single-arm studies that presented the incidence of MACE among patients with PA after treatment were included. Furthermore, data relevant to the incidence of MACE in patients with PA after treatment from any comparative studies were extracted and used for estimating the incidence rate of MACE. In cases where there were disagreements, the third reviewer (Y.F.Y.) was consulted to achieve a consensus.

Data Extraction

The essential data from eligible studies were extracted by 2 reviewers (C.W.H. and T.Y.H.) independently through a standardized data abstraction form. The extracted data encompassed characteristics of studies including author, publication year, country, study design, follow-up period, outcomes of interest, treatment modality and number of enrolled patients, as well as clinical features of patients, including age at diagnosis, sex, body mass index (BMI), diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum potassium level, plasma aldosterone concentration and PRA, estimated glomerular filtration rate, posttreatment PRA, the use of antihypertensive medications after treatment, posttreatment SBP, and posttreatment DBP. To convert PRA measured in ng/mL per hour to direct renin concentration measured in mU/L, one should multiply the PRA value by 12 when using the commonly used automated direct renin concentration assay and by 8.2 when using older methods.[34] The primary outcomes examined in the study was MACE, which comprised mainly the following: cardiovascular death, CAD, stroke, HF, and arrhythmia. The term "arrhythmia" encompassed both AF and clinically significant ventricular arrhythmias, such as ventricular tachycardia and ventricular fibrillation. The individual components were subsequently evaluated as secondary outcomes to investigate the incidence of each specific event following treatment. We reached out to the authors of the enrolled studies to obtain additional information. Full-text papers were evaluated for data synthesis and quality assessment. Any discrepancies got resolved by consensus or discussion with a third author (Y.F.Y.).

Quality Assessment

Two reviewers (C.W.H. and Y.F.Y.) independently evaluated the methodological quality of each study using the critical appraisal tool for noncomparative studies derived by Murad et al.[35] This tool provided an algorithm for assessing the quality of noncomparative studies and case reports/series by considering the domains of selection, ascertainment, causality, and reporting. It contained 8 key clarifying questions to assist evidence-based systematic reviewers in their assessment. Nevertheless, 3 questions related to cases of adverse drugs events were not assessed in this study.[35] Thus, each enrolled article was evaluated based on 5 characteristics and has the potential to receive up to 5 stars.

Subgroup and Meta-Regression Analyses

We conducted subgroup analyses to investigate potential factors that contribute to the differences in heterogeneity and to acquire a deeper comprehension of the incidence of MACE following treatment among patients with PA. These subgroups were defined based on the following criteria: follow-up period (<5 years, 5–10 years, or >10 years), treatment modality (adrenalectomy or MRA treatment), age (≥50 or <50 years old), BMI (≥30 or<30 kg/m^2, and ≥27.5 or<27.5 kg/m^2),[36] serum potassium level (>3.5 or ≤3.5 mmol/L), posttreatment PRA (>2, 1–2, or<1 ng/mL per hour), preexisting cardiovascular disease, trial setting (single center or multicenters), and ethnicity (American, European, Chinese, Japanese, or Korean). We also evaluated the influence of treatment modality on the incidence of individual secondary outcomes. Additionally, we employed random-effects meta-regression analyses to examine potential influences of variables such as

follow-up period, age, male sex, BMI, diabetes, blood pressure parameters (including SBP, DBP, posttreatment SBP, posttreatment DBP, the change in SBP, and the change in DBP), serum potassium level, plasma aldosterone concentration, PRA, estimated glomerular filtration rate, and treatment modality adjustment on the incidences of MACE and individual secondary outcomes. The changes in SBP or DBP were defined as the difference between posttreatment and baseline SBP or DBP. We also examined the influence of preexisting cardiovascular disease and use of antihypertensive medications after treatment on posttreatment PRA in MRA-treated patients with PA using meta-regression analyses. Furthermore, we conducted the generalized estimating equations (GEE) Poisson regression to assess the relationship between the post-treatment PRA and the incidence of MACE. The outcome measured is the number of MACE, and the offset is the person-years. Because most studies provided >1 observation, we used GEE with an exchangeable correlation matrix to address the dependence of data within the same study. Initially, we fitted a linear trend and subsequently applied a restricted cubic spline with 3 knots to investigate the potential nonlinear relationship between posttreatment PRA and the incidence of MACE. To compare the difference between the linear and nonlinear models, we performed a Wald test.

Statistical Analysis

To calculate the incidence rate of MACE and individual secondary outcomes, we extracted the number of MACE or individual secondary outcomes among patients with PA after treatment, as well as the total observation time. The total patient numbers and the mean or median follow-up time were used to estimate the total observation time. To address the proportional data with inherent heterogeneity among studies, we used a random-effects model with log-transformation of incidence rates to calculate the pooled incidence rate estimates and 95% CIs. Between-trial heterogeneity was assessed using the Cochrane Q test, with homogeneity rejected if the P value was <0.05. The extent of heterogeneity was categorized as mild (I^2<30%), moderate (30%≤I^2<50%), and substantial (I^2≥50%). Additionally, τ^2 was used to estimate the variance between studies. All statistical analyses were performed using the "meta" and "metafor" package in R software (Version 4.3.1, April 21, 2023), Comprehensive Meta-Analysis (Version 4, August 30, 2022), and Stata (MP 18, April 25, 2023).

Analyses of Bibliometric Tendencies in Research

We conducted a bibliometric investigation to elucidate the research relationship between PA and MACE as a preliminary step toward our primary meta-analysis and foundational works in distinct scientific domains.[37] The investigation was carried out using the Science Citation Index Expanded data from the Web of Science Core Collection on March 6, 2024. A combination of keywords that were relevant to both PA and MACE were applied. The records obtained by the Web of Science Core Collection were downloaded and subsequently transformed into plain text format in preparation for export. This exported data comprised full records and references. The data were subsequently imported into CiteSpace 5.7.R2 and VOSviewer 1.6.20 by 2 authors (C.W.H. and L.Y.C.) for bibliometric and visual analysis. Additional detailed methodology for bibliometric analysis are available in Data S1.

RESULTS

Trends in Research Evolution

Figure S1 presents the temporal variations and distributions of keywords associated with both PA and MACE, with circle size depending on their occurrences. A prominent trend in recent years is the evident increase in the frequency of keywords including AF, arterial stiffness, cardiovascular event, diagnosis, management, outcomes, prevalence, and treated PA. The co-citation network of references is represented in Figure S2, using CiteSpace. The analysis disclosed the existence of 6 clusters, each of which was linked to a distinct keyword. Cluster 0, which primarily addressed the topic of "AF" was noticeably the largest of the clusters. A timeline view of co-cited references is provided in Figure S2B, which is critical to assess the evolution of research hotspots throughout time. The colors revealed the number of papers and the extent of citations associated with each cluster. Prominent recent clusters on the timeline included "#0 AF," "#3 obstructive sleep apnea," and "#5 taipai (Taiwan Primary Aldosteronism Investigators)." These findings indicate the criticality of the ongoing study into the incidence of MACE among patients with PA after treatment as well as the necessity to examine the occurrence of arrhythmia in this population.

Search Results and Study Characteristics

Figure S3 illustrates the process of literature search and identification. A total of 1051 articles were initially identified through the electronic database search. Following the removal of 455 duplicate records, the remaining 596 articles underwent screening at the title and abstract levels. Of these, 543 articles were excluded based on title or abstract, resulting in 53 studies selected for comprehensive full-text review to determine eligibility. Ultimately, 20 studies fulfilled the eligibility criteria and were included in our study,[8–27] and 33 studies

were excluded for various reasons (Table S4), including 1 study being excluded owing to a lack of total observation time[38] and 2 studies due to insufficient observation time.[39,40] Within the cohort of included studies, 16 studies presented data regarding the incidence of MACE among patients with PA who underwent adrenalectomy, 17 studies reported data on the incidence of MACE among patients with PA treated with MRA, and 3 studies presented data on the incidence of MACE among patients with PA who received either adrenalectomy or MRA treatment. Table 1 depicts the study design and characteristics of the subjects in the included studies. The studies were published between 2008 and 2024 with sample size ranging from 24 to 2516 patients per single arm population. There were 7 prospective[8,11,12,15,22,25,26] and 13 retrospective[9,10,13,14,16–21,23,24,27] cohort studies with the follow-up duration ranging from 1.0 to 12.0 years. Among the studies, 3 evaluated outcomes in a single-center,[8,10,12] whereas 17 followed a multicenter approach.[9,11,13–27] Additionally, 11 studies focused on Asian patients, 8 studies examined European patients, and 1 study investigated American patients. The mean age was 51.6 years and about half of total participants (48.1%) were male. There were 7 studies that reported posttreatment PRA,[10,14,20–23,27] with most of these studies being conducted after 2021.[20–23,27] The majority of studies indicated comparable baseline characteristics, such as age, sex, BMI, diabetes, SBP, DBP, serum potassium levels, plasma aldosterone concentration, and PRA. Nevertheless, there remained some discrepancies between single-arm populations. Table S5 presents studies that documented posttreatment SBP or DBP.

Quality Assessment

Table S6 depicts a summary of the methodological quality of included studies. Among the 20 studies included in our analysis, 19 studies were assigned a maximum of 5 stars. The study conducted by Turchi et al. was given a 4-star grade due to the lack of clear clarification of the definitions of cardiovascular risk.[12] Almost all of studies consistently obtained a 5-star rating, indicating a worthwhile level of quality in essential aspects.

Primary Outcomes

This study aims to explore the incidence of MACE post treatment with adrenalectomy or MRA among patients with PA. The definition of MACE varied throughout the 20 studies (Table 1). The composite MACE in most studies encompassed CAD, stroke, HF, or arrhythmia. Cardiovascular death was assessed in six studies.[9,15,19,24–26] Among the 16 927 samples in the data set, the incidence rate of MACE post treatment among patients with PA was estimated to be 2.20/100 patient-years, with a 95% CI from 1.70 to 2.80/100 patient-years (Figure 1).[8–27] There was a significant heterogeneity within these studies (I^2=94%, τ^2=0.534, P<0.01). Using GEE Poisson regression with an exchangeable correlation structure, the incidence rate of MACE among treated patients with PA was 3.00 per 100 patient-years (95% CI: 2.90–3.16/100 patient-years). The differences in the estimated average incidence rates between these two models arise from fundamental differences in the model assumption and weighting mechanisms. The random-effects model assigned higher weights to small studies, thereby increasing the influence of smaller studies on the pooled estimate. In contrast, the GEE model estimated a population average incidence rate. As many small studies in our meta-analysis reported very low incidence rates, the random-effects model yielded a lower estimate of the average incidence rate than the GEE model. Moreover, we conducted a meta-analysis including only studies with exclusive outcomes of MACE encompassing cardiovascular death, CAD, stroke, and HF. The results enrolling 16 studies revealed that the incidence of MACE among patients with PA after treatment was 1.60/100 patient-years (95% CI, 1.20–2.20/100 patient-years, Figure S4). The pooled incidence rate of MACE among patients with non-PA hypertension extracted from the enrolled studies was 1.20/100 patient-years (95% CI, 0.70–2.10/100 patient-years, Figure S5).

Secondary Outcomes

In random-effects models, we calculated the incidence rate of secondary outcomes including cardiovascular death (0.20/100 patient-years [95% CI, 0.10–0.50/100 patient-years]), CAD (0.50/100 patient-years [95% CI, 0.30–0.90/100 patient-years]), stroke (0.70/100 patient-years [95% CI, 0.40–1.30/100 patient-years]), HF (0.60/100 patient-years [95% CI, 0.40–1.00/100 patient-years]), and arrhythmia (0.70/100 patient-years [95% CI, 0.40–1.10/100 patient-years]) among patients with PA after adrenalectomy or MRA treatment (Figure S6). The heterogeneities in these secondary outcomes assessments were high with I^2 ranging from 74% to 96%.

Subgroup Analyses

Given the observed heterogeneity among the included studies, a detailed subgroup analysis was performed, considering the baseline characteristics, as depicted in Figure 2. The incidence rate of MACE following treatment was 1.80/100 patient-years (95% CI, 1.00–2.50/100 patient-years) for patients with PA who were followed up <5 years. The incidence rate of MACE after therapy rose to 3.40/100 patient-years (95% CI, 2.40–4.40/100 patient-years) among those with a follow-up

Table 1. Characteristics of Included Studies

Study, country	Study design, follow-up period, y	Outcome definitions	Treatment modality (n)	Age, y*	Male sex, %	BMI, kg/m^2 *	Diabetes, %	SBP/DBP, mm Hg*	K, meq/L	PAC/PRA‡, ng/dL/ng/mL/h	eGFR, mL/min per 1.73 m^2*	Posttreatment PRA, ng/mL/h
Catena (2008)[8] Italy	Prospective 7.4*	CAD, stroke, arrhythmia	Adrenalectomy (24)	54.0	72.4	28.7	NR	167/103	3.2*	26.0*/NR	NR	NR
			MRA (30)	52.0	68.0	28.4	NR	166/103	3.3*	23.0*/NR	NR	NR
Reincke (2012)[9] Germany	Retrospective 5.2†	Cardiovascular death	Adrenalectomy or MRA (300)	50.0	61.3	28.0	13.7	168/99	3.2†	27.9†/0.2†	NR	NR
Mulatero (2013)[10] Italy	Retrospective 12.0†	CAD, stroke, HF, arrhythmia	Adrenalectomy (57)	45.0	57.9	25.8	1.8	158/97	3.3*	41.7†/0.2†	NR	2.1†
			MRA (213)	43.0	59.4	27.1	3.8	153/96	3.9*	28.5†/0.2†	NR	NR
Rossi (2013)[11] Italy	Prospective 3.0†	MACE	Adrenalectomy or MRA (180)	51.1	57.0	26.5	NR	164/100	3.3*	37.4†/0.53†	NR	NR
Turchi (2014)[12] Italy	Prospective 3.7*	MACE	Adrenalectomy or MRA (66)	51.0	50.0	27.1	NR	154/96	3.7*	50.1*/0.4†	NR	NR
Wu (2016)[13] Taiwan	Retrospective 5.8*	MACE	Adrenalectomy (846)	46.6	43.6	NR	15.7	NR	NR	NR	NR	NR
			MRA (2516)	52.9	47.2	NR	24.0	NR	NR	NR	NR	NR
Hundemer (2018)[14] United States	Retrospective 7.0*	CAD, stroke, HF, AF	Adrenalectomy (205)	50.0	58.0	30.6	13.0	133/76	3.6*	42.0†/NR	82.2	NR
			MRA (602)	58.0	55.0	31.1	19.6	137/81	3.6*	23.0†/NR	79.2	NR
Rossi (2018)[15] Italy	Prospective 11.8†	Cardiovascular death, CAD, stroke, HF, arrhythmia	Adrenalectomy (41)	50.9	56.1	27.8	NR	158/98	3.5†	25.4†/0.26†	85.0	NR
			MRA (66)	49.6	59.1	27.2	NR	154/99	3.8†	21.5†/0.32†	86.0	NR
Huang (2019)[16] Taiwan	Retrospective 5.2*	HF	Adrenalectomy (605)	47.0	42.0	NR	9.6	NR	NR	NR	NR	NR
			MRA (83)									
Chang (2020)[17] Taiwan	Retrospective 4.7*	Stroke	Adrenalectomy (799)	47.4	43.9	NR	9.6	NR	NR	NR	NR	NR
			MRA (2368)	52.5	46.1	NR	14.7	NR	NR	NR	NR	NR
Pan (2020)[18] Taiwan	Retrospective 4.5*	CAD, stroke, AF	Adrenalectomy (534)	51.8	46.4	NR	9	NR	NR	NR	NR	NR
			MRA (1668)		47.2	NR	13.8	NR	NR	NR	NR	NR
Kim (2021)[19] South Korea	Retrospective 5.0†	Cardiovascular death, CAD, stroke, HF, AF	Adrenalectomy (755)	46.7	42.5	NR	12.6	NR	NR	NR	NR	NR
			MRA (663)	51.3	50.7	NR	22.5	NR	NR	NR	NR	NR

(*Continued*)

Table 1. Continued

Study, country	Study design, follow-up period, y	Outcome definitions	Treatment modality (n)	Age, y*	Male sex, %	BMI, kg/m² *	Diabetes, %	SBP/DBP, mm Hg*	K, meq/L	PAC/PRA‡, ng/dL/ng/mL/h	eGFR, mL/min per 1.73 m²*	Posttreatment PRA, ng/mL/h
Nakamaru (2021)[20] Japan	Retrospective 3.0*	CAD, stroke, HF, arrhythmia peripheral artery disease	Adrenalectomy (96)	67.0	61.0	23.7	NR	143/81	NR	28.1†/0.2†	67.4	0.7†
			MRA (57)	68.0	46.0	23.6	NR	142/81	NR	18.6†/0.2†	66.6	0.4†
			Adrenalectomy (526)	50.0	50.0	24.2	NR	141/88	NR	31.6†/0.3†	81.6	1.1†
			MRA (176)	53.0	62.0	25.4	NR	143/88	NR	19.5†/0.3†	76.4	0.8†
Puar (2021)[21] Singapore	Retrospective 5.7*	CAD, stroke, HF, AF	Adrenalectomy (86)	51.0	57.0	26.1	22.1	152/89	2.5*	37.7†/0.28†	90.7	1.4†
			MRA (68)	55.0	67.6	26.0	33.8	152/86	2.5*	38.3†/0.31†	83.8	1.6†
Wu (2021)[22] Taiwan	Prospective 6.3*	CAD, stroke, HF, AF	Adrenalectomy (545)	50.8	43.7	25.6	15.4	156/93	3.5*	46.3*/0.93*	NR	3.3*
			MRA (313)	58.1	46.3	25.5	16.6	150/88	3.8*	47.9*/1.08*	NR	2.9*
Araujo-Castro (2022)[23] Spain	Retrospective 2.0†	CAD, HF, AF, ventricular arrhythmia, VHD	Adrenalectomy (100)	52.7	45.4	29.1	15.0	150/92	3.5*	38.7*/0.5*	90.7	1.6*
			MRA (168)	54.7	58.3	30.0	19.6	151/91	3.7*	36.5*/0.5*	83.5	2.1*
Nomura (2022)[24] Japan	Retrospective 3.0†	Cardiovascular death, CAD, stroke, HF, AF	MRA (1115)	54.1	44.3	NR	12.0	141/87	NR	NR	NR	NR
Sheu (2023)[25] Taiwan	Prospective 5.7*	Cardiovascular death, CAD, stroke, HF	MRA (208)	54.2	41.4	24.8†	12.5	151/90	3.8*	41.7†/0.4†	91.4	NR
Chen (2024)[26] Taiwan	Prospective 5.0*	Cardiovascular death, CAD, stroke, HF, AF	Adrenalectomy (445)	50.5	55.1	25.3†	14.8	156/94	3.5*	45.8†/0.22†	90.7	NR
Ramírez (2024)[27] Spain	Retrospective 1.0†	CAD, HF, AF, ventricular arrhythmia, VHD	Adrenalectomy (275)	54.5	53.5	29.3	17.9	151/90	3.5*	51.0†/0.2†	89.0	1.94*
			MRA (160)	56.8	61.3	29.5	20.6	151/90	3.9*	34.4†/0.2†	84.0	2.45*

AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; K, serum potassium level; MACE, major adverse cardiovascular event; MRA, mineralocorticoid receptor antagonist; NR, not reported; PAC, plasma aldosterone concentration; PAD, peripheral artery disease; PRA, plasma renin activity; SBP, systolic blood pressure; and VHD, valvular heart disease.

Values are *mean, and †median.

‡To convert PRA (ng/mL per h) to direct renin concentration (mU/L), multiply by 12 for the commonly used automated direct renin concentration assay, and 8.2 for older methods.[34]

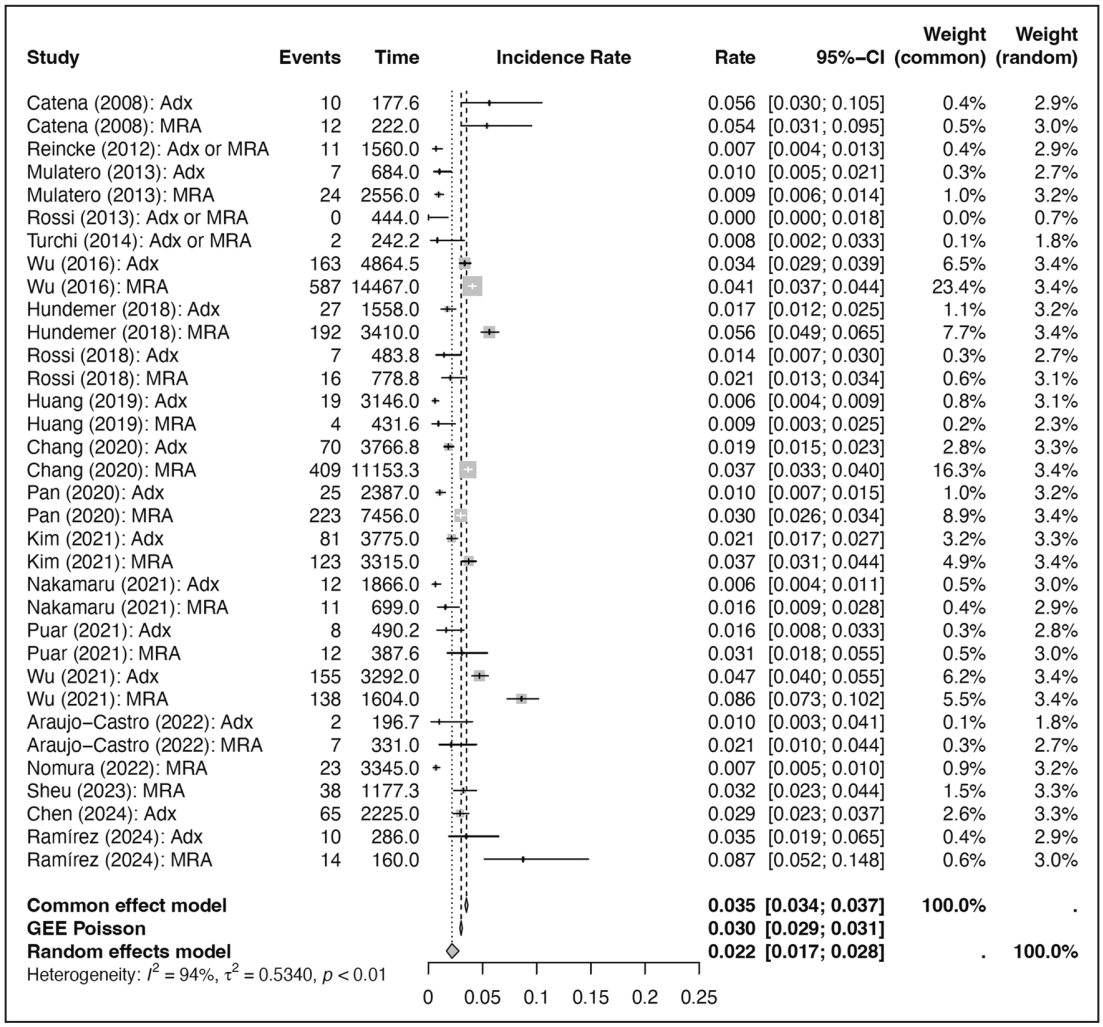

Figure 1. Forest plot illustrating the incidence of major adverse cardiovascular events following treatment among patients with primary aldosteronism.
Incidence rate: event/patient-year; Time: patient-year. GEE indicates generalized estimating equations; and MRA, mineralocorticoid receptor antagonist.

duration of 5 to 10 years. However, it decreased to 1.20/100 patient-years (95% CI, 0.80–1.70/100 patient-years) for those with a follow-up duration >10 years. Patients with PA after adrenalectomy had a lower posttreatment MACE incidence rate of 2.00/100 patient-years (95% CI, 1.40–2.60/100 patient-years) compared with those undergoing MRA treatment (3.30/100 patient-years [95% CI, 2.40–4.10/100 patient-years]; *P* for interaction=0.017). Patients with PA aged 50 years or older had a posttreatment MACE incidence rate of 3.10/100 patient-years (95% CI, 2.20–3.90/100 patient-years) whereas those <50 years old had a posttreatment MACE incidence rate of 1.70/100 patient-years (95% CI, 1.00–2.40/100 patient-years; *P* for interaction=0.024). Of note, a trend was observed suggesting that patients with PA with higher BMI or serum potassium levels ≤3.5 mmol/L had an increased incidence of MACE compared with those with lower BMI or serum potassium levels >3.5 mmol/L, although this association did not achieve statistical significance. Similarly, there was an observed trend indicating that patients with PA with posttreatment PRA levels between 1 and 2 ng/mL per hour had a lower incidence of MACE compared with those with PRA levels either <1 ng/mL per hour or >2 ng/mL per hour; however, this trend also did not reach statistical significance. The incidence rate of MACE was highest among American patients (3.20/100 patient-years [95% CI, 1.00–10.00/100 patient-years]) and lowest among Japanese patients (1.10/100 patient-years [95% CI, 0.50–2.40/100 patient-years]). However, these differences were not statistically significant. There was no significant difference in MACE occurrence between patients with PA with and without baseline cardiovascular disease. The

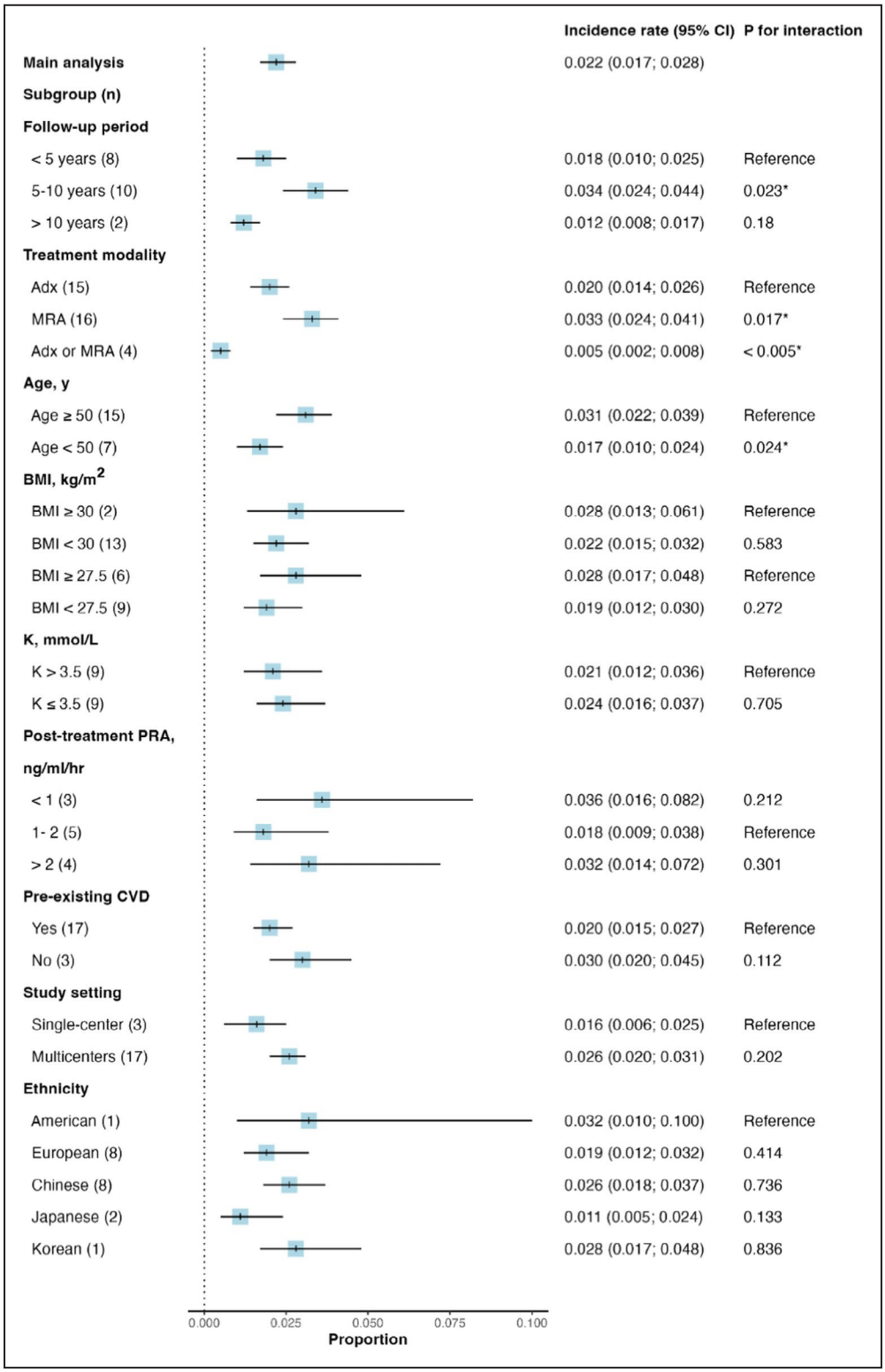

Figure 2. Subgroup analysis of the incidence of major adverse cardiovascular event following treatment among patients with primary aldosteronism.
Incidence rate: event/patient-year; n: number of enrolled studies. BMI indicates body mass index; CVD, cardiovascular disease; MRA, mineralocorticoid receptor antagonist; and PRA, plasma renin activity. *P<0.050.

Table 2. Meta-Regression Analysis for Major Adverse Cardiovascular Event Following Treatment Among Patients With Primary Aldosteronism

Moderators	Coefficient	SE	*Z* value	*P* value	95% CI
MACE					
Age	0.071	0.025	2.844	<0.001*	0.022 to 0.120
Male sex	0.010	0.017	0.592	0.554	−0.022 to 0.042
Diabetes	0.070	0.020	3.470	0.001*	0.030 to 0.109
K	0.387	0.476	0.813	0.416	−0.546 to 1.319
PAC	0.007	0.018	0.373	0.709	−0.003 to 0.042
PRA	1.283	0.683	1.877	0.061	−0.057 to 2.622

K indicates serum potassium level; MACE, major adverse cardiovascular event; PAC, plasma aldosterone concentration; and PRA, plasma renin activity.
*P<0.050.

incidence rate of secondary outcomes in patients with PA did not reveal any significant variations across different treatment groups, as illustrated in Figure S7.

Meta-Regression Analyses

We conducted a random-effect meta-regression to evaluate the interaction between each factor and the incidence of MACE among patients with PA after treatment (Table 2 and Table S7). Advanced age (coefficient: 0.071, P<0.001) and diabetes (coefficient: 0.070, P=0.001) were likely to be associated with a higher of development MACE among patients with PA after treatment. Other factors including follow-up period, sex, BMI, SBP, DBP, posttreatment SBP or DBP, the change in SBP or DBP, the serum potassium level, plasma aldosterone concentration, PRA, and estimated glomerular filtration rate did not significantly affect the incidence of MACE following treatment in the meta-regression analysis. Data on preexisting cardiovascular disease and posttreatment PRA in MRA-treated patients with PA were available from 4 studies, and data on the use of antihypertensive medications after treatment and posttreatment PRA in MRA-treated patients with PA were available from 3 studies. The results of meta-regression analyses revealed that CAD, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEis/ARBs), calcium channel blockers, diuretics, and beta blockers did not significantly affect the levels of therapeutic PRA (Tables S8 and S9). Due to limited sample sizes, the potential effects of HF and AF on therapeutic PRA could not be assessed. Seven studies were enrolled in the GEE Poisson regression for evaluation the relationship between the posttreatment PRA and the incidence of MACE among patients with PA after treatment (Table S10).[10,14,20–23,27] Figure 3 shows the results of the linear and nonlinear dose–response relationship. The sizes of the circles represent

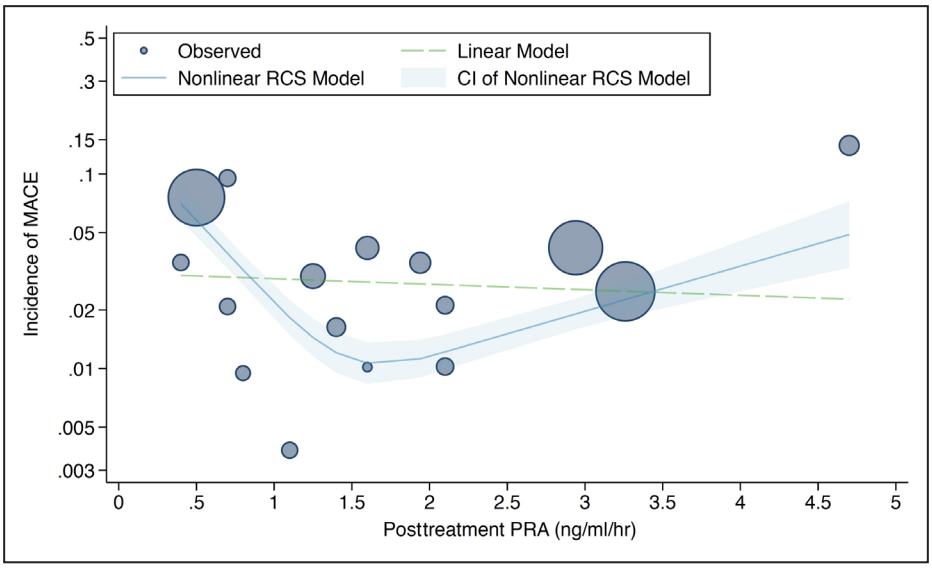

Figure 3. The linear and nonlinear associations of posttreatment plasma renin activity with the incidence of major adverse cardiovascular event.
MACE indicates major adverse cardiovascular event; PRA, plasma renin activity; and RCS, restricted cubic spline.

the statistical precision of each observation, calculated as the inversed variance of the incidence rate. The linear trend in the GEE Poisson model is not statistically significant (P=0.279). The nonlinear relationship between the posttreatment PRA and the incidence rate of posttreatment MACE showed the lowest MACE incidence risks at posttreatment PRA ≈1.0 to 2.0 ng/mL per hour ($P_{nonlinearity}$<0.001). We conducted a sensitivity analysis excluding the outlier study in the upper right corner and found a similar nonlinear trend (Figure S8). Table S11 shows the random-effect meta-regression assessing the interaction between covariates and the incidence of individual secondary outcomes post treatment. Advanced age had a significant increased risk of HF (coefficient: 0.113, P=0.033) and arrhythmia (coefficient: 0.119, P=0.005) in patients with PA after treatment. Moreover, diabetes substantially increased the likelihood of developing CAD (coefficient: 0.080, P=0.003), HF (coefficient: 0.099, P=0.016), and arrhythmia (coefficient: 0.070, P=0.018) in patients with PA after treatment. Follow-up period was associated with an increased risk of cardiovascular death (coefficient: 0.166, P=0.018).

DISCUSSION

Our studies revealed that the incidence rate of MACE among patients with PA after therapy, either adrenalectomy or MRA treatment, was 2.20/100 patient-years (95% CI, 1.70–2.80/100 patient-years), which is higher than that observed in patients with non-PA hypertension. Furthermore, patients with PA after adrenalectomy had a lower risk of MACE occurrence compared with those undergoing MRA treatment. Advanced age and diabetes were associated with a higher risk of MACE. There was a significant U-shaped relationship between posttreatment PRA and the incidence rate of MACE among patients with PA, with the lowest MACE incidence rates at posttreatment PRA levels of 1.0 to 2.0 ng/mL per hour.

Patients with PA have an increased risk of cardiovascular diseases attributed by overproduction of aldosterone, which leads to insulin resistance, mineralocorticoid receptor overactivity, endothelial dysfunction, and vascular and cardiac remodeling.[3,10,41] Additionally, PA is associated with a higher prevalence of metabolic comorbidities, such as diabetes and obstructive sleep apnea, both of which contribute to cardiovascular complications.[42,43] There are studies proposing that myocardial fibrosis or left ventricular dysfunction in patients with PA can be rescued via treatment either adrenalectomy or MRA.[44,45] However, the influence of PA therapy on the incidence rate of MACE among patients with PA is still unclear. Our findings indicated that the incidence rate of MACE in patients with PA who received treatment was comparable to but still higher than that observed in patients with non-PA hypertension. This elevated risk may be partly due to clinical guidance, which recommended screening for PA in patients with hypertension-mediated organ damage, thereby selecting a cohort with inherently higher baseline cardiovascular risk compared with those with non-PA hypertension.[34,46] As a result, although PA is a common cause of hypertension, it is often underdiagnosed, with cases typically detected only in advanced stages after significant comorbidities have developed.[47] Additionally, suboptimal management of PA, such as inadequate dosing of MRA, may reduce the effectiveness of cardiovascular risk reduction post treatment. These factors may explain our findings. Nevertheless, these findings provide additional evidence supporting the current guidelines recommending screening for PA in all adults with confirmed hypertension, as well as treatments to reduce the risk of cardiovascular diseases in patients with PA.[6,48]

The influence of treatment modality, either adrenalectomy or MRA treatment on the incidence rate of posttreatment MACE in patients with PA remains inconclusive. One prospective study conducted by Wu et al. found that patients with PA after adrenalectomy had a lower incidence of cardiovascular outcomes and all-cause mortality compared with those receiving MRA treatment.[22] Possible factors related to the suboptimal cardiovascular outcomes among patients with PA undergoing MRA treatment may include insufficient MRA dose leading to sustained mineralocorticoids receptor overactivation.[14] In addition, patients with PA who underwent adrenalectomy were generally younger than those undergoing MRA therapy, which could confound the interpretation of treatment effects.[20] The co-secretion of mineralocorticoid and glucocorticoid, which is common in patients with PA and associated with an elevated metabolic risk, might be mitigated through adrenalectomy.[49] Certain patients with unilateral PA who are unwilling or unable to receive adrenalectomy would be administered MRA treatment, which may compromise cardiovascular outcomes associated with MRA treatment. Our study, in alignment with previous studies, found that patients with PA who were treated with adrenalectomy had a lower risk of posttreatment MACE compared with those treated with MRA. However, it is important to note that there are currently no randomized controlled trials demonstrating the superiority of adrenalectomy over medical treatment. Based on these findings, it is recommended to consider titrating MRA dose, surgery or alternative treatments, such as adrenal ablation, for patients with PA who present poor response to MRA treatment. New research is also exploring the effects of nonsteroidal MRAs on patients with PA, the development of aldosterone synthase inhibitors, and personalized

pharmacotherapy for PA targeting calcium signaling.[50,51] Nevertheless, a recent study by Cohen et al. found that there was no significant difference in cardiovascular outcomes between adrenalectomy and MRA treatment for patients with PA and chronic kidney disease. This could be due to the permanent kidney and cardiac fibrosis caused by chronic mineralocorticoid receptor overactivation in this population, which could not be reversed even after diminishing aldosterone excess with adrenalectomy.[52] All these findings underscore the necessity for further research, with robust prospective randomized controlled trials to definitively compare the outcomes of adrenalectomy and MRA treatment in patients with PA.

Our analysis found that the risk of MACE in patients with PA is lower in follow-up periods exceeding 10 years compared with the 5- to 10-year period. This is likely due to the limited number of studies and smaller sample sizes in longer follow-up periods, which reduces statistical power to detect differences or trends, leading to an underestimation of the true incidence. However, the incidence of MACE is higher during the 5 to 10 years of follow-up than in the first 5 years, possibly due to the accumulation of additional cardiovascular risk factors, such as diabetes, dyslipidemia, or chronic kidney disease, which can compound the risk of MACE.[4] Additionally, the initial benefits of PA treatment in reducing cardiovascular risk may diminish over time, especially if patients experience incomplete biochemical remission or poor long-term adherence to therapy.[53] These findings highlight the need for further research with larger cohorts and longer follow-up to validate these trends. Age was associated with an increased risk of MACE occurrence among patients with PA after treatment shown in the subgroup and meta-regression analysis. The Primary Aldosteronism Surgery Outcomes (PASO) study indicated that older patients with PA had a lower likelihood of achieving complete clinical success and clinical benefit after adrenalectomy.[54] Among older patients diagnosed with PA, it is likely that they have endured a prolonged duration of hypertension or have remained undiagnosed with PA for many years. This addition captures the idea that some patients may have been misclassified and therefore not correctly diagnosed with PA for an extended period. These adverse conditions may explain our findings that age was associated with posttreatment MACE occurrence.

The coexistence of diabetes and PA is likely to have further adverse consequences on the cardiovascular system, given that both diabetes and PA independently contribute to poorer cardiovascular outcomes.[55] A study conducted by Tsai et al. indicated that the presence of diabetes in patients with PA was independently associated with poor baseline condition and less improvement of arterial stiffness after PA-specific treatment, a reliable approach to predict cardiovascular events.[56] Our finding that diabetes was independently associated with the occurrence of posttreatment MACE in patients with PA provides further evidence supporting the previous finding.

A growing body of studies has explored the association between the posttreatment renin level and the prognosis of patients with PA after treatment. Several studies suggested that optimal MRA treatment to reverse renin suppression improved hypertrophy and function of left ventricle,[28,29] as well as arterial stiffness.[57] Furthermore, the reversal of renin suppression had been associated with lower risks of MACE, AF, and mortality.[14,22,58] It is suggested that an increase in renin levels in patients with PA after treatment indicates a reversal of the underlying pathophysiology of PA.[14,31] However, the study conducted by Ramírez et al. found that patients with PA who were treated with MRA, with or without renin suppression, had comparable cardiovascular, kidney, and metabolic outcomes.[27] Nomura et al.'s study suggests that significant renin changes after MRA treatment in patients with PA do not necessarily predict better cardiovascular outcomes.[24] In the study, we observed a significant U-shaped relationship between the posttreatment PRA and the incidence rate of MACE among patients with PA after treatment. The incidence of MACE was lowest when the posttreatment PRA levels were between 1.0 and 2.0 ng/mL per hour. Vaidya et al. hypothesized that when renin levels increase, there is a corresponding increase in the risk of hyperkalemia, hypotension, and renal hypoperfusion. In line with our result. they also proposed that an unsuppressed PRA level between 1.0 to 2.0 ng/mL per hour is the optimal range to target for patients with PA who received MRA treatment.[30,31] Potential reasons for the increased risk of MACE in patients with PA after treatment and exhibited persistently low posttreatment renin levels may result from patients who underwent adrenalectomy still exhibit suppressed renin if aldosterone-producing micronodules are present in the contralateral adrenal gland. Given that aldosterone-producing micronodules are classified as nonneoplastic/hyperplastic and exhibit a nonclassical pattern, undetected aldosterone-producing micronodules in the nonresected adrenal gland could continue to produce aldosterone autonomously, maintaining low renin levels post adrenalectomy.[59] Alternatively, certain patients with a high cardiovascular risk profile may be on beta blockers, which could also contribute to suppressed renin levels. On the other hand, possible factors for an elevated risk of MACE in patients with higher posttreatment renin levels include inadequate MRA dosing or the use of ACEis/ARBss in high-risk patients with cardiovascular issues, which may lead to increased renin levels by disrupting the negative feedback mechanism of angiotensin II on renin release.

Given the limited sample size, our meta-regression analysis results did not reveal a significant effect of ACEis/ARBs and beta blockers on therapeutic PRA levels. Nonetheless, the wide CIs—attributable to the limited sample size, especially at elevated renin activity levels, and the persistence of only a similar nonlinear trend in the sensitivity analysis after excluding the outlier study in the upper right corner—emphasize that these findings should be interpreted with caution. Further investigations are needed to validate the discovery.

Strengths and Limitations

This meta-analysis provides the most up-to-date insights into the incidence of MACE in patients with PA after treatment. A key strength of this study is the identification of a U-shaped relationship between posttreatment PRA and MACE incidence, suggesting the potential importance of maintaining PRA within an optimal range to minimize cardiovascular risks. Additionally, the study reveals that advanced age and diabetes are significant factors associated with increased posttreatment MACE risk in patientswith PA. These findings underscore the importance of PA-specific treatment strategies to reduce MACE risk, while also revealing that MACE incidence remains elevated compared with that in treated non-PA hypertension, which warrants continued investigation and clinical vigilance.

Nevertheless, several limitations warrant careful interpretation of our findings. First, the absence of randomized controlled trials in this study led to variations in protocols for defining PA and selecting treatment strategies, such as adrenalectomy or MRA, across studies, which reflects real-world clinical practices. This variation could result in potential misclassification, particularly for patients with bilateral PA who may have been inaccurately considered candidates for surgery, potentially impacting the accuracy and comparability of our findings. Second, the studies varied in follow-up duration, potentially leading to length time bias. To mitigate the potential bias, we conducted subgroup analysis based on follow-up duration and assessed the effect of follow-up duration in meta-regression analyses. Third, caution is warranted when interpreting arrhythmia as a secondary outcome, as this study focused on the incidence of MACE in patients with PA after treatment. Therefore, studies that exclusively investigated AF without broader cardiovascular outcomes were not included, which may have limited the scope of arrhythmia data analyzed. Fourth, the incidence rate of MACE in patients with non-PA hypertension was derived from studies identified using a search strategy centered on PA, posttreatment status, and MACE incidence. As these studies were not specifically designed to assess populations with non-PA hypertension, this approach may introduce potential selection bias. Fifth, in examining the relationship between posttreatment PRA and MACE in patients with PA, data availability was limited, with only 7 studies ultimately providing data on posttreatment PRA, covering 16 PRA levels in the GEE Poisson regression analysis. This limited sample size means that subgroup analyses of posttreatment PRA revealed only a trend of association, warranting caution in interpretation and highlighting the need for further research. Sixth, both single-arm and comparative studies were included in this meta-analysis, which may have increased heterogeneity. A sensitivity analysis including only comparative studies was conducted, and the results were consistent with the overall findings of our study (Figure S9). Finally, only 1 included study stratified results by biochemical cure status, limiting our ability to assess its impact on long-term outcomes in patients with PA.[22]

CONCLUSIONS

In summary, the incidence of MACE following treatment for patients with PA, either through adrenalectomy or administration of MRA, was observed to be approximately 2.20 per 100 patient-years, which was higher than that for patients with non-PA hypertension. Maintaining posttreatment PRA between 1.0 and 2.0 ng/mL per hour may help reduce cardiovascular risk.

ARTICLE INFORMATION

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Affiliations

Division of Nephrology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (C.-W.H.); School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan (C.-W.H.); Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan (C.-W.H.); Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital Hsinchu Branch, Hsinchu, Taiwan (T.-Y.H.); Division of Nephrology, Department of Internal Medicine, China Medical University Hsinchu Hospital, Zhubei, Taiwan (Y.-F.Y.); College of Medicine (L.-Y.C.) and Institute of Health Data Analytics and Statistics, College of Public Health (Y.-K.T.), National Taiwan University, Taipei, Taiwan; Department of Internal Medicine, Primary Aldosteronism Center, National Taiwan University Hospital, Taipei, Taiwan (V.-C.W.); Division of Nephrology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan (J.-Y.C.); and Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan (J-Y.C.).

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S11
Figures S1–S9
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