Journal of the American Heart Association

ORIGINAL RESEARCH

Heightened Cardiovascular Risk in Hypertension Associated With Renin-Independent Aldosteronism Versus Renin-Dependent Aldosteronism: A Collaborative Study

Jinbo Hu, MD, PhD*; Hang Shen, MD*; Peiqi Huo, MD*; Jun Yang, MBBS, PhD; Peter J Fuller, MBBS, PhD; Kanran Wang, MD; Yi Yang, PhD; Linqiang Ma, MD, PhD; Qingfeng Cheng, MD, PhD; Lilin Gong, MD, PhD; Wenwen He, MD; Ting Luo, PhD; Mei Mei, MD, PhD; Yue Wang, MD, PhD; Zhipeng Du, MD; Rong Luo, MD; Jun Cai, MD, PhD; Qifu Li, MD, PhD; Ying Song, MD, PhD; Shumin Yang, MD, PhD

BACKGROUND: While both renin-dependent and renin-independent aldosterone secretion contribute to aldosteronism, their relative associations with cardiovascular disease (CVD) risk has not been investigated.

METHODS AND RESULTS: A total of 2909 participants from the FOS (Framingham Offspring Study) with baseline, serum aldosterone concentration, and plasma renin concentration who attended the sixth examination cycle and were followed up until 2014 and who were free of CVD were included. We further recruited 2612 hypertensive participants from the CONPASS (Chongqing Primary Aldosteronism Study). Captopril challenge test was performed to confirm renin-dependent or -independent aldosteronism in CONPASS. Among 1433 hypertensive subjects of FOS, when compared with those with serum aldosterone concentration <10 ng dL^{-1} (normal aldosterone), participants who had serum aldosterone concentration ≥10 ng dL^{-1} and plasma renin concentration ≤15 mIU L^{-1} (identified as renin-independent aldosteronism) showed a higher risk of CVD (hazard ratio, 1.40 [95% CI, 1.08–1.82]), while those who had serum aldosterone concentration ≥10 ng dL^{-1} and plasma renin concentration >15 mIU L^{-1} (identified as renin-dependent aldosteronism) showed an unchanged CVD risk. In CONPASS, renin-independent aldosteronism carried a significantly higher risk of CVD than normal aldosterone (odds ratio, 2.57 [95% CI, 1.13–5.86]), while the CVD risk remained unchanged in renin-dependent aldosteronism. Elevation of the urinary potassium-to-sodium excretion ratio, reflective of mineralocorticoid receptor activity, was only observed in participants with renin-independent aldosteronism.

CONCLUSIONS: Among patients with hypertension, renin-independent aldosteronism is more closely associated with CVD risk than renin-dependent aldosteronism.

Key Words: cardiovascular disease ■ hypertension ■ mineralocorticoid receptor activity ■ renin-dependent aldosteronism ■ renin-independent aldosteronism

Excess or inappropriate release of aldosterone activates the mineralocorticoid receptor (MR) to induce endothelial dysfunction and adverse cardiorenal remodeling.[1–4] Both renin-dependent and renin-independent aldosterone secretion contribute to aldosteronism.[5–7] It is widely known that inhibition

Correspondence to: Ying Song, MD, PhD, and Shumin Yang, MD, PhD, Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi St, Yuzhong District, Chongqing 400016, China. E-mail: shuiyunying@126.com; 443068494@qq.com

*J. Hu, H. Shen, and P. Huo are joint first authors.

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023082

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Renin-independent aldosteronism may confer a higher risk of cardiovascular disease than renin-dependent aldosteronism among patients with hypertension, likely because of an increase in mineralocorticoid activity.

What Are the Clinical Implications?

- More attention to the renin-independent aldosteronism may be required for interventions on the renin–angiotensin–aldosterone system and cardiovascular disease prevention.

Nonstandard Abbreviations and Acronyms

CCT	captopril challenge test
CONPASS	Chongqing Primary Aldosteronism Study
FOS	Framingham Offspring Study
PAC	plasma aldosterone concentration
PRC	plasma renin concentration
SAC	serum aldosterone concentration

of renin-dependent aldosteronism, also recognized as an activated renin–angiotensin–aldosterone system,[5] confers cardiovascular benefits.[8–10] Subjects with renin-independent aldosteronism also exhibited a higher risk of cardiovascular diseases (CVD) than essential hypertension.[11] However, the risk of CVD in renin-independent compared with renin-dependent aldosteronism has not been systematically examined.

Previous data on the relationship between aldosterone, renin, and CVD were equivocal. In the general population of the FOS (Framingham Offspring Study), neither renin nor aldosterone was found to be associated with CVD incidence during a median of 7 years follow-up.[12,13] In contrast, the Jackson Heart Study showed that in a population of Black patients, either elevated baseline serum aldosterone concentration or plasma renin activity was associated with a higher risk of CVD after 12 years of follow-up.[14] In other studies, among participants who had a high risk of CVD or cardiovascular comorbidities, the effects of circulating aldosterone and renin on the incidence of CVD were contradictory between different cohorts.[15–23] These inconsistent results may be ascribed, at least partially, to the failure to distinguish between renin-independent and renin-dependent aldosteronism, as well as confounders of aldosterone and renin measurements such as medications and hypokalemia. A more recent study of 948 adults from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort who were not taking antihypertensive medications identified an association between aldosterone and risk of all-cause mortality when plasma renin activity was suppressed, but mortality caused by CVD was not evaluated.[24]

Here, using the 20-year longitudinal data from the FOS (exploration cohort), we compared the long-term risk of CVD in renin-dependent and renin-independent aldosteronism. In the cross-sectional analysis of the CONPASS (Chongqing Primary Aldosteronism Study), we enrolled hypertensive participants who were not taking interfering medications. The captopril challenge test (CCT), together with indirect measurements of MR activity, was conducted to distinguish the types of aldosteronism. We hypothesized that renin-independent aldosteronism would confer a higher risk of CVD compared with renin-dependent aldosteronism.

METHODS

Reproducible Research Statement

Study protocol and statistical code are available from Ying Song (e-mail: shuiyunying@126.com) or Shumin Yang (e-mail:443068494@qq.com).

Data Availability Statement

Data are available to approved people through written agreements with the authors and the data partner.

Study Population

The prospective cohort of the FOS has been evaluated since 1971 to 1975 with the study design previously published.[12,13,25] For the current analyses, FOS participants were included if they attended the sixth examination cycle (1995–1998, baseline) and were followed up until December 31, 2014; had serum aldosterone and plasma renin concentration measured at baseline; and had available medical records of baseline and follow-up cardiovascular events. For the analysis of CVD outcomes, subjects with a history of CVD at baseline were excluded. The institutional review board at the Boston Medical Center approved the FOS.

We used the database (2014–2020) of CONPASS (Chongqing Primary Aldosteronism Study) to perform cross-sectional analyses.[26–28] Participants of CONPASS were recruited from primary care and the largest tertiary referral center in Chongqing, China. The CONPASS recruited a wide range of patients, from those with newly diagnosed hypertension in primary

care,[26] to those with resistant hypertension in the referral center with the objectives of evaluating the prevalence of primary aldosteronism and long-term CVD outcomes in patients with primary aldosteronism and essential hypertension.[27–29] The CONPASS was approved by the ethical committee of Chongqing Medical University. Written informed consent was obtained from all study participants.

Physical Examination and Laboratory Measurement

Evaluations of physical examination, anthropometry, and other laboratory assessments were described in previous publications.[12,13,25–31] For FOS, plasma renin concentration (PRC) was measured with an immunochemiluminometric assay, and serum aldosterone concentration (SAC) was measured by radioimmunoassay. The antihypertensive medications were not withdrawn. In CONPASS, before the evaluation of renin and aldosterone concentration, all antihypertensive medications that can interfere with renin–angiotensin–aldosterone system activity were withdrawn. Hypokalemia was also corrected. Blood samples were collected in the morning. Plasma aldosterone concentration (PAC) and PRC were measured with automated chemiluminescence immunoassays. In the FOS, circulating renin and aldosterone measurement was performed in the sixth examination cycle, while MR activity was evaluated in ninth examination cycle. Detailed information is provided in Data S1.

Renin-Independent and Renin-Dependent Aldosteronism

In the FOS population, because no suppression test for aldosteronism was performed, renin-independent and renin-dependent aldosteronism was defined by SAC and PRC. Based on previous studies, circulating levels of aldosterone ≥10 ng·dL^{-1} (1 ng/dL = 27 pmol/l) were deemed to be aldosteronism,[5,32] and PRC ≤15 mU/L was considered as low-renin status.[7] Hence, in the FOS population, subjects with PRC ≤15 mU/L and SAC ≥10 ng·dL^{-1} were considered to have renin-independent aldosteronism, while subjects with PRC >15 mU/L and SAC ≥10 ng·dL^{-1} were considered to have renin-dependent aldosteronism. In the CONPASS population, aldosteronism was categorized by the PAC and the results of the CCT. Subjects with PAC <10 ng dL^{-1} before CCT were grouped as normal aldosterone. Subjects with PAC ≥10 ng dL^{-1} before and after the CCT were grouped as renin-independent aldosteronism, while these who had PAC ≥10 ng dL^{-1} before CCT and PAC <10 ng dL^{-1} after CCT were grouped as renin-dependent aldosteronism. Detailed methods on laboratory assessments are summarized in Data S2-Data S4.

Assessment of Outcomes

In FOS, the primary outcome in this analysis is the incidence of CVD, which included coronary heart disease, congestive heart failure, stroke, or transient ischemic attack. In CONPASS, CVD was confirmed if there was a definite manifestation of coronary heart disease, stroke (including transient ischemic attack) or congestive heart failure. The diagnosis of CVD was based on evaluations by at least 2 senior physicians from the First Affiliated Hospital of Chongqing Medical University. Detailed information on the assessment of CVD is provided in Data S5.

Statistical Analysis

Normality was assessed using the Kolmogorov–Smirnov test for continuous variables. Data were presented as means and 95% CI for normal distributed variables, median (interquartile range) for skewed normal distributed variables, and percentages for categorical variables. One-way ANOVA was conducted for the comparison of 3 groups, and least-square difference was used for post hoc multiple comparisons. Chi-square test was used to analyze the categorical data. All analyses were done using SPSS version 22.0 and Stata version 15.

In FOS, analyses were individually performed in the normotensive and hypertensive populations. Restricted cubic spline regression analyses were used to explore the relationship between continuous variables and CVD. The cubic spline curves were delineated on the basis of 4 equally spaced knots at 25th, 50th, 75th, and 95th percentiles. Estimated hazard ratios (HRs) with 95% CI were graphically represented. We used Cox proportional hazards regression to explore combined effects of different aldosteronism and blood pressure categories on the risk of CVD. We used multivariate models for controlling potential confounders, including age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, and sodium intake.

In CONPASS, we used restricted cubic spline regression analyses to explore the relationship between aldosterone production, MR activity, and CVD. Multivariable logistic-regression models were used to compute the associations among different forms of aldosteronism, MR activity, and CVD, in the whole group and matched subgroup. Estimated odds ratios (OR) with 95% CI are graphically represented. We conducted multiple linear regression analysis with MR activity as the dependent variable and aldosterone and other metabolic parameters as independent variables, respectively. Potential confounders enrolled in multivariable adjustments were the same as in the FOS.

RESULTS

Demographic and Biochemical Characteristics of Included Participants

The flow chart for the FOS and CONPASS cohorts is summarized in Figure 1. There were 1476 participants with nonhypertension and 1433 with hypertension included in FOS at baseline. The primary care and referral center cohorts from CONPASS consisted of 1020 and 1592 hypertensive participants, respectively. Characteristics of the study participants from FOS (baseline) and CONPASS are shown in Table 1. We also described baseline characteristics of FOS subjects who were classified as normal aldosterone, renin-dependent aldosteronism, and renin-independent aldosteronism in Table S1.

Aldosterone, Renin, and CVD Risk

Among 2909 participants from FOS who were free of CVD at baseline, 591 subjects developed CVD during a median of 18 years of follow-up. In the nonhypertension group, neither PRC nor SAC was associated with the risk of CVD. Among participants with hypertension, the risk of CVD was significantly increased with an increasing SAC (HR, 1.11 [95% CI, 1.02–1.21]), but not with an increasing PRC (HR, 0.97 [95% CI, 0.83–1.13]) (Table 2). Relationships between circulating concentrations of aldosterone and renin at baseline and long-term risk of CVD are further delineated in Figure S1. Among 2612 hypertensive participants from CONPASS, 160 participants (6.1%) had a history of CVD. The risk of CVD was similarly increased with increasing aldosterone (Figure S2A), but only in those with PRC <15 mU/L (Figure S2C) (Table 2).

Risk of CVD in Renin-Independent and Renin-Dependent Aldosteronism

In hypertensive participants of FOS, the risk of CVD was significantly increased with an increasing SAC in the setting of PRC ≤15 mIU/L (HR, 1.19 [95% CI, 1.02–1.39]), but not in the subset with PRC >15 mIU/L (HR, 1.09 [95% CI, 0.98–1.23]) (Table 2, Figure S3). Hypertensive participants classified as having renin-independent aldosteronism showed a higher risk of CVD when compared with these with normal-aldosterone levels, namely, SAC <10 ng dL^{-1} (HR, 1.40 [95% CI, 1.08–1.82]), while participants who were classified as renin-dependent aldosteronism did not show any increased risk of CVD (HR, 1.19 [95% CI, 0.89–1.60]) (Figure 2, Table 2).

In CONPASS, when compared with participants with normal aldosterone (PAC <10 ng dL^{-1}), the increased risk of CVD was observed in participants who had

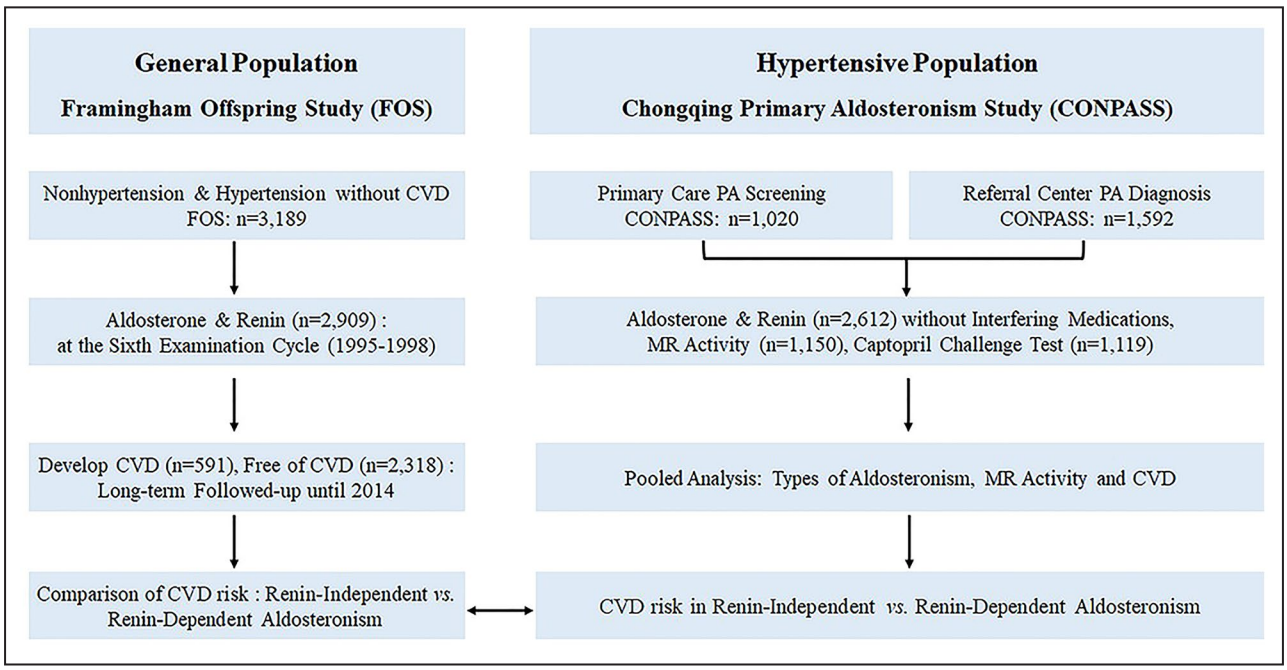


Figure 1. Study flow chart for FOS and CONPASS cohort.
The current study includes a prospective analysis of Framingham Offspring Study FOS (Framingham Offspring Study) and post hoc analyses of CONPASS (Chongqing Primary Aldosteronism Study). In FOS, participants who measured aldosterone and renin did not withdraw interfering medications, and no confirmatory test was performed to explore the cause of aldosteronism. In CONPASS, participants from primary care and referral center were included, and all participants were asked to withdraw interfering medications and correct the electrolyte imbalance (if comorbid) for screening. Participants with positive screening received confirmatory tests to demonstrate the cause of aldosteronism. CVD indicates cardiovascular diseases; PA, primary aldosteronism; and MR, mineralocorticoid receptor.

Table 1. Demographic, Clinical, and Biochemical Characteristics of Participants from FOS and CONPASS

	Participants from FOS		Participants from CONPASS	*P* value for hypertension‡
	Nonhypertension	Hypertension	Hypertension	
Total number	1476	1433	2612	…
Median age, y	54 (48, 61)	61 (54, 68)	50 (40, 59)	<0.001
Women, %	894 (61)	712 (50)	1295 (50)	0.974
Body mass index, kg/m^2	26 (23, 29)	28 (25, 32)	25 (23, 27)	<0.001
Average SBP, mm Hg	117 (109, 125)	138 (127, 149)	151 (140, 163)	<0.001
Average DBP, mm Hg	72 (67, 78)	80 (72, 85)	93 (84, 101)	<0.001
History of diabetes, %	39 (3)	208 (15)	313 (12)	0.024
Current smoker, no., %	252 (17)	180 (13)	634 (24)	<0.001
Alcohol user, no., %	1032 (70)	704 (49)	783 (30)	<0.001
Triglyceride, mg/dL	101 (71, 148.75)	129 (93, 184)	130 (89, 193)	0.032
HDL-c, mg/dL	52 (42, 63)	47 (39, 59)	48 (39, 57)	0.078
LDL-c, mg/dL	126 (102, 148)	126 (107, 148)	111 (89, 134)	<0.001
FPG, mg/dL	94 (88, 101)	100 (93, 111)	97 (88, 110)	<0.001
Aldosterone concentration, ng/dL*	10 (7, 14)	10 (7, 15)	12 (8, 20)	<0.001
Plasma renin concentration, mIU/L†	13 (8, 20)	12 (6, 24)	9 (3, 22)	<0.001

Data are expressed as median (interquartile range) and number (%). CONPASS indicates Chongqing Primary Aldosteronism Study; DBP, diastolic blood pressure; FOS, the Framingham Offspring Study; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*Serum aldosterone concentration was measured by radioimmunoassay in FOS; plasma aldosterone concentration was measured with automated chemiluminescence immunoassays in CONPASS.

†Plasma renin concentration was measured with an immunochemiluminometric assay in FOS, and with automated chemiluminescence immunoassays in CONPASS. For circulating aldosterone concentration, 1 ng/dL = 27 pmol/L.

‡*P* value for hypertension: comparison between hypertensive participants from FOS and CONPASS.

PRC ≤15 mU/L and PAC ≥10 ng dL^{-1} (OR, 1.59 [95% CI, 1.10–2.31]) or CCT-confirmed renin-independent aldosteronism (OR, 2.57 [95% CI, 1.13–5.86]), but not among participants who had PRC >15 mU/L and PAC≥10 ng dL^{-1} (OR, 1.43 [95% CI, 0.88–2.32]) or CCT-confirmed renin-dependent aldosteronism (OR, 1.78 [95% CI, 0.72–4.41]) (Table 2, Figure 3A through 3B).

Estimated MR Activity in Renin-Independent and Renin-Dependent Aldosteronism

Relationships among estimated MR activity (24-h urinary potassium-to-sodium excretion ratio), different subtypes of aldosteronism, and CVD risk are provided in Figure S4. In the CONPASS cohort, participants who had renin-independent aldosteronism showed a higher 24-hour urinary potassium-to-sodium excretion ratio than participants with renin-dependent aldosteronism (0.41±0.28 versus 0.33±0.31, *P*=0.001) or normal aldosterone (0.41±0.28 versus 0.23±0.11, *P*<0.001) (Figure 3C).

DISCUSSION

Using longitudinal data from FOS and cross-sectional data from CONPASS, we demonstrated that a higher level of aldosterone was associated with a higher incidence of CVD in hypertensive subjects but not in normotensive subjects. Importantly, hypertensive patients with renin-independent aldosteronism carried a higher risk of CVD than those with renin-dependent aldosteronism or normal-aldosterone levels. Moreover, a persistently increased estimated MR activity, as reflected by the 24-hour urinary potassium-to-sodium excretion ratio, may account for the increased CVD risk.

Our results extend the earlier observations on the relationship between aldosterone and CVD by differentiating the population with hypertension from those with normal blood pressure at baseline. Several previous studies demonstrated an association between aldosterone and CVD. The Jackson Heart Study,[14] Chronic Renal Insufficiency Cohort (CRIC),[21] and Ludwigshafen Risk and Cardiovascular Health (LURIC)[18] confirmed the potential detrimental effects of aldosterone on major adverse cardiovascular events. However, these studies did not evaluate the risk separately in normotensive and hypertensive patients. Our study identified that the risk of CVD was significantly higher with increasing aldosterone only in the group of patients with hypertension at baseline.

Table 2. Different Phenotypes of Aldosterone and Renin at Baseline and Long-Term Risk of Cardiovascular Diseases, Among Participants from FOS and Hypertensive Participants from CONPASS

	Nonhypertensive participants		Hypertensive participants	
	Incident/total	HR (95% CI)	Incident/total	HR/OR (95% CI)†
Continuous increment of aldosterone and renin in FOS				
1-SD increment of PRC	193/1476	1.00 (0.90, 1.12)	398/1433	0.97 (0.83, 1.13)
1-SD increment of SAC		0.90 (0.76, 1.07)		1.11 (1.02, 1.21)‡
Continuous increment of aldosterone, by renin phenotype in FOS				
1-SD increment of SAC when PRC >15 mIU/L	61/544	0.84 (0.61, 1.17)	141/562	1.09 (0.98, 1.23)
1-SD increment of SAC when PRC ≤15 mIU/L	132/932	0.97 (0.74, 1.26)	257/871	1.19 (1.02, 1.39)‡
Categories of aldosterone and renin phenotype in FOS*				
SAC <10 ng/dL	105/715	Reference	161/644	Reference
SAC ≥10 ng/dL and PRC >15 mIU/L	32/357	0.86 (0.61, 1.23)	93/357	1.19 (0.89, 1.60)
SAC≥10 ng/dL and PRC ≤15 mIU/L	56/404	1.16 (0.86, 1.56)	144/432	1.40 (1.08, 1.82)‡
Continuous increment of aldosterone and renin in CONPASS				
1-SD increment of PRC	…	…	160/2612	1.01 (0.88, 1.18)
1-SD increment of PAC		…		1.12 (1.01, 1.27)‡
Continuous increment of aldosterone, by renin phenotype in CONPASS				
1-SD increment of SAC when PRC >15 mIU/L	…	…	51/1002	1.04 (0.78, 1.54)
1-SD increment of SAC when PRC ≤15 mIU/L	…	…	109/1610	1.28 (1.10, 1.46)‡
Categories of aldosterone and renin phenotype in CONPASS*				
PAC<10 ng/dL	…	…	58/1080	Reference
PAC ≥10 ng/dL and PRC >15 mIU/L	…	…	28/568	1.43 (0.88, 2.32)
PAC ≥10 ng/dL and PRC ≤15 mIU/L	…	…	74/964	1.59 (1.10, 2.31)‡
Categories of aldosteronism in CONPASS§				
Normal aldosterone: PAC <10 ng/dL	…	…	58/1080	Reference
Confirmed renin-dependent aldosteronism by CCT	…	…	24/575	1.78 (0.72, 4.41)
Confirmed renin-independent aldosteronism by CCT	…	…	78/957	2.57 (1.13, 5.86)‡

All of these effects are based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, and sodium status. CCT indicates captopril challenge test; CONPASS, Chongqing Primary Aldosteronism Study; FOS, Framingham Offspring Study; HR, hazard ratio; OR, odds ratio; PAC, plasma aldosterone concentration (ng/dL); PRC, plasma renin concentration (mIU/L); and SAC, serum aldosterone concentration (ng/dL). For SAC, 1 ng/dL = 27 pmol/L.

*SAC ≥10 ng dL^{-1} was suspected as aldosteronism. PRC ≤15 mU/L was considered as low-renin status. Subjects with PRC ≤15 mU/L and SAC ≥10 ng dL^{-1} were considered as renin-independent aldosteronism, and subjects with PRC >15 mU/L and SAC ≥10 ng dL^{-1} were considered as renin-dependent aldosteronism.

†HR/OR (95% CI): HR (95% CI) for FOS, OR (95% CI) for CONPASS.

‡*P* value was <0.05.

§PAC <10 ng dL^{-1} was considered as normal aldosterone. Subjects with PAC ≥10 ng dL^{-1} at screening and unsuppressed aldosterone secretion in the captopril challenge test (defined as PAC ≥10 ng dL^{-1} after the test) were confirmed as renin-independent aldosteronism, while subjects with PAC ≥10 ng dL^{-1} and suppressed aldosterone secretion in CCT (defined as PAC <10 ng dL^{-1} after the test) were confirmed as renin-dependent aldosteronism.

The excess secretion of aldosterone, also known as aldosteronism, is often classified into renin-independent and renin-dependent.[5,33] Physiologically, renin-dependent aldosterone secretion is activated in response to intravascular volume depletion such as hypovolemia and renal hypoperfusion, while renin-independent aldosterone secretion is secondary to extracellular hyperkalemia.[5] Pathologically, renin-dependent aldosteronism (also recognized as renin–angiotensin–aldosterone system activation), characterized by high levels of renin and aldosterone, was associated with metabolic disorders and vascular injuries.[5,34] In contrast, renin-independent aldosteronism,

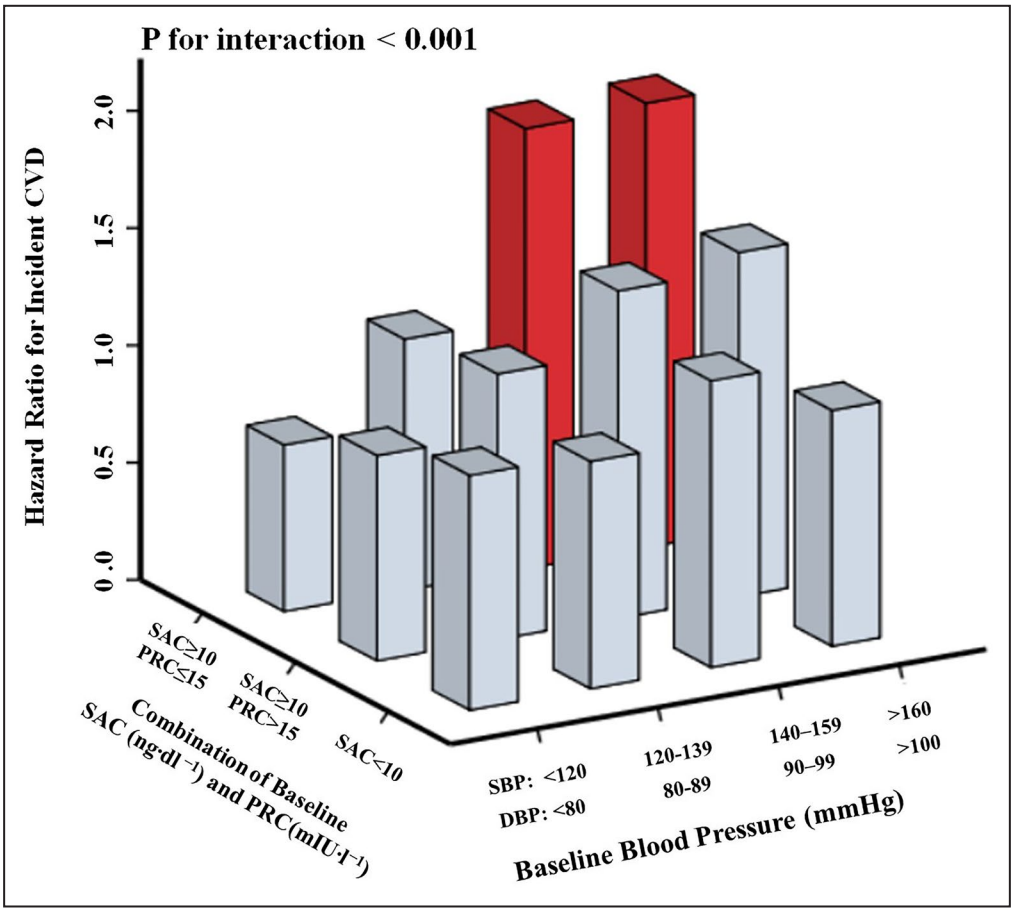


Figure 2. Categories of aldosterone and renin phenotype at baseline and long-term risk of cardiovascular diseases, according to classifications of blood pressure in the whole group of FOS (Framingham Offspring Study).

Serum aldosterone concentration (SAC) ≥10 ng dL^{-1} was suspected as aldosteronism; plasma renin concentration (PRC) ≤15 mU/L was considered as low-renin status; subjects with PRC ≤15 mU/L and SAC ≥10 ng dL^{-1} were classified as renin-independent aldosteronism, and subjects with PRC >15 mU/L and SAC ≥10 ng dL^{-1} were classified as renin-dependent aldosteronism. Baseline blood pressure was stratified on the basis of definitions for normotension, prehypertension, and stages 1–3 of hypertension. For SAC, 1 ng/dL = 27 pmol/L. All of these effects are based on the multivariate model, which adjusted for age, sex, body mass index, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, and sodium status. Columns colored in red indicate that the false discovery rate is <0.05. CVD indicates cardiovascular disease; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

defined as increased aldosterone production with a suppressed renin level, ranges from subtle autonomous aldosterone secretion to overt aldosteronism caused by bilateral adrenal hyperplasia or aldosterone-producing adenomas.[5]

It is widely explored that renin-independent aldosteronism is associated with an increased risk for hypertension,[3,25,35] which is an important risk factor of CVD. However, we are unaware of previous studies that directly compare the associations of renin-dependent and renin-independent aldosteronism with the risk of CVD, although they were individually evaluated in observational and interventional studies among varied populations. In the general population of 883 Japanese, an increased risk of stroke incidence was observed with each 1-SD increase in the aldosterone-to-renin ratio, which is typically elevated in renin-independent aldosteronism.[36] In another cohort of 125 patients with hypertension, a high level of aldosterone-to-renin ratio carried a 2.7-fold higher risk of CVD than a low aldosterone-to-renin ratio.[20] However, these studies had relatively limited sample size and did not segregate by aldosterone or renin level to compare the effects of renin-dependent and renin-independent aldosteronism on CVD risk. Beyond these observational studies, results from double-blind randomized clinical trials offer clues to the cardiovascular effects of renin-dependent and renin-independent aldosteronism: aliskiren, a direct

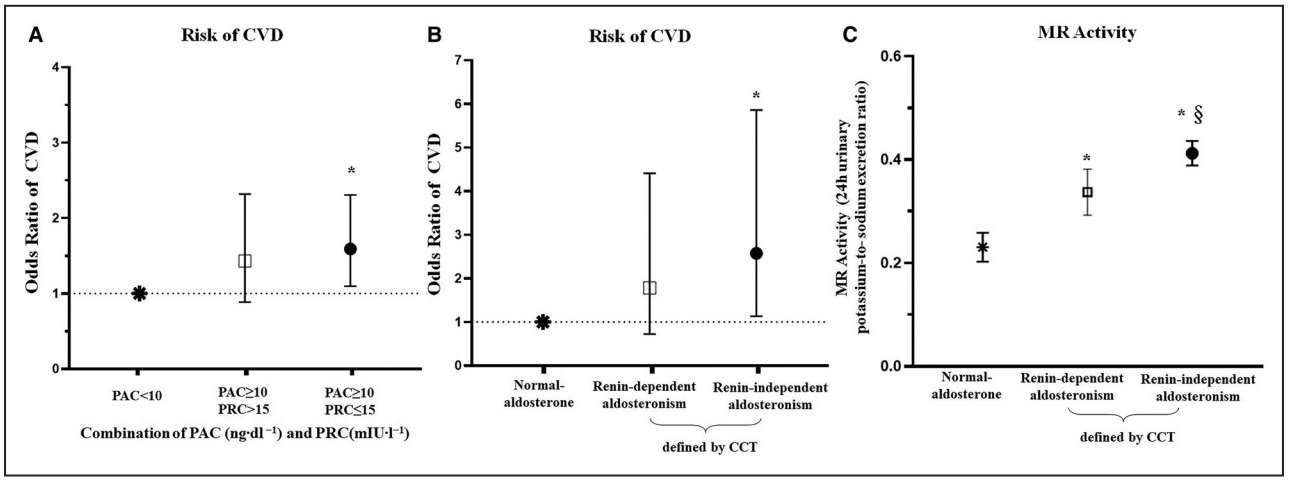


Figure 3. Different types of aldosteronism and risk of cardiovascular diseases (CVD) or mineralocorticoid receptor (MR) activity, among hypertensive participants from CONPASS.

For PAC, 1 ng/dL = 27 pmol/L. **A**, PAC <10 ng dL^{-1} was classified as normal aldosterone; PAC ≥10 ng dL^{-1} was classified as aldosteronism; PRC ≤15 mU/L was classified as low-renin status. Subjects with PRC ≤15 mU/L and PAC ≥10 ng dL^{-1} were classified as renin-independent aldosteronism, and subjects with PRC >15 mU/L and PAC ≥10 ng dL^{-1} were classified as renin-dependent aldosteronism. **B,** Shows the odd ratios and 95% CIs of CVD for renin-dependent or renin-independent aldosteronism as determined by the captopril challenge test (CCT). PAC <10 ng dL^{-1} was considered as normal aldosterone. Subjects with PAC ≥10 ng dL^{-1} at screening and unsuppressed aldosterone secretion in the CCT (defined as PAC ≥10 ng dL^{-1} after the test) were confirmed as renin-independent aldosteronism, while subjects with PAC ≥10 ng dL^{-1} and suppressed aldosterone secretion in CCT (defined as PAC <10 ng dL^{-1} after the test) were confirmed as renin-dependent aldosteronism. All of these effects were based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, and sodium status. **C,** Further comparison of the MR activity across 3 groups in the CONPASS (Chongqing Primary Aldosteronism Study). PAC indicates plasma aldosterone concentration; and PRC, plasma renin concentration. *P value <0.05 when compared with subjects with normal aldosterone, §P value <0.05 when compared with subjects with renin-dependent aldosteronism. P value <0.05 was considered as significantly different.

renin inhibitor, was not associated with improved cardiovascular outcomes[37–40]; in contrast, MR antagonists, including eplerenone and finerenone, have been shown to be associated with lower risk of CVD.[41–43] Although these randomized clinical trials were not performed in patients with hypertension, the observational evidence and indirect comparisons of renin inhibitor versus MR antagonists suggest that renin-independent aldosteronism exerts more detrimental cardiovascular effects than renin-dependent aldosteronism. In the current analyses of FOS, among hypertensive subjects, renin-independent aldosteronism was associated with a 1.4-fold higher CVD risk compared with normal aldosterone, while renin-dependent aldosteronism was not associated with an increased risk of incident CVD. Moreover, these findings were consistent with the cross-sectional data from CONPASS, in which renin-independent aldosteronism was confirmed using the CCT without the interference of medications and hypokalemia.

One explanation for renin-independent aldosteronism promoting CVD is the enhanced aldosterone-induced MR activity. Among normotensive persons from the MESA study, higher aldosterone concentrations were associated with increased estimated MR activity only when plasma renin activity was suppressed to ≤0.50 μg/L per hour.[3] Our cross-sectional analysis of CONPASS, when adjusted for confounding factors in a multiple regression analysis, indicated that a 1-unit increment in PAC was associated with a significantly higher level of MR activity in renin-independent aldosteronism, but not renin-dependent aldosteronism. Moreover, in CONPASS, we observed an increased OR of CVD with a higher MR activity (Figure S4A), and only hypertensive subjects with combined renin-independent aldosteronism and high MR activity exhibited significantly higher risk of CVD (Figure S4B). Another explanation for the relationship between renin-independent aldosteronism and CVD is that low renin is a sensitive marker of MR activity. In patients with primary aldosteronism treated with MR antagonists, those who had a plasma renin activity ≥1 μg/L per hour did not exhibit an increased CVD risk, while patients with a suppressed plasma renin activity (<1 μg/L per hour) showed a 2.8-fold higher CVD risk than essential hypertension.[44] A low renin in the context of an inappropriate or elevated aldosterone is therefore reflective of the magnitude of MR activity and predictive of incident cardiovascular events over time.

The main strengths of the current study included the large sample size, long-term follow-up data from the FOS cohort, detailed evaluation of renin–angiotensin–aldosterone system activity without interfering factors

in the CONPASS cohort, and confirmation of the study outcomes in 2 independent populations. There are several limitations of the current study. First, confirmatory tests for renin-independent aldosteronism were not performed in FOS and confounders such as interfering medications and electrolyte imbalance could not be eliminated. However, in CONPASS, these confounders were controlled and the final outcomes were the same. Secondly, presence or absence of renin-independent aldosteronism in the CONPASS cohort was determined by the CCT, which is not considered the criterion standard for the diagnosis of primary aldosteronism. However, it has previously been shown to be a robust confirmatory test in the Chinese population,[27] and recommended by the European Society of Hypertension.[45] Thirdly, MR activity was not measured at baseline in FOS, and to evaluate the short-term impact of aldosterone and renin on MR activity, cross-sectional data from CONPASS was used. Fourthly, the FOS and CONPASS cohorts are inherently different because of their ethnicity, geographic location, time of data collection, and the different measurement methods of renin and aldosterone. To obtain the same outcomes in both cohorts is therefore significant, although the findings should be tested prospectively in other populations where multiple measurements of aldosterone and renin are performed and potential confounders can be fully controlled. Finally, we did not observe a relationship between renin-independent aldosteronism and CVD incidence among nonhypertensive participants. Given that nonhypertensive participants with low renin are more likely to develop hypertension over time which then predisposes them to CVD,[3,35] a longer follow-up duration and larger sample size may be needed to demonstrate cardiovascular events in these participants.

In conclusion, data from FOS and CONPASS jointly suggested that among patients with hypertension, renin-independent aldosteronism is more closely associated with CVD risk than renin-dependent aldosteronism, likely because of a sustained increase in MR activity. Given the wide availability of MR antagonists, the timely detection of renin-independent aldosteronism would lead to active intervention. Given the concordance of the results from FOS and CONPASS, our study emphasizes the need for the timely evaluation of renin and aldosterone in all hypertensive patients so as to offer a more precise measure of cardiovascular risk and enable selection of targeted therapy to achieve optimal cardiovascular outcomes.

ARTICLE INFORMATION

Received August 2, 2021; accepted November 2, 2021.

Affiliations

Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China (J.H., H.S., P.H., K.W., Y.Y., L.M., Q.C., L.G., W.H., T.L., M.M., Y.W., Z.D., R.L., Q.L., Y.S., S.Y.); Centre for Endocrinology and Metabolism, Hudson Institute of Medical Research, Clayton, Vic., Australia (J.Y., P.J.F.); Department of Medicine, Monash University, Clayton, Vic., Australia (J.Y., P.J.F.); and Hypertension Center, , Fuwai Hospital, State Key Laboratory of Cardiovascular Disease, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (J.C.).

Acknowledgments

We thank the participants and staff of the Framingham Offspring Study. We also thank Laboratory of Endocrine and Laboratory of Lipid and Glucose Metabolism, as well as the First Affiliated Hospital of Chongqing Medical University. Membership of the Chongqing Primary Aldosteronism Study (CONPASS) Group: Qifu Li, MD, PhD, Ying Song, MD, Shumin Yang, MD, PhD, Wenwen He, MD, Mei Mei, MD, PhD, Jinbo Hu, PhD, Suxin Luo, MD, PhD, Kangla Liao, MD, Yao Zhang, MD, PhD, Yunfeng He, MD, PhD, Yihong He, MD, Ming Xiao, PhD, and Bin Peng, PhD. Author Contributions: Conception and design: Q.F. Li, S.M. Yang, Y. Song, J. Cai, and J.B. Hu; Analysis and interpretation of the data: J.B. Hu, H. Shen, and P.Q. Huo; Drafting of the article: J.B. Hu, H. Shen, and P.Q. Huo, P. Fuller, Yang, J.B. Hu, S.M. Yang and J. Cai; Critical revision of the article for important intellectual content: P. Fuller, J. Yang, J. Cai, Q.F. Li, and S.M. Yang; Statistical expertise: J.B. Hu, K.R. Wang, and Y. Yang; Obtaining of funding: Q.F. Li, S.M. Yang, Y. Song, and J.B. Hu; Administrative, technical, or logistic support: R. Luo, Y. Song, T. Luo, and W.W. He; Collection and assembly of data: W.W. He, Z.P. Feng, Q.F. Cheng, Z.P. Du, M. Mei, and L.Q. Ma. All authors have read the journal's authorship agreement and the manuscript has been reviewed by and approved by all named authors.

Sources of Funding

This work was supported by the National Natural Science Foundation of China (81670785, 81800701, 81870567, 81800731, and 81970720). Joint Medical Research Project of Chongqing Science and Technology Commission & Chongqing Health and Family Planning Commission (Youth Project, 2018QNXM001). Outstanding Talents of the First Affiliated Hospital of Chongqing Medical University 2019 (2019-4-22). Chongqing Outstanding Youth Funds (cstc2019jcyjjq0006). Bethune Merck Diabetes Research Foundation (G2018030).

Disclosures

None.

Supplementary Material

Data S1–S5
Table S1
Figures S1–S4

REFERENCES

1. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. *Am J Hypertens*. 2018;31:1165–1174.
2. Ferrario CM, Schiffrin EL. Role of mineralocorticoid receptor antagonists in cardiovascular disease. *Circ Res*. 2015;116:206–213.
3. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, Allison MA, Baudrand R, Ix JH, Kestenbaum B, de Boer IH, Vaidya A. The spectrum of subclinical primary aldosteronism and incident hypertension: a cohort study. *Ann Intern Med*. 2017;167:630–641.
4. Baudrand R, Guarda FJ, Fardella C, Hundemer G, Brown J, Williams G, Vaidya A. Continuum of renin-independent aldosteronism in normotension. *Hypertension*. 2017;69:950–956. doi: 10.1161/HYPERTENSIONAHA.116.08952
5. Vaidya A, Mulatero P, Baudrand R, Adler GK. The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. *Endocr Rev*. 2018;39:1057–1088.
6. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both inside and outside the kidney. *Physiol Rev*. 2016;96:1327–1384.
7. Buffolo F, Monticone S, Pecori A, Pieroni J, Losano I, Cavaglia G, Tetti M, Veglio F, Mulatero P. The spectrum of low-renin hypertension. *Best Pract Res Clin Endocrinol Metab*. 2020;34(3):101399. doi: 10.1016/j.beem.2020.101399
8. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359:1225–1237.

9. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet*. 2007;369:1208–1219. doi: 10.1016/S0140-6736(07)60242-6
10. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Investigators C, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the charm-preserved trial. *Lancet*. 2003;362:777–781. doi: 10.1016/S0140-6736(03)14285-7
11. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:41–50.
12. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355:2631–2639.
13. Parikh NI, Gona P, Larson MG, Wang TJ, Newton-Cheh C, Levy D, Benjamin EJ, Kannel WB, Vasan RS. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. *Eur Heart J*. 2007;28:2644–2652. doi: 10.1093/eurheartj/ehm399
14. Joseph JJ, Echouffo-Tcheugui JB, Kalyani RR, Yeh HC, Bertoni AG, Effoe VS, Casanova R, Sims M, Wu WC, Wand GS, et al. Aldosterone, renin, cardiovascular events, and all-cause mortality among African Americans: the Jackson heart study. *JACC. Heart Failure*. 2017;5:642–651.
15. Verma S, Gupta M, Holmes DT, Xu L, Teoh H, Gupta S, Yusuf S, Lonn EM. Plasma renin activity predicts cardiovascular mortality in the heart outcomes prevention evaluation (hope) study. *Eur Heart J*. 2011;32:2135–2142. doi: 10.1093/eurheartj/ehr066
16. Tomaschitz A, Pilz S, Ritz E, Morganti A, Grammer T, Amrein K, Boehm BO, März W. Associations of plasma renin with 10-year cardiovascular mortality, sudden cardiac death, and death due to heart failure. *Eur Heart J*. 2011;32:2642–2649. doi: 10.1093/eurheartj/ehr150
17. Yuyun MF, Jutla SK, Quinn PA, Ng LL. Aldosterone predicts major adverse cardiovascular events in patients with acute myocardial infarction. *Heart Asia*. 2012;4:102–107. doi: 10.1136/heartasia-2012-010129
18. Tomaschitz A, Pilz S, Ritz E, Meinitzer A, Boehm BO, Marz W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the ludwigshafen risk and cardiovascular health (luric) study. *Eur Heart J*. 2010;31:1237–1247. doi: 10.1093/eurheartj/ehq019
19. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, März W. Association of plasma aldosterone with cardiovascular mortality in patients with low estimated gfr: the ludwigshafen risk and cardiovascular health (luric) study. *Am J Kidney Dis*. 2011;57:403–414. doi: 10.1053/j.ajkd.2010.10.047
20. Kisaka T, Ozono R, Ishida T, Higashi Y, Oshima T, Kihara Y. Association of elevated plasma aldosterone-to-renin ratio with future cardiovascular events in patients with essential hypertension. *J Hypertens*. 2012;30:2322–2330. doi: 10.1097/HJH.0b013e328359862d
21. Deo R, Yang W, Khan AM, Bansal N, Zhang X, Leonard MB, Keane MG, Soliman EZ, Steigerwalt S, Townsend RR, et al. Serum aldosterone and death, end-stage renal disease, and cardiovascular events in blacks and whites: findings from the chronic renal insufficiency cohort (cric) study. *Hypertension*. 2014;64:103–110. doi: 10.1161/HYPERTENSIONAHA.114.03311
22. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med*. 1993;329:616–619.
23. Doyle AE, Jerums G, Johnston CI, Louis WJ. Plasma renin levels and vascular complications in hypertension. *Br Med J*. 1973;2:206–207.
24. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: the multi-ethnic study of atherosclerosis. *Hypertension*. 2020;76:113–120. doi: 10.1161/HYPERTENSIONAHA.120.15006
25. Vasan RS, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:33–41.
26. Xu Z, Yang J, Hu J, Song Y, He W, Luo T, Cheng Q, Ma L, Luo R, Fuller PJ, et al. Chongqing primary aldosteronism study G. primary aldosteronism in patients in China with recently detected hypertension. *J Am Coll Cardiol*. 2020;75:1913–1922.
27. Song Y, Yang S, He W, Hu J, Cheng Q, Wang Y, Luo T, Ma L, Zhen Q, Zhang S, et al. Chongqing primary aldosteronism study G. Confirmatory tests for the diagnosis of primary aldosteronism: a prospective diagnostic accuracy study. *Hypertension*. 2018;71:118–124. doi: 10.1161/HYPERTENSIONAHA.117.10197
28. Wang K, Hu J, Yang J, Song Y, Fuller PJ, Hashimura H, He W, Feng Z, Cheng Q, Du Z, et al. Development and validation of criteria for sparing confirmatory tests in diagnosing primary aldosteronism. *J Clin Endocrinol Metab*. 2020;105(7):e2449–e2456. doi: 10.1210/clinem/dgaa282
29. Yang YI, Williams TA, Song Y, Yang S, He W, Wang K, Cheng Q, Ma L, Luo T, Yang J, et al. Nomogram-based preoperative score for predicting clinical outcome in unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2020;105:e4382–e4392. doi: 10.1210/clinem/dgaa634
30. Lin C, Yang J, Fuller PJ, Jing H, Song Y, He W, Du Z, Luo T, Cheng Q, Yang S, et al. Chongqing primary aldosteronism study G. A combination of captopril challenge test after saline infusion test improves diagnostic accuracy for primary aldosteronism. *Clin Endocrinol (Oxf)*. 2020;92:131–137.
31. Ma L, Song Y, Mei M, He W, Hu J, Cheng Q, Tang Z, Luo T, Wang Y, Zhen Q, et al. The chongqing primary aldosteronism study G. Age-related cutoffs of plasma aldosterone/renin concentration for primary aldosteronism screening. *Int. J. Endocrinol*. 2018;2018:8647026.
32. Young WF Jr. Diagnosis and treatment of primary aldosteronism: practical clinical perspectives. *J Intern Med*. 2019;285:126–148.
33. Byrd JB, Turcu AF, Auchus RJ. Primary aldosteronism. *Circulation*. 2018;138:823–835. doi: 10.1161/CIRCULATIONAHA.118.033597
34. Jia G, Aroor AR, Hill MA, Sowers JR. Role of renin-angiotensin-aldosterone system activation in promoting cardiovascular fibrosis and stiffness. *Hypertension*. 2018;72:537–548. doi: 10.1161/HYPERTENSIONAHA.118.11065
35. Newton-Cheh C, Guo C-Y, Gona P, Larson MG, Benjamin EJ, Wang TJ, Kathiresan S, O'Donnell CJ, Musone SL, Camargo AL, et al. Clinical and genetic correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. *Hypertension*. 2007;49:846–856. doi: 10.1161/01.HYP.0000258554.87444.91
36. Satoh M, Kikuya M, Ohkubo T, Mori T, Metoki H, Hara A, Utsugi MT, Hashimoto T, Hirose T, Obara T, et al. Aldosterone-to-renin ratio as a predictor of stroke under conditions of high sodium intake: the ohasama study. *Am J Hypertens*. 2012;25:777–783.
37. Solomon SD, Hee Shin S, Shah A, Skali H, Desai A, Kober L, Maggioni AP, Rouleau JL, Kelly RY, Hester A, et al. Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction. *Eur Heart J*. 2011;32:1227–1234. doi: 10.1093/eurheartj/ehq522
38. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med*. 2016;374:1521–1532.
39. Nicholls SJ, Bakris GL, Kastelein JJP, Menon V, Williams B, Armbrecht J, Brunel P, Nicolaides M, Hsu A, Hu BO, et al. Effect of aliskiren on progression of coronary disease in patients with prehypertension: the aquarius randomized clinical trial. *JAMA*. 2013;310:1135–1144. doi: 10.1001/jama.2013.277169
40. Gheorghiade M, Böhm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the astronaut randomized trial. *JAMA*. 2013;309:1125–1135. doi: 10.1001/jama.2013.1954
41. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
42. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
43. Filippatos G, Anker SD, Agarwal R, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Schloemer P, Tornus I, Joseph A, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation*. 2021;143(6):540–552. doi: 10.1161/CIRCULATIONAHA.120.051898. doi: 10.1161/CIRCULATIONAHA.120.051898
44. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6:51–59.
45. Mulatero P, Monticone S, Deinum J, Amar L, Prejbisz A, Zennaro M-C, Beuschlein F, Rossi GP, Nishikawa T, Morganti A, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens*. 2020;38:1919–1928. doi: 10.1097/HJH.0000000000002510

Supplemental Material

#

Data S1. Physical Examination and Blood Pressure Measurement.

Evaluations of physical examination, anthropometry and other laboratory assessments were described in previous publications. In FOS, blood pressure measurement was performed according to a standardized protocol: using a mercury-column sphygmomanometer and a cuff of the appropriate size, a physician measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) twice in the left arm while the participant kept seated. The average of two readings was considered the blood pressure at each examination. A diagnosis of hypertension was established on the basis of SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or a history of hypertension, or taking antihypertensive medication at previous visits. In CONPASS, blood pressure was measured in both of the patient's arms by an electronic sphygmomanometer, and the average of two readings was documented as the measured blood pressure. A diagnosis of hypertension was established by SBP ≥140 mmHg and/or DBP ≥90 mmHg on at least 3 occasions on different days (including at least 1 out-of-office BP measurement).

Subjects were categorized into different groups according to their blood pressure: normotension (SBP < 120 mmHg and DBP < 80 mmHg, and no history of hypertension, and not taking antihypertensive medication), prehypertension (SBP 120-139 mmHg and DBP 80-89 mmHg, and no history of hypertension, and not taking antihypertensive medication), stage 1 hypertension (SBP 140–159 mmHg and DBP 90–99 mmHg), stage 2 hypertension (SBP 160–179 mmHg and DBP 100–109 mmHg), stage 3 hypertension (SBP >180 mmHg or DBP >110 mmHg). Non-hypertension was defined as normotension or prehypertension, or subjects who did not meet the diagnostic criteria of hypertension.

Data S2. Laboratory assessment.

For FOS, the procedures of venous blood collection, serum/plasma separation and specimen storage have been previously described. Plasma renin concentration (PRC) was measured with an immunechemiluminometric assay (Nichols Advantage ® Direct Renin assay), and serum aldosterone concentration (SAC) was measured by radioimmunoassay (Quest Diagnostics). In CONPASS, before the evaluation of renin and aldosterone concentration, all antihypertensive medications that can interfere with RAAS activity (including diuretics, β-blockers, angiotensin-converting enzyme inhibitors [ACEi], and angiotensin-1 receptor blockers[ARBs]) were withdrawn, or changed to verapamilor α-adrenergic blockers. Hypokalemia was also corrected. Blood samples were collected in the morning. Plasma aldosterone concentration (PAC) and PRC were measured with automated chemiluminescence immunoassays (LIAISON; DiaSorin, Italy).

Data S3. Renin-independent and renin-dependent aldosteronism.

In the FOS population, in addition to SAC and PRC, as intravascular volume depletion is thought to be a main promotor of renin-dependent aldosteronism, we used pro-atrial natriuretic peptide (proANP) and B-type natriuretic peptide (BNP), well recognized markers of intravascular fluid volume, to validate the classification of aldosteronism. A lower level of circulating proANP or BNP indicates a relative intravascular volume depletion that would increase renin-dependent aldosterone production.

In CONPASS population, the procedure of CCT has previously been described in detail. In brief, patients received 50 mg captopril orally at 8-9 a.m. after sitting or standing for at least 1 h; blood samples were drawn at time zero and 2 h after the challenge; PAC-post CCT (cutoff 10 $ng \cdot dl^{-1}$) was used for differentiating renin-dependent aldosteronism and renin-independent aldosteronism.

Data S4. Mineralocorticoid Receptor (MR) Activity in CONPASS.

The 24-hour urine samples were routinely collected to measure urinary potassium and sodium excretion. The degree of MR activation was indirectly assessed via 24-hour urinary potassium-to-sodium excretion based on a previous report.

Data S5. Assessment of Outcomes.

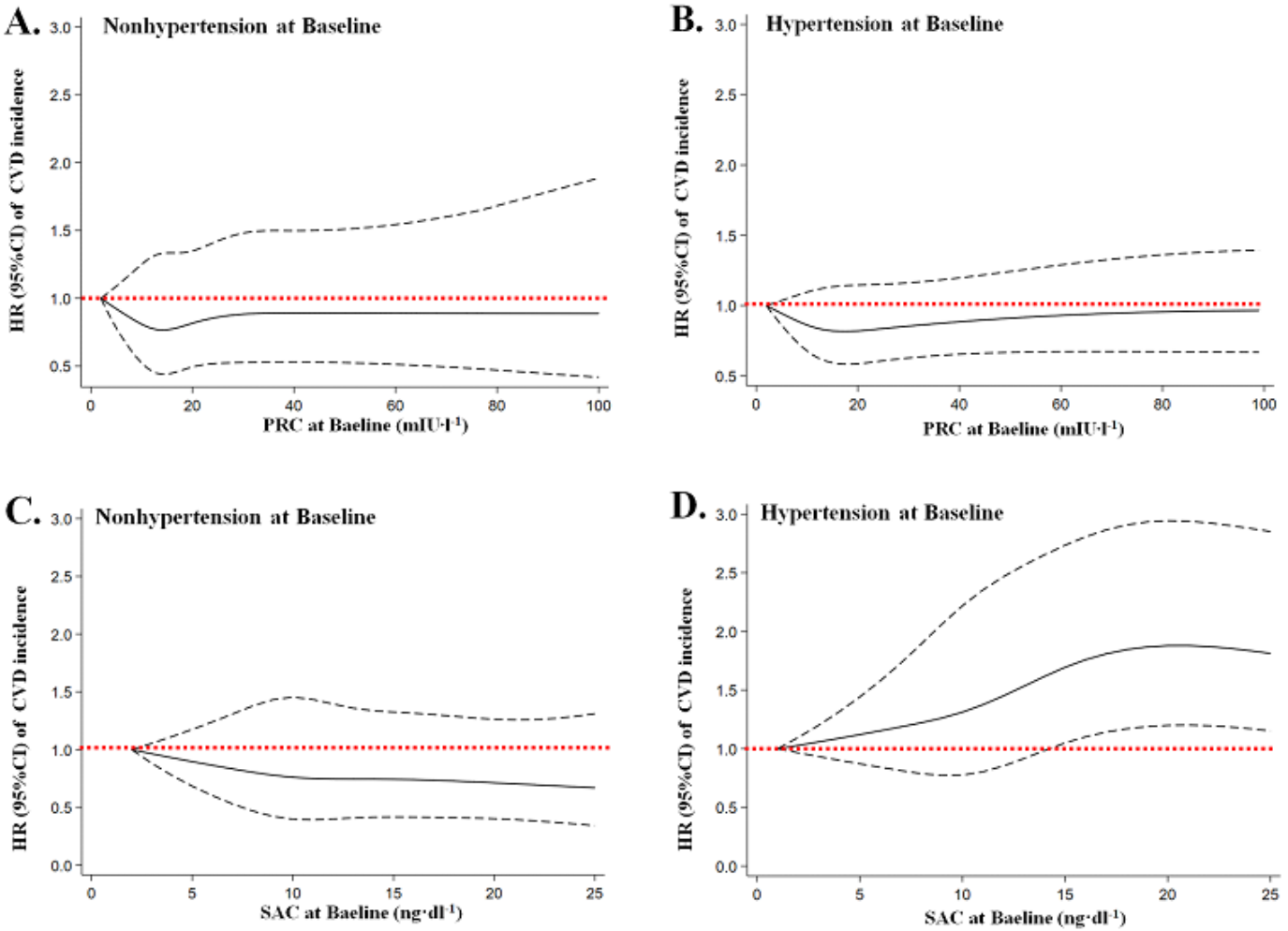
In FOS, the primary outcome in this analysis is the incidence of CVD, which included coronary heart disease (CHD), congestive heart failure (CHF), stroke or transient ischemic attack (TIA). A person having more than one cardiovascular manifestation within the follow-up period was counted as an incident case only at the time of the first event. All cardiovascular events were assessed based on the FOS sequence of events protocols. Subjects were diagnosed as having developed CHD if upon review of the case a panel of three investigators (the Framingham Endpoint Review Committee) agreed on one of the following definite manifestations of CHD: myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, non-sudden death from CHD. The diagnosis of cerebrovascular disease (stroke and TIA) was based on the occurrence of a clinically evident stroke documented by clinical records reviewed by at least two neurologists. Stroke was defined as the sudden or rapid onset of a focal neurologic deficit persisting for greater than 24 hours. TIA was defined as a focal neurologic deficit of sudden or rapid onset that fully resolved in less than 24 hours. A diagnosis of CHF depended on symptoms, physical signs and x-ray. In CONPASS, CVD was confirmed if there was a definite manifestation of CHD, stroke (including TIA) or CHF. The diagnosis of CVD was based on evaluations by at least two senior physicians from the First Affiliated Hospital of Chongqing Medical University.

Table S1. Demographic, Clinical and Biochemical Characteristics among hypertensive subgroup of FOS.

	Normal Aldosterone	Renin-Dependent Aldosteronism	Renin-Independent Aldosteronism	P Value
Women/Men	281/363	179/178	252/180	<0.001
Median age (yr)	60.96(60.27,61.66)	59.77(58.79,60.75)	62.11(61.29,62.93)	0.001
Body-mass index (kg/m^2)	29.08(28.64,29.52)	29.38(28.84,29.91)	29.36(28.85,29.88)	0.604
Average SBP (mmHg)	139(138,141)	134 (132,136)	142 (140,143)	<0.001
Average DBP (mmHg)	79(78,80)	78 (77,79)	80 (79,81)	0.002
Current smoker (%)	13.2	14.3	10.2	0.180
History of diabetes (%)	14.9	16.5	12.3	0.223
Fasting Plasma Glucose (mg/dl)	108.51(106,111.02)	111.73(107.93,115.53)	106.28(103.76,108.81)	0.059
HDL-c(mg/dl)	49.25(48.06,50.45)	50.66(48.95,52.38)	50.17(48.63,51.71)	0.370
Triglyceride (mg/dl)	151.44(142.14,160.74)	144.85(135.70,154)	161.30(152.79,169.82)	0.080
LDL-c(mg/dl)	127.03(124.63,129.44)	128.24(124.9,131.57)	130.49(127.43,133.55)	0.214
Serum aldosterone concentration (ng/dl)	6.48(6.33,6.62)	18.96(17.87,20.06)	14.67(14.17,15.16)	<0.001
Plasma renin concentration (mIU/l)	41.95(29.11,54.79)	73.08(49.51,96.65)	8.04(7.66,8.41)	<0.001
Urine sodium (mmol/day)	110.62(106.67,114.56)	87.93(82.55,93.32)	92.96(88.52,97.39)	<0.001
BNP (pg/ml)	17.01(15.35,18.66)	13.54(11.54,15.54)	17.90(16.02,19.78)	0.007
proANP (pmol/l)	426.07(404.38,447.76)	340.81(315.85,365.77)	405.01(381.84,428.18)	<0.001

Data were expressed as mean (95% CI) and the number (%).Normal Aldosterone: serum aldosterone concentration (SAC)<10 ng·dl^{-1}; Renin-Dependent Aldosteronism: SAC≥10 ng·dl^{-1} and plasma renin concentration (PRC) >15 mU/l ; Renin-Independent Aldosteronism:SAC≥10 ng·dl^{-1} and PRC ≤15 mU/l; SBP: systolic blood pressure, DBP:diastolic blood pressure, LDL-c: Low Density Lipoprotein cholesterol, HDL-c: High Density Lipoprotein cholesterol. BNP:B-type natriuretic peptide; NT_ANP: N-Terminal pro-atrial natriuretic peptide. For SAC, 1 ng/dl=27 pmol/l.

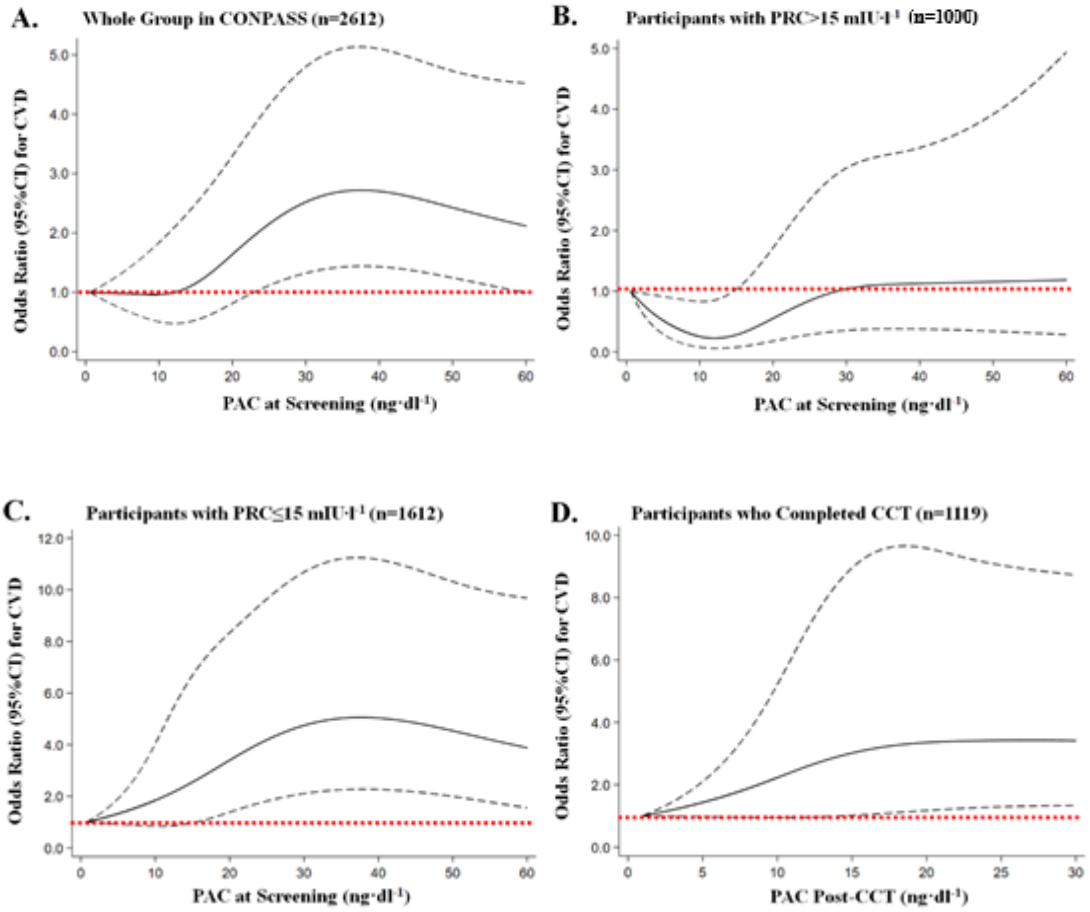
Figure S1. Relationships between circulating concentrations of aldosterone and renin at baseline and long-term risk of cardiovascular diseases, among nonhypertensive and hypertensive participants from FOS.



The hazard ratios (HR) and 95% CIs were delineated on the basis of restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles. Red dot line of vertical axis (HR=1.0) was used as reference for risk of CVD incidence. Panel A and panel B showed the HR (95% CIs) of plasma renin concentration (PRC) and CVD incidence among nonhypertensive (A) and hypertensive (B) participants, respectively. Panel C and panel D showed the HR (95% CIs) of serum aldosterone concentration (SAC) and CVD incidence among nonhypertensive (C) and hypertensive (D) participants, respectively. For SAC, 1 ng/dl=27 pmol/l.

All of these effects were calculated based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, sodium status.

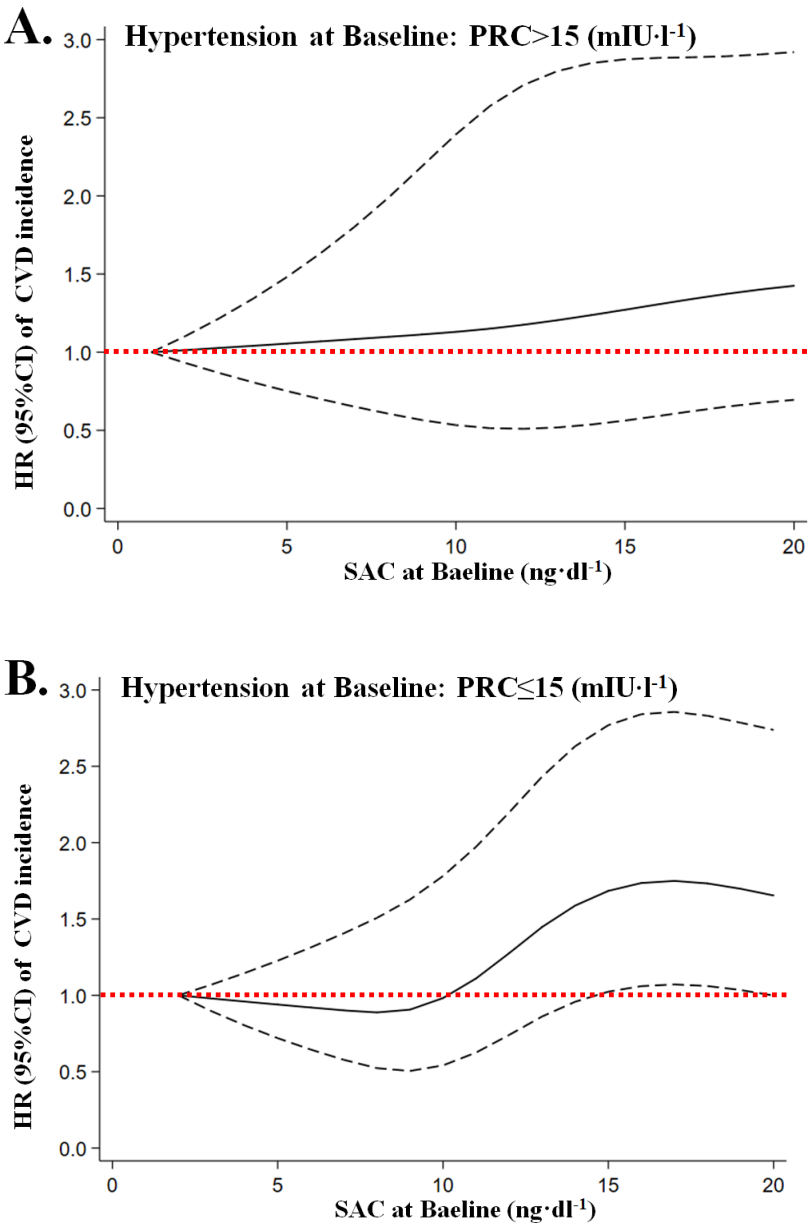
Figure S2. Cardiovascular diseases risk for aldosterone and renin among validation hypertensive population of CONPASS.



The restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles was used for delineation. Panel A showed the odd ratios (OR) and 95% CIs of CVD for plasma aldosterone concentration (PAC). Panel B showed the OR and 95% CIs of CVD for PAC in the setting of plasma renin concentration (PRC) >15 $mIU \cdot l^{-1}$. Panel C showed the odd ratios and 95% CIs of PAC in the condition of PRC≤15 $mIU \cdot l^{-1}$. Panel D showed the odd ratios and 95% CIs of PAC-post captopril challenge test (CCT). For PAC, 1 ng/dl=27 pmol/l.

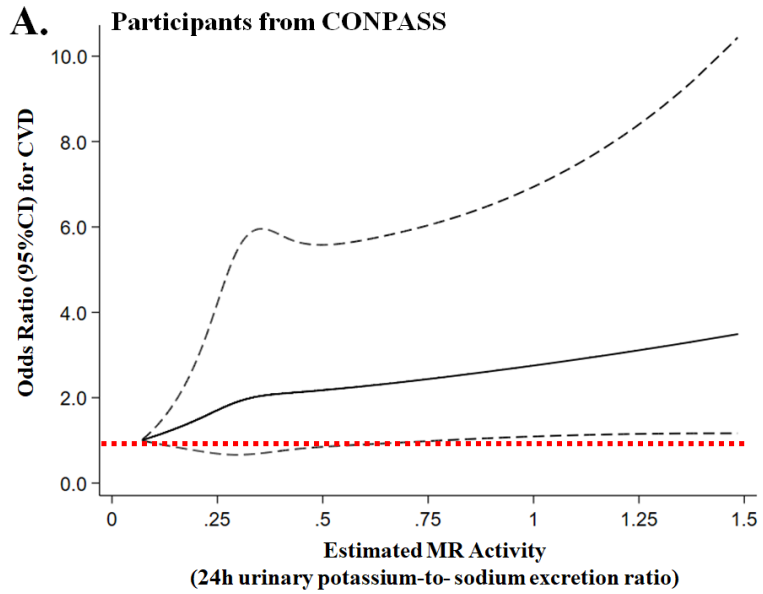
All of these effects were based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, sodium status.

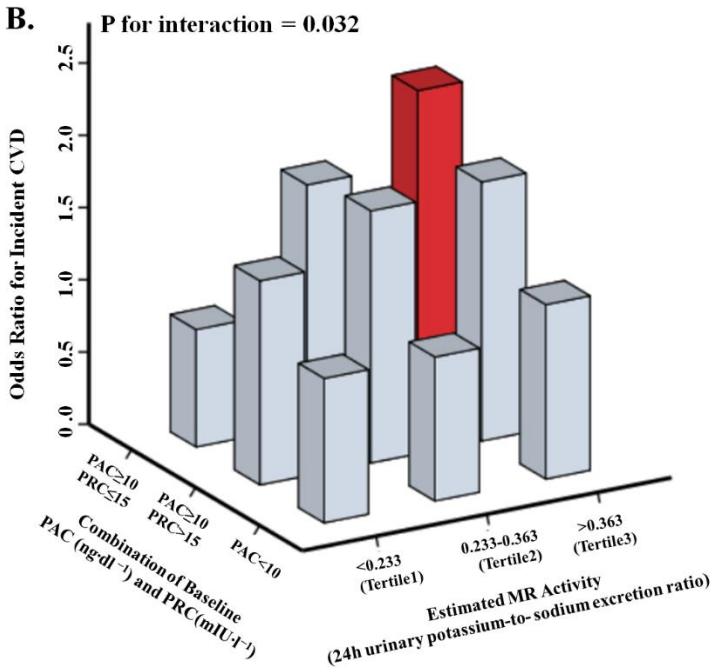
Figure S3. Relationship between aldosterone and cardiovascular diseases in settings of different renin phenotypes, among hypertensive population from FOS.



The hazard ratios and 95% Cis were calculated on the basis of restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles. Red dot line of vertical axis (HR=1.0) was used as reference for risk of cardiovascular diseases (CVD) incidence. Panel A showed the hazard ratios of CVD with increasing serum aldosterone concentration (SAC) in the condition of plasma renin concentration (PRC) >15 mU/l screening at baseline. Panel B showed the hazard ratios of CVD with an increasing SAC in the condition of PRC ≤15 mU/l screening at baseline. For SAC, 1 ng/dl=27 pmol/l. All of these effects based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, sodium status.

Figure S4. Mineralocorticoid receptor activity, different subtypes of aldosteronism, and risk of cardiovascular diseases among validation hypertensive population from CONPASS.





The restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles were used for delineation. Panel A showed the odd ratios and 95% CIs of estimated MR Activity (calculated by the 24h urinary potassium-to- sodium excretion ratio). In Panel B, subjects with PRC ≤15 mU/l and SAC≥10 ng·dl^{-1} were suspected as renin-independent aldosteronism, and subjects with PRC >15 mU/l and SAC≥10 ng·dl^{-1} were suspected as renin-dependent aldosteronism.

All of these effects were based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes. Columns colored as red indicated the false discovery rate is less than 0.05.