



Original Article

Plasma renin activity and risk of cardiovascular and mortality outcomes among individuals with elevated and nonelevated blood pressure

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Background: We sought to evaluate plasma renin activity (PRA) levels and risk of mortality and cardiovascular events among individuals with elevated blood pressure [systolic blood pressure (SBP) \geq 140 mmHg] and those with controlled blood pressure (SBP < 140 mmHg) in a large diverse population.

Methods: A retrospective cohort study between January 1, 2007, and December 31, 2013, among adults (\geq 18 years) within an integrated health system was conducted. Subjects were categorized by SBP into 2 groups: SBP < 140 mmHg and SBP \geq 140 mmHg and then further categorized into population-based PRA tertiles within each SBP group. Cox proportional hazard modeling was used to estimate hazard ratios for cardiovascular and mortality outcomes among tertiles of PRA levels.

Results: Among 6,331 subjects, 32.6% had SBP \geq 140 mmHg. Multivariable hazard ratios and 95% confidence interval for PRA tertiles T2 and T3 compared to T1 in subjects with SBP \geq 140 mmHg were 1.42 (0.99–2.03) and 1.61 (1.12–2.33) for ischemic heart events; 1.40 (0.93–2.10) and 2.23 (1.53–3.27) for congestive heart failure; 1.10 (0.73–1.68) and 1.06 (0.68–1.66) for cerebrovascular accident; 1.23 (0.94–1.59) and 1.43 (1.10–1.86) for combined cardiovascular events; and 1.39 (0.97–1.99) and 1.35 (0.92–1.97) for all-cause mortality, respectively. Among the SBP < 140 mmHg group, there was no relationship between PRA levels and outcomes.

Conclusion: Higher PRA levels demonstrated increased risk for ischemic heart events and congestive heart failure and a trend toward higher mortality among individuals with SBP \geq 140 mmHg but not among those with SBP < 140 mmHg.

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Introduction

Using plasma renin activity (PRA) levels in clinical practice may provide insights into hypertension (HTN) and help improve cardiovascular and mortality outcomes [1]. PRA is a surrogate of renin–angiotensin system (RAS) activity and potentially serves as a biomarker for increased risk for cardiovascular events and mortality in the congestive heart failure (CHF), ischemic heart disease (IHD), and HTN populations

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[1–13]. The inclusion of PRA in HTN management, particularly in those with difficult-to-control blood pressure, may help to reveal blood pressure physiology and ultimately improve efficiency and efficacy of treatment. Low-PRA individuals are presumed to have volume-related HTN, whereas high-PRA individuals are considered to have vasoconstriction-dependent HTN [14,15]. A paradoxical rise in blood pressure can occur when medication does not target the underlying mechanism of HTN [14]. Moreover, it has been shown that a PRA-guided treatment algorithm led to clinically significant reductions in blood pressure and a decrease in the number of antihypertensive medications in those with uncontrolled blood pressure [16].

Historically, inconsistent findings have been reported about the prognostic value of PRA in predicting cardiovascular outcomes [4,13,17–19]. Studies on the hypertensive population have demonstrated an association between PRA and increased risk of cardiovascular events and mortality [1–5]. PRA values have also been shown to be associated with an increased risk of cardiovascular events and all-cause mortality in individuals with preexisting cardiovascular disease [6–13]. We previously found that elevated PRA levels were associated with greater rates of chronic kidney disease (CKD) among a predominantly hypertensive population [20]. However, other studies have found no association between PRA and cardiovascular morbidity or mortality [13,17,18]. Given the inconsistent findings in prior studies, clinicians have debated the utility in targeting PRA levels in guiding treatment. The relevance of PRA as a biomarker for prognostication and assistance with management of chronic cardiovascular conditions remains unclear. Admittedly, prior studies evaluating the role of PRA as a biomarker for vascular disease and outcomes have been limited. Many were performed in specialized smaller populations, normotensive populations, and as part of post hoc analyses of clinical trials in subjects with preexisting cardiovascular disease.

We hypothesize that PRA has prognostic value and may help to characterize HTN in individuals with elevated blood pressure, whereas in those with controlled blood pressure, PRA values merely reflect normal physiology. Using a large diverse population from a routine clinical practice environment, we sought to evaluate PRA levels and risk of mortality and cardiovascular events among individuals with elevated blood pressure [systolic blood pressure (SBP) \geq 140 mmHg] and also those with normal or controlled blood pressure (SBP < 140 mmHg).

Methods

Study population

A retrospective, longitudinal cohort study of Kaiser Permanente Southern California (KPSC) members was performed between January 1, 2007, and December 31, 2013. KPSC is a prepaid integrated health system providing comprehensive care to over 3.9 million members throughout Southern California, from Bakersfield to San Diego at 13 medical centers and over 200 satellite clinics. As of December 2010, there were over 2.5 million adult members within KPSC. The patient population is racially, ethnically, and socioeconomically diverse, reflecting both the general population of the practicing area and the overall population in the state of California.

All KPSC members have similar benefits and access to health-care services, clinic visits, procedures, copays for medications, and deductibles for health care. Complete health-care encounters are tracked using a common electronic health record from which all study information was extracted. All data for this study were collected as part of routine clinical encounters where health-care providers determined the need for laboratory measurements, procedures, and medications. The study protocol was reviewed and approved by the KPSC Institutional Review Board and was exempt from informed consent.

Individuals 18 years or older with HTN and at least 1 documented outpatient measurement of PRA were identified in the study period between January 1, 2007, and December 31, 2011 (Fig. 1). Individuals were followed until they experienced any outcome, for up to 2 years following PRA measurement date, or until the end of the observation period (December 31, 2013). Individuals had to have a minimum of 1 outpatient blood pressure measurement available within 30 days of PRA measurement to be included in the study cohort. In addition, all individuals were required to have 1-year continuous membership (with no more than a 45-day gap) in the health-care plan before the serum PRA measurement to accurately capture any comorbidities. To eliminate confounding of comorbidities on incidence/outcomes, individuals were excluded if they had prevalent coronary artery disease, CHF, and cerebrovascular disease which were determined by inpatient and outpatient International Classification of Diseases (ICD) diagnosis coding. Patients who had previous procedural coding for coronary artery bypass grafting and percutaneous coronary intervention were also excluded from the study population. To eliminate confounding from volume accumulation on blood pressure present within the end-stage renal disease (ESRD) population, we excluded all ESRD patients. Patients with a diagnosis of renovascular disease (ICD-9 code 405.9/ICD-10 I15.0) were also excluded. Patients with hyperaldosteronism were not excluded from the study population.

Data collection

All laboratory data, vital sign assessments (including blood pressure measurements), and diagnostic studies and procedures are collected and stored in the KPSC electronic health record as part of routine clinical care encounters. All laboratory measurements are performed and reported from an American College of Pathology/Clinical Laboratory Improvement Act–certified laboratory. All baseline laboratory values reported were those obtained within 60 days of PRA measurement. If multiple laboratory values were available, value closest to the date of PRA measurement was used for analysis. Comorbidities, including diabetes mellitus, coronary artery disease, CHF, and cerebrovascular disease, were assessed based on inpatient and outpatient ICD-9 diagnosis coding. CKD was identified and defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m² estimated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration Equation [21]. ESRD, defined as maintenance hemodialysis, peritoneal dialysis, or renal transplantation, was identified from electronic medical records, procedure coding data, Medicare Form 2728, and internal information from the KPSC Renal Program Administration. Data on hospitalizations and diagnoses that occurred outside the

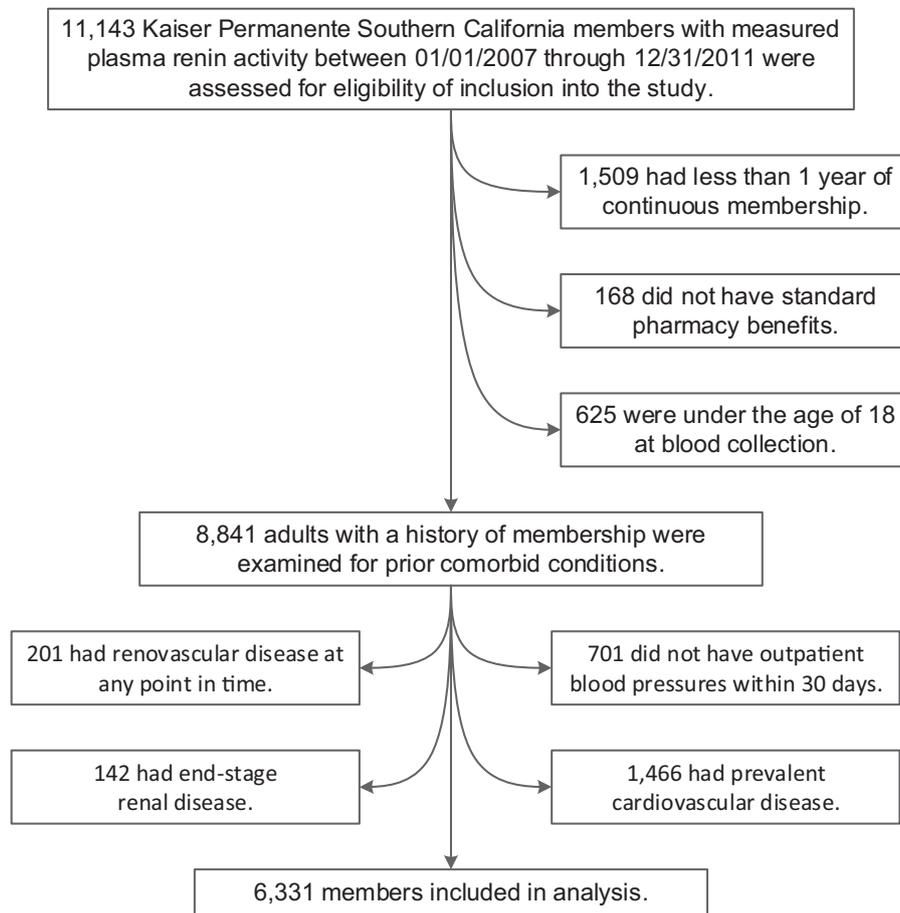


Figure 1. Patient enrollment. During the period from January 1, 2007 through December 31, 2011, 11,143 individuals were identified with PRA measurements. Of this population, 8,841 with at least 1-year continuous membership in the health plan were examined for inclusion, of which 1,466 had preexisting cardiovascular disease, 201 had preexisting renovascular disease, and 701 were missing blood pressure within 30 days of their PRA level and were excluded from analysis. PRA, plasma renin activity.

health-care system were available through administrative billing and claims records.

Antihypertensive medication use was retrieved from KPSC internal pharmacy dispensing records. Prescription orders, pharmacy fills, and refills are tracked for KPSC members with pharmacy benefits, which accounts for over 95% of members. Individuals were determined to be on antihypertensive medication if it was prescribed and dispensed within 90 days before the PRA measurement date. They were considered to be taking concomitant antihypertensive medications if there was a greater than 7-day overlap in medications. Medications that were prescribed and filled for less than 7 days were not considered as being on treatment with those particular medications. Single-pill combination drugs were classified into their different respective components. The total number of blood pressure medications was defined by the number of different antihypertensive medications taken by each subject and may have included multiple medications from the same drug class. Antihypertensive medications were further categorized as diuretics/natriuretics (i.e., mineralocorticoid receptor blockers, thiazide diuretics, calcium channel blockers, loop diuretics), RAS blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), or RAS suppressors (β -blockers, centrally acting α -agonists, methyl dopa, and direct renin inhibitors).

PRA measurement and blood pressure measurement

All PRA measurements were made with an enzyme kinetic assay that quantifies angiotensin I generation by radioimmunoassay in an American College of Pathology/CLIA-certified laboratory. The PRA test was performed by Quest Diagnostics Nichols Institute using the Sealey PRA assay [22]. PRA values are reported as ng/mL/h. PRA values were single measurements obtained during routine outpatient clinical encounters for various indications as determined by individual health-care practitioners. PRA values at the highest and lowest 0.5 percentiles and those done in the inpatient setting were excluded. There was no standardization of predraw activity, and measurements were obtained at varying times throughout the day. For subjects with multiple PRA values, the first value in the study period was used and all data were relative to that date. Sensitivity analyses were performed for those with multiple PRA values using the arithmetic mean values of PRA. Subjects were categorized into tertiles according to PRA levels and SBP (< 140 mmHg and ≥ 140 mmHg). Blood pressure measurements throughout KPSC are performed in a standardized manner, which has previously been shown to result in a high level of reliability [23]. All providers who perform blood pressure measurements are trained to have individuals seated with both feet on the ground for 3–5 minutes, arms supported

at heart level, and patients are instructed to refrain from talking during the measurements. An automated aneroid sphygmomanometer is used to perform all measurements.

Outcomes

The primary outcomes evaluated were cardiovascular events and all-cause mortality as separate competing outcomes. Cardiovascular events included any incident ischemic heart event (IHE), CHF event, and cerebrovascular event (CED). Any hospitalization with the primary or secondary diagnoses of IHE, CHF, and CED was used to identify these outcomes (Supplemental Table 1). The IHE was defined as any code for myocardial infarction, angina, coronary occlusion, myocardial necrosis, and any procedure codes for percutaneous coronary intervention or coronary artery bypass grafting. CHF was defined as any hospitalization for heart failure and cardiomyopathy. CED was defined as stroke, central nervous system bleed, or cerebrovascular disease/accident not otherwise specified. Mortality information for the cohort was obtained from a comprehensive database that combines 6 data sources including California State Death Master Files, California State Multiple Cause of Death Master Files, Social Security Administration, Death Master Files, KPSC Hospital and Emergency Department records, KPSC Membership System, KPSC Perinatal Data Mart, and Outside Claims Processing System. Individuals were followed until the occurrence of that particular event, disenrollment from the health plan, or for up to 2 years following the PRA measurement date. Follow-up was not censored when another event occurred, with the exception of death. Each outcome was also followed up separately without competing outcomes as part of a sensitivity analysis.

Statistical analyses

Individuals included for analysis were categorized by SBP into 2 groups: (1) SBP < 140 mmHg and (2) SBP ≥ 140 mmHg. The demographic characteristics and comorbidities of individuals with SBP < 140 mmHg were compared to those with SBP ≥ 140 mmHg. The chi-square or Fisher exact test was used for comparison of categorical variables and *t* test or Kruskal–Wallis tests were used for continuous variables, as appropriate; the Shapiro–Wilk test was used for normality assumptions. Subjects were further categorized into population-based PRA tertiles based on their SBP group. In subjects with SBP < 140 mmHg, PRA tertiles were 0–0.90 (T1), 0.91–2.66 (T2), and > 2.66 (T3). For SBP > 140 mmHg, PRA tertiles were 0–0.55 (T1), 0.56–1.90 (T2), and > 1.90 (T3). Event rates were determined within each PRA tertile for both SBP groups. The primary analysis was to evaluate different levels of PRA and the risk of IHE, CHF, CED, combined cardiovascular events, and all-cause mortality among those with (1) SBP < 140 mmHg and (2) SBP ≥ 140 mmHg separately. Within each PRA tertile, IHE, CHF, CED, combined cardiovascular events, and all-cause mortality rates were calculated. Unadjusted and multivariable Cox proportional hazards models were used to examine the relationship between PRA levels and incident IHE, CHF, CED, combined cardiovascular events, and mortality with the lowest tertile (T1) used as the reference range in each SBP group. Multivariable hazard ratios (HRs) were calculated with adjustment for potential confounders including age, sex, race/ethnicity, Charlson comorbidity index, and use of

diabetic and antihypertensive medication (including RAS inhibitors, RAS blockers, diuretics/natriuretics). All statistical analyses were generated using the SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). All tests were 2 sided and considered significant at the 5% type I error rate.

Results

Cohort characteristics

A total of 6,331 individuals were identified for inclusion in the study cohort (Fig. 1). The PRA levels of the cohort and by SBP categories demonstrated a Poisson distribution (Fig. 2). PRA levels ranged from undetectable to as high as 58.8 ng/mL/h. The median PRA level was 1.4 ng/mL/h for the entire study cohort.

The mean age of the study population was 55.4 years, with women accounting for 62.1%. The racial/ethnic composition of the PRA cohort was with 40% whites, 23% Hispanics, 22% blacks, and 11% Asians (Table 1). Diabetes mellitus was present in 20.9% with a mean hemoglobin A1c level of 6.8 (Supplemental Table 2). The mean estimated glomerular filtration rate was 81 mL/min/1.73 m² for the study cohort and CKD was present in 16.8% (Table 1). Diagnosed HTN was prevalent in 75.3% of the study cohort. The mean blood pressure of the cohort was 134/77 mmHg. Diuretics/natriuretics were the most frequently used medication class, accounting for 74% of the cohort.

SBP ≥ 140 mmHg accounted for 32.6% of the PRA study cohort, with the average blood pressure in this group being 156/85 mmHg. In the remaining cohort with SBP < 140 mmHg, the mean blood pressure was 123/73 mmHg. The individuals in the SBP ≥ 140 mmHg group were more frequently male (44% vs. 35%), more likely to be black (26% vs. 20%), and had greater overall usage of all antihypertensive medication classes (Table 1). Compared with the SBP < 140 mmHg population, the SBP ≥ 140 mmHg population had a greater prevalence of comorbid conditions including CKD (20.9% vs. 14.8%), greater usage of diabetic medications (28% vs. 24%), and a greater

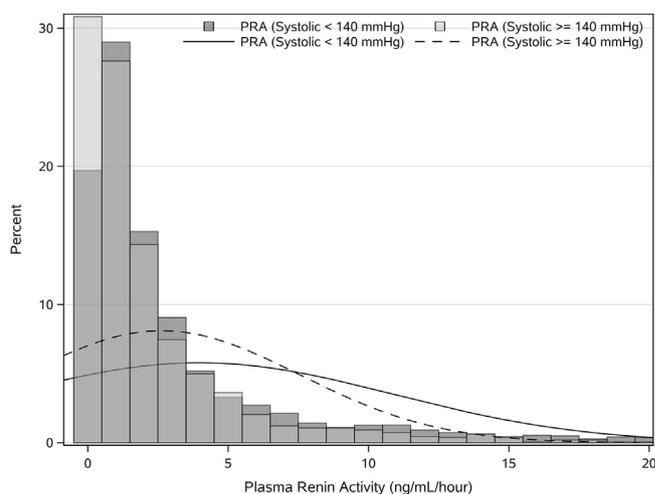


Figure 2. Distribution of plasma renin activity by systolic blood pressure at baseline. The PRA levels of the cohort by SBP categories demonstrated a Poisson distribution. PRA levels ranged from undetectable to as high as 58.8 ng/mL/h. The median PRA level was 1.40 ng/mL/h for the entire cohort study.

PRA, plasma renin activity; SBP, systolic blood pressure.

Table 1. Study population characteristics by categories of blood pressure at the time of PRA measurement

Variable	SBP < 140 mmHg, n = 4,268 (67.4)	SBP ≥ 140 mmHg, n = 2,063 (32.6)	Total, N = 6,331	P
PRA (ng/mL/h)				< 0.001
N	4,268	2,063	6,331	
Mean (SD)	4.0 (6.89)	2.6 (4.92)	3.5 (6.35)	
Median	1.5	1.1	1.4	
Range	0.0–58.8	0.0–58.5	0.0–58.8	
Age at index date (y)				0.204
N	4,268	2,063	6,331	
Mean (SD)	55.3 (15.45)	55.5 (16.79)	55.4 (15.90)	
Median	57	58	57	
Range	18.0–94.0	18.0–96.0	18.0–96.0	
Patient sex, n (%)				< 0.001
Female	2,769 (64.9)	1,164 (56.4)	3,933 (62.1)	
Male	1,499 (35.1)	899 (43.6)	2,398 (37.9)	
Race/ethnicity, n (%)				< 0.001
Asian, non-Hispanic	479 (11.2)	211 (10.2)	690 (10.9)	
Black, non-Hispanic	844 (19.8)	531 (25.7)	1,375 (21.7)	
Hispanic	985 (23.1)	477 (23.1)	1,462 (23.1)	
Other, non-Hispanic	170 (4)	98 (4.8)	268 (4.2)	
White, non-Hispanic	1,790 (41.9)	746 (36.2)	2,536 (40.1)	
Charlson comorbidity index, n (%)				0.001
0	2,075 (48.7)	1,004 (48.8)	3,079 (48.8)	
1–2	1,708 (40.1)	764 (37.1)	2,472 (39.1)	
3 or more	474 (11.1)	290 (14.1)	764 (12.1)	
Baseline SBP (mmHg)				< 0.001
N	4,268	2,063	6,331	
Mean (SD)	123.1 (11.85)	155.7 (15.06)	133.7 (20.05)	
Median	125	151	132	
Range	63.0–139.0	140.0–240.0	63.0–240.0	
Baseline DBP (mmHg)				< 0.001
N	4,268	2,063	6,331	
Mean (SD)	72.6 (10.32)	85.3 (13.74)	76.7 (12.99)	
Median	73	85	76	
Range	32.0–104.0	8.0–144.0	8.0–144.0	
Prevalent hypertension, n (%)	2,953 (69.2)	1,815 (88)	4,768 (75.3)	< 0.001
Prevalent diabetes mellitus, n (%)	869 (20.4)	455 (22.1)	1,324 (20.9)	0.030
Chronic kidney disease,* n (%)	630 (14.8)	432 (20.9)	1,062 (16.8)	< 0.001
No chronic kidney disease, n (%)	3,638 (85.2)	1,631 (79.1)	5,269 (83.2)	
Antihypertensive medication use, n (%)				
RAS suppressors†	2,179 (51.1)	1,452 (70.4)	3,631 (57.4)	< 0.001
RAS blocker‡	2,352 (55.1)	1,541 (74.7)	3,893 (61.5)	< 0.001
Diuretics/natriuretics§	2,857 (66.9)	1,820 (88.2)	4,677 (73.9)	< 0.001
Others	146 (3.4)	49 (2.4)	195 (3.1)	0.024
Antidiabetic medication use, n (%)	1,026 (24.0)	581 (28.2)	1,607 (25.4)	< 0.001

* Defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m² using the closest serum creatinine measured within 60 days of the PRA measurement date.

† RAS suppressors included β-blockers, central acting α-agonists, methyl dopa, and direct renin inhibitors.

‡ RAS blockers included angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

§ Diuretics/natriuretics included loop diuretics, thiazide diuretics, calcium channel blockers, and mineralocorticoid receptor blockers.

DBP, diastolic blood pressure; PRA, plasma renin activity; RAS, renin–angiotensin system; SBP, systolic blood pressure; SD, standard deviation.

percentage of individuals with a Charlson comorbidity index of 3 or higher (14% vs. 11%, $P < 0.0001$ for all). Individuals with SBP ≥ 140 mmHg had a greater usage of all antihypertensive medication classes compared to those with SBP < 140 mmHg.

Those with SBP < 140 mmHg had a higher median PRA level (1.5 vs. 1.1 ng/mL/h) compared with those with SBP ≥ 140 mmHg (Table 1). In those who had available serum studies for analysis, there were no clinically meaningful differences in baseline serum aldosterone, sodium, bicarbonate, phosphorus, albumin, hemoglobin, ferritin, hemoglobin A1C, or cholesterol between those with SBP < 140 mmHg and those with SBP ≥ 140 mmHg (Supplemental Table 2).

Event rates

During 2 years of observation, the overall mortality rate was 7.1% (448 individuals). A total of 798 cardiovascular events

occurred. The total number of outcomes was 490 in the SBP ≥ 140 mmHg population and 598 in the SBP < 140 mmHg. Compared with the SBP < 140 mmHg population, the SBP ≥ 140 mmHg population had higher rates of IHE (9.2% vs. 6.1%), CHF (8.2% vs. 4.0%), CED (6.3% vs. 4.0%), and mortality (9.0% vs. 6.1%, $P < 0.001$ for all). The mortality incidence rate was higher in the SBP ≥ 140 mmHg population compared to SBP < 140 mmHg population (33 vs. 23 deaths per 1,000 person-years; Table 2).

Regression analyses: outcomes in SBP < 140 mmHg versus SBP ≥ 140 mmHg population

In crude models, analysis of the 2-year outcomes showed that patients with SBP ≥ 140 mmHg with measured PRA levels were at greater risk for all outcomes compared with those with measured PRA levels and SBP < 140 mmHg. In adjusted models,

Table 2. Incidence rates and relative risks of study outcomes in patients with measured plasma renin activity^{a,†}

Study outcome	Group	Number of events	Person-years	Incidence rate per 1,000 person-years	Unadjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
Overall mortality	SBP < 140 mmHg	262	11,411	22.96	1.00 (Reference)	1.00 (Reference)
	5-Unit increment [‡]	—	—	—	0.99 (0.94, 1.04)	0.96 (0.91, 1.01)
Cardiovascular events (combined)	SBP ≥ 140 mmHg	186	5,768	32.25	1.35 (1.12, 1.63)	1.22 (1.00, 1.48)
	5-Unit increment [‡]	—	—	—	1.09 (1.03, 1.15)	1.05 (0.99, 1.10)
Cardiovascular events (combined)	SBP < 140 mmHg	446	11,018	40.48	1.00 (Reference)	1.00 (Reference)
	5-Unit increment [‡]	—	—	—	1.01 (0.97, 1.05)	0.95 (0.91, 0.99)
	SBP ≥ 140 mmHg	352	5,430	64.83	1.57 (1.37, 1.81)	1.24 (1.08, 1.43)
	5-Unit increment [‡]	—	—	—	1.07 (1.03, 1.11)	1.01 (0.97, 1.06)

^a The adjusted hazards for each study outcome was modeled using the Cox proportional hazards model that included the SBP group variable and the following confounders: age at baseline, sex, race/ethnicity, Charlson comorbidity index, and use of antidiabetic medications, RAS inhibitors, RAS blockers, diuretic/natriuretics, or other antihypertensive medications.

[†] Only data for incident outcomes were modeled. Patients with a prevalent diagnosis of each study outcome were excluded from that model. In the hypertension and diabetes models, prevalence ischemic heart disease was also excluded.

[‡] The model includes SBP as a continuous variable and reported hazards are for a 5-unit increment in the continuous scale within each SBP group. CI, confidence interval; HR, hazard ratio; RAS, renin–angiotensin system; SBP, systolic blood pressure.

compared with those with SBP < 140 mmHg, individuals with SBP ≥ 140 mmHg were at greater risk for all-cause mortality, combined cardiovascular events, and CHF. Risks for IHE and CED were similar between those with SBP < 140 mmHg and SBP ≥ 140 mmHg. After adjustment for age, sex, race/ethnicity, Charlson comorbidity index, and antihypertensive and diabetic medication usage, HRs (95% confidence intervals) were 1.09 (0.90–1.32), 1.38 (1.11–1.71), 1.26 (0.99–1.59), 1.24 (1.08–1.43), and 1.22 (1.00–1.48) for IHE, CHF, CED, combined cardiovascular events, and all-cause mortality, respectively, in the SBP ≥ 140 mmHg group (Tables 2 and 3).

Regression analyses: outcomes by PRA tertile

In subjects with SBP < 140 mmHg, PRA tertiles were 0–0.89 (T1), 0.90–2.64 (T2), and > 2.64 (T3). For SBP ≥ 140 mmHg, PRA tertiles were 0–0.56 (T1), 0.57–1.90 (T2), and > 1.90 (T3). Higher PRA levels were associated with increased HR within the SBP ≥ 140 mmHg group. During the 2-year observation, patients with SBP ≥ 140 mmHg in the highest baseline PRA tertile (T3) had increased risk for combined cardiovascular events compared with those in the lowest PRA tertile (T1) (Table 4). Among the cardiovascular event outcomes, T3 was associated with increased risk for IHE and CHF compared with T1 but not with CED (Table 5). With adjustment for age, sex,

race/ethnicity, Charlson comorbidity index, and antihypertensive medication usage, the HRs (95% confidence intervals) were 1.42 (0.99–2.03) and 1.61 (1.12–2.33) for IHE, 1.40 (0.93–2.10) and 2.23 (1.53–3.27) for CHF, 1.10 (0.73–1.68) and 1.06 (0.68–1.66) for CED, 1.23 (0.94–1.59) and 1.43 (1.10–1.86) for combined cardiovascular events, and 1.39 (0.97–1.99) and 1.35 (0.92–1.97) for all-cause mortality for PRA quartiles T2 and T3, respectively, compared to T1 in subjects with SBP ≥ 140 mmHg (Tables 4 and 5).

Among the SBP < 140 mmHg group, there was no relationship between PRA levels and outcomes. The association between elevated PRA tertile and IHE, CHF, CED, combined cardiovascular events, and overall mortality outcomes seen in the SBP ≥ 140 mmHg was not observed.

Discussion

Our study comprising 6,331 individuals with PRA measurements found that higher PRA levels were prognostic of greater cardiovascular outcomes *only* among patients with SBP ≥ 140 mmHg. In addition, there was a trend toward higher mortality in those with higher PRA and SBP ≥ 140 mmHg. In individuals with SBP < 140 mmHg, there was no relationship between PRA levels and outcomes suggesting that PRA merely reflects physiologic mechanisms to maintain hemodynamics in

Table 3. Incidence rates and relative risks of cardiovascular event outcomes in patients with measured plasma renin activity^{a,†}

Study outcome	Group	Number of events	Person-years	Incidence rate per 1,000 person-years	Unadjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
Cardiovascular events (combined)	SBP < 140 mmHg	446	11,018	40.48	1.00 (Reference)	1.00 (Reference)
	SBP ≥ 140 mmHg	352	5,430	64.83	1.57 (1.37, 1.81)	1.24 (1.08, 1.43)
Ischemic heart event	SBP < 140 mmHg	259	11,206	23.11	1.00 (Reference)	1.00 (Reference)
	SBP ≥ 140 mmHg	189	5,584	33.85	1.43 (1.19, 1.73)	1.09 (0.90, 1.32)
Congestive heart failure	SBP < 140 mmHg	169	11,289	14.97	1.00 (Reference)	1.00 (Reference)
	SBP ≥ 140 mmHg	170	5,626	30.22	1.97 (1.59, 2.43)	1.38 (1.11, 1.71)
Cerebrovascular accident	SBP < 140 mmHg	170	11,264	15.09	1.00 (Reference)	1.00 (Reference)
	SBP ≥ 140 mmHg	131	5,652	23.18	1.50 (1.19, 1.89)	1.26 (0.99, 1.59)

^a The adjusted hazards for each study outcome was modeled using the Cox proportional hazards model that included the SBP group variable and the following confounders: age at baseline, sex, race/ethnicity, Charlson comorbidity index, and use of antidiabetic medications, RAS inhibitors, RAS blockers, diuretic/natriuretics, or other antihypertensive medications.

[†] Only data for incident events were modeled. Patients with a prevalent event of each study outcome were excluded from that model. CI, confidence interval; HR, hazard ratio; RAS, renin–angiotensin system; SBP, systolic blood pressure.

Table 4. Incidence rates and relative risks of study outcomes stratified by baseline systolic blood pressure^{*,†,‡}

Strata	Study outcome	Group	Number of events	Person-years	Incidence rate per 1,000 person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Systolic blood pressure < 140 mmHg	Overall mortality	1 st Tertile	95	3,787	25.09	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	79	3,787	20.86	0.83 (0.61, 1.11)	0.88 (0.65, 1.19)
		3 rd Tertile	88	3,837	22.93	0.89 (0.67, 1.19)	1.04 (0.77, 1.41)
	Cardiovascular events (combined)	1 st Tertile	166	3,658	45.38	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	148	3,663	40.40	0.68 (0.50, 0.93)	0.84 (0.61, 1.17)
		3 rd Tertile	132	3,696	35.71	0.75 (0.54, 1.05)	0.90 (0.63, 1.28)
Systolic blood pressure ≥ 140 mmHg	Overall mortality	1 st Tertile	58	1,891	30.67	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	68	1,905	35.70	1.15 (0.81, 1.64)	1.39 (0.97, 1.99)
		3 rd Tertile	60	1,971	30.44	0.97 (0.68, 1.39)	1.35 (0.92, 1.97)
	Cardiovascular events (combined)	1 st Tertile	116	1,790	64.80	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	115	1,799	63.92	0.98 (0.76, 1.27)	1.23 (0.94, 1.59)
		3 rd Tertile	121	1,841	65.73	1.00 (0.78, 1.29)	1.43 (1.10, 1.86)

* The adjusted hazards for each study outcome was modeled using the Cox proportional hazards model that included PRA tertiles and the following confounders: age at baseline, sex, race/ethnicity, Charlson comorbidity index, and use of antidiabetic medications, RAS inhibitors, RAS blockers, diuretic/natriuretics, or other antihypertensive medications.

† Only data for incident outcomes were modeled. Patients with a prevalent diagnosis of each study outcome were excluded from that model.

‡ PRA tertiles were determined within the 2 baseline systolic blood pressure strata. In those with baseline SBP < 140 mmHg, the tertile cutoffs were 0.90 and 2.66 ng/mL/h; in the higher ≥ 140 mmHg strata, tertile cutoffs were 0.55 and 1.90 ng/mL/h.

CI, confidence interval; HR, hazard ratio; PRA, plasma renin activity; RAS, renin-angiotensin system; SBP, systolic blood pressure.

this population. The SBP ≥ 140 mmHg group as a whole had a greater risk for combined cardiovascular events compared with the SBP < 140 mmHg group emphasizing the importance of blood pressure control overall. Among the SBP ≥ 140 mmHg group, there was a 43% increased risk in combined cardiovascular events with 61% increased risk for IHD and over 2-fold

increased risk of CHF in the highest PRA tertile compared with the lowest tertile after adjustment for multiple confounders including medication usage. Traditional factors including higher blood pressure, diabetes, older age, and black race were also associated with an increased risk for combined cardiovascular events and all-cause mortality (results not shown).

Table 5. Incidence rates and relative risks of cardiovascular events stratified by baseline systolic blood pressure^{*,†,‡}

Strata	Study outcome	Group	Number of events	PY	Incidence rate per 1,000 PY	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Systolic blood pressure < 140 mmHg	Cardiovascular events (Combined)	1 st Tertile	166	3,658	45.38	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	148	3,663	40.40	0.88 (0.70, 1.10)	1.07 (0.86, 1.35)
		3 rd Tertile	132	3,696	35.71	0.77 (0.61, 0.97)	0.90 (0.71, 1.14)
	Ischemic heart event	1 st Tertile	93	3,718	25.01	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	82	3,721	22.04	0.87 (0.65, 1.17)	1.11 (0.82, 1.51)
		3 rd Tertile	84	3,767	22.30	0.87 (0.65, 1.17)	1.03 (0.76, 1.39)
	Congestive heart failure	1 st Tertile	69	3,735	18.47	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	51	3,756	13.58	0.73 (0.51, 1.05)	0.98 (0.68, 1.42)
		3 rd Tertile	49	3,798	12.90	0.69 (0.48, 0.99)	0.87 (0.60, 1.26)
Cerebrovascular accident	1 st Tertile	59	3,745	15.75	1.00 (Reference)	1.00 (Reference)	
	2 nd Tertile	63	3,740	16.84	1.05 (0.74, 1.50)	1.23 (0.86, 1.78)	
	3 rd Tertile	48	3,779	12.70	0.79 (0.54, 1.16)	0.91 (0.62, 1.35)	
Systolic blood pressure ≥ 140 mmHg	Cardiovascular events (combined)	1 st Tertile	116	1,790	64.80	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	115	1,799	63.92	0.98 (0.76, 1.27)	1.23 (0.94, 1.59)
		3 rd Tertile	121	1,841	65.73	1.00 (0.78, 1.29)	1.43 (1.10, 1.86)
	Ischemic heart event	1 st Tertile	57	1,832	31.11	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	65	1,855	35.04	1.12 (0.79, 1.60)	1.42 (0.99, 2.03)
		3 rd Tertile	67	1,897	35.32	1.12 (0.78, 1.59)	1.61 (1.12, 2.33)
	Congestive heart failure	1 st Tertile	46	1,856	24.78	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	50	1,867	26.78	1.07 (0.72, 1.60)	1.40 (0.93, 2.10)
		3 rd Tertile	74	1,903	38.89	1.54 (1.06, 2.22)	2.23 (1.53, 3.27)
	Cerebrovascular accident	1 st Tertile	47	1,854	25.35	1.00 (Reference)	1.00 (Reference)
		2 nd Tertile	45	1,865	24.13	0.94 (0.62, 1.41)	1.10 (0.73, 1.68)
		3 rd Tertile	39	1,932	20.19	0.78 (0.51, 1.19)	1.06 (0.68, 1.66)

* The adjusted hazards for each study outcome was modeled using the Cox proportional hazards model that included PRA tertiles and the following confounders: age at baseline, sex, race/ethnicity, Charlson comorbidity index, and use of antidiabetic medications, RAS suppressors, RAS blockers, diuretic/natriuretics, or other antihypertensive medications.

† Only data for incident outcomes were modeled. Patients with a prevalent diagnosis of each study outcome were excluded from that model.

‡ PRA tertiles were determined within the 2 systolic blood pressure strata. In those with baseline SBP < 140 mmHg, the tertile cutoffs were 0.90 and 2.66 ng/mL/h; in the higher ≥ 140 mmHg strata, tertile cutoffs were 0.55 and 1.90 ng/mL/h.

CI, confidence interval; HR, hazard ratio; PRA, plasma renin activity; PY, person-year; RAS, renin-angiotensin system; SBP, systolic blood pressure.

While higher blood pressure was associated with an increased risk for CED, an association between higher PRA levels and CED risk was not observed in our study. Our findings underscore the fact that PRA is a reflection of physiological compensation in normotension, whereas higher PRA levels in those with elevated blood pressure denote a pathophysiologic state.

Our study lends insight into the conflicting findings from past observations. PRA as a prognosticator may have a role only in specific populations. In normotensive individuals, PRA may reflect the normal physiology of RAS activity where high or low PRA represent the mechanisms to maintain hemodynamic pressures for optimal perfusion. This is in contrast to those with high blood pressure or cardiac stress states where elevated PRA may represent inappropriate overactivity of the RAS. Thus, our findings among patients with SBP \geq 140 mmHg are consistent with prior observations demonstrating elevated PRA and greater cardiovascular and mortality risk in high-risk populations. Previous studies among patients with preexisting cardiovascular disease have demonstrated that PRA is associated with an increased risk of cardiovascular events and all-cause mortality [6–13]. Similar to our observations, prior studies focusing on hypertensive populations have also demonstrated an association between PRA and increased risk of cardiovascular outcomes [1–5].

The negative findings in our SBP < 140 mmHg group are also consistent with past observations that found no relationship with PRA and cardiovascular outcomes. We found that PRA did not have an association with risk of cardiovascular and mortality outcomes among individuals with controlled blood pressure independent of prior diagnosis of HTN [13,17–19]. A prospective community-based study of 803 subjects also found no association between PRA and risk of myocardial infarction and sudden cardiac death. This study excluded anyone with prior diagnosis of HTN, and the majority of those enrolled were normotensive with a mean SBP < 140 mmHg [17]. Similarly, the Anglo-Scandinavian Cardiac Outcomes Trial in a hypertensive population did not find an association between higher baseline PRA and risk of cardiovascular disease and mortality. While baseline blood pressure was > 140/80 mmHg in this cohort, the mean blood pressure at the final visit was < 140/80 mmHg in both arms of this study. Thus, PRA values may have lacked utility in this cohort given the normalization of blood pressure [18,19]. Similar to the negative findings in our SBP < 140 mmHg individuals, studies have consistently shown a lack of predictive value of PRA in those without elevated blood pressure.

PRA is the rate-limiting step of the RAS, and RAS activity is regulated by changes in total body volume and blood pressure in normal physiologic states to maintain hemodynamic stability [24]. PRA is frequently not suppressed among hypertensive individuals and can lead to inappropriate vasoconstriction and cellular injury [2,3,5,14]. In addition to stimulating angiotensin II and aldosterone production, the upstream RAS pathway is also thought to directly cause cellular injury and myocardial remodeling through renin and prorenin receptors [25,26]. Animal studies suggest that prorenin receptor activation leads to increase in transforming growth factor- β 1, tumor necrosis factor- α , and fibronectin all of which act as prothrombotic inflammatory markers [25]. Persistently elevated RAS activity is thus thought to lead to vascular, renal, and myocardial injury. We previously found that in a population of over 7,000 subjects, higher PRA levels were associated with prevalent IHD, CHF, and

CKD [27,28]. In limited observations, it has been shown that suppression of RAS can prevent vascular injury and end-organ damage [5,29–32].

There may be opportunities to lessen vascular/cellular injury and improve both blood pressure and outcomes by using a PRA-based approach [29–32]. RAS blockade in general has been shown to be beneficial for preventing cardiovascular events and mortality in patients with known IHD, CHF, and HTN [31,33–35]. PRA has also been used to more efficiently and effectively control blood pressure in difficult-to-control hypertensive individuals [16]. Hypertensive individuals have been previously shown to differ in their blood pressure responses to various classes of antihypertensive medications [24,36]. A PRA-guided treatment algorithm led to clinically significant reductions in blood pressure and a decrease in the number of antihypertensive medications used [16]. Low-PRA subjects are presumed to have volume-related HTN, whereas high-PRA subjects are considered to have vasoconstriction-dependent HTN [14]. Low-renin subjects have been shown to not respond well to anti-RAS medications, whereas high-renin subjects have been shown to respond poorly to diuretics [14,16,36]. Moreover, subjects may experience a paradoxical rise in blood pressure when prescribed an antihypertensive medication class not suggested by their PRA level [14]. In evaluating our hypertensive population with PRA levels, we previously found that the lowest PRA quartile had the highest usage of PRA-suppressing medications (i.e., β -blockers and direct renin inhibitors) and the lowest rates of diuretic usage [15]. Prior studies in patients with CHF have shown that elevated PRA levels were significantly associated with cardiovascular and renal outcomes despite patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as optimal treatment regimens [7,8,10]. It would be of interest to further investigate the effects of antihypertensive medications that directly affect renin including direct renin inhibitors on both PRA levels and outcomes in patients with both elevated blood pressure and persistently elevated PRA levels. Given our findings, the inclusion of PRA in HTN management particularly in those with difficult-to-control blood pressure and elevated PRA levels may help to improve both efficiency and efficacy of medication use, and subsequent reduction of PRA may ultimately help to improve cardiovascular and mortality outcomes.

Limitations

There are several potential limitations to our study that may confound interpretation of our findings. The effects of medication usage on PRA levels are a potential confounder in our analyses. The majority of our subjects had PRA levels evaluated while concurrently on antihypertensive medication known to influence PRA levels [37]. It was not possible to have subjects stop antihypertensive medications that affect PRA levels given the retrospective observational nature of our study. However, given the fact that the majority of our population were on multiple medications, there were likely offsetting where some antihypertensive medications raised and others lowered PRA levels in the same subjects. While antihypertensive therapy can variably influence plasma renin levels, the increased risk for cardiovascular events in hypertensive subjects with elevated PRA levels was seen after adjustment and control for antihypertensive medications. While 74% of subjects were on

diuretics, 62% on RAS blockers, and 57% on RAS inhibitors, effects of these medications on PRA levels can also offset each other. However, the use of PRA as a biomarker to predict risk for outcomes in the hypertensive population was not affected by simultaneous medication usage in prior observations [6–8,13].

PRA is generally not considered a routine laboratory test, and confounding by indication may be possible. PRA measurements were ordered during real-world clinical encounters and for various indications as determined by individual providers. Thus, our study findings may not generalize to the entire hypertensive population or the general population. PRA levels in our study subjects were not all obtained at the same time or in a standardized fashion, which may reflect diurnal variations in PRA and not necessarily RAS activity [38]. In addition, subjects likely had different levels of physical activity, dietary salt intake, and had blood samples drawn at various times throughout the day. These factors may all contribute to variability in the PRA levels that we found [38,39]. Given the large sample size of our population, we feel that potential diurnal variations in PRA may have averaged out and lessened the relative differences within our study population. While we excluded patients diagnosed with renovascular HTN ($N = 201$), we were not fully able to account for those with hyperaldosteronism. In our past observations, we had observed that up to 17% of our patients who had concurrent PRA and serum aldosterone levels drawn met the criteria for hyperaldosteronism based on the aldosterone-to-PRA ratio [40].

We used a single blood pressure measurement to categorize into SBP \geq or $<$ 140 mmHg groups without being able to take into consideration blood pressure variations over time. We did perform a sensitivity analysis obtaining mean blood pressure in both SBP groups and found that the differences in blood pressure between the groups were sustained throughout the observation period. The mean blood pressure throughout the observation period was 140/75 mmHg in the baseline SBP \geq 140 mmHg group compared with 127/72 mmHg in the SBP $<$ 140 mmHg group. In addition, we were unable to evaluate or control for additional biomarkers and lifestyle modifications such as tobacco abuse, which may be relevant and influence cardiovascular and mortality outcomes. Potentially relevant laboratory measurements including brain natriuretic peptide, C-reactive protein, and 24-hour urinary excretion of sodium were not available for a majority of our study population. Lastly, we evaluated outcomes for only a 2-year follow-up period but may need to consider long-term outcomes for our study population.

Conclusion

Among a large racially diverse PRA study cohort derived from a routine clinical practice environment, higher PRA levels were associated with increased risk for IHEs and CHF and were associated with a trend toward higher mortality only among individuals with SBP \geq 140 mmHg but not in those with SBP $<$ 140 mmHg. PRA determination may have a role as a biomarker to prognosticate cardiovascular and mortality outcomes in addition to its role in defining mechanisms of HTN.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.krcp.2016.07.004>.

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