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Plasma renin activity and its association with ischemic heart disease, congestive heart failure, and cerebrovascular disease in a large hypertensive cohort

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Abstract

Plasma renin activity (PRA) may be a surrogate for vascular damage. We hypothesize that PRA is associated with cardiovascular and cerebrovascular disease. Cross sectional study (1/1/1998–12/31/2009) on hypertensive individuals >/=18yrs using multivariable logistic regression models to estimate odds ratios (OR) for ischemic heart disease (IHD), congestive heart failure (CHF), and cerebrovascular disease (CED) based on PRA quartiles controlling for age, sex, race, diabetes mellitus (DM), and medication use. Among 7887 individuals (60% women, 34% whites, 23% blacks, 19% Hispanics and 29% DM), adjusted OR (95% CI) for IHD were 0.94 (0.80–1.10), 1.09 (0.92–1.29) and 1.18 (1.00–1.39); CHF OR's were 1.23 (0.99–1.53), 1.27 (1.01–1.61) and 1.41 (1.13–1.77); CED OR were 0.95 (0.78–1.17), 0.77 (0.61–0.97) and (0.97 (0.78–1.20) for 2nd, 3rd and 4th quartiles compared to 1st quartile. Higher PRA were associated with greater likelihood for prevalent IHD and CHF but not CED in our large ethnically diverse population of hypertensive individuals.

Keywords

Plasma renin activity; cardiovascular disease; epidemiology

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Conflicts of interest

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Introduction

Renin–angiotensin system (RAS) activity is reflected by the plasma renin activity (PRA) level. The RAS works to physiologically maintain blood pressure in normal states and in times of physical stress [1]. People with high blood pressure are expected to have suppression of the renin–angiotensin-aldosterone system because elevated blood pressure usually results from volume overload or systemically elevated vascular pressures. Consequently, hypertensive individuals in whom PRA is not suppressed are likely to have inappropriately over active RAS and therefore prone to detrimental vascular outcomes.

Past observations have been inconsistent in their assessment of PRA as a risk factor for cardiovascular disease and its related mortality[2–8]. Studies that have demonstrated that PRA is predictive of cardiovascular outcomes have been conducted primarily in populations with hypertension and/or preexistent cardiovascular disease[2–5,9–11]. In those without hypertension, PRA has not been shown to be prognostic since it would merely reflect the physiology of RAS to maintain normal blood pressure[1,6,12–14]. The preponderance of studies that have demonstrated the association between PRA and risk of cardiovascular and mortality outcomes were performed as post-hoc analyses of large heart failure or ischemic heart disease trials wherein PRA was not assessed as the primary or independent predictor [9,10,15–17]. While these past observations and studies have examined cardiovascular outcomes, the cross sectional relationship between PRA and prevalent cardiovascular disease has not been well described. We sought to examine whether higher PRA was associated with increased likelihood for prevalent ischemic heart disease (IHD), congestive heart failure (CHF), and cerebrovascular disease (CED) within a large ethnically diverse hypertensive population.

Methods

Study population

The Kaiser Permanente Southern California (KPSC) health system is a prepaid integrated health plan with 14 medical centers and over 200 satellite clinics. Geographically, the centers span from San Diego to Bakersfield, California. The patient population is ethnically and socioeconomically diverse reflective of the underlying population in southern California[18]. As of October 2009, KPSC had an active membership of 3.3 million. All members have similar benefit structures with co-pays and deductibles for medications and healthcare. Members have similar access to all healthcare facilities, procedures, and referrals. The data for this study were collected as part of routine clinical practice wherein individual healthcare providers had determined the need for the laboratory measurements, medications, and procedures. The health information is tracked through the electronic health records (EHR). Each member is given a unique medical record number for tracking of health care encounters and outcomes. The study protocol was approved by the regional institutional review board and exempted from informed consent.

This cross-sectional study covered the period 1 January 1998 through 31 October 2009. The study population has been previously described[19,20]. The current study cohort included individuals ages 18 years or older who were identified with hypertension and had

documented outpatient measurement of PRA and serum aldosterone. A hypertension diagnosis was based on 2 separate outpatient International Classification of Diseases, Ninth Revision (ICD-9) codes specific to hypertension. The accuracy of this identification schema has been previously validated [21].

All PRA measurements were made with an activity assay that measures angiotensin I generation in an American College of Pathology/Clinical Laboratory Improvement Act (CLIA)-certified laboratory and are reported as ng/ml per h. The test is performed by Quest Diagnostics Nichols Institute using the Sealey PRA test [22], which utilizes radioimmunoassay for quantification. PRA measurements made in the inpatient setting were excluded for consideration in the study because of the potential confounding by acute volume shifts and physiologic stress that may be present during hospitalizations. If individuals had multiple outpatient PRA measurements, the single first value in the observation period was used and all associated results were determined relative to that PRA result date.

The PRA test is a radioimmunoassay which quantifies the production of angiotensin I. Overall PRA and absolute renin values show a strong correlation [23]. This value is a functional measurement of renin levels as renin is the upstream and rate-limiting factor for RAS activity. PRA may be a better indicator compared with absolute renin concentration due to the fact that certain conditions such as chronic liver disease are more prone to alter absolute renin levels, whereas PRA values would not be affected [24].

PRA values used in this study were single measurements obtained at varying times and with different clinical scenarios. Thus, PRA levels can fluctuate and may not necessarily reflect RAS status but rather physiologic variations from activity and daily rhythm [25,26]. Thus both serum aldosterone levels and the aldosterone-to-PRA ratio (ARR) were also used as explanatory variables in an attempt to control for confounding variations in PRA. Particularly the ARR would control for any variations in both PRA and aldosterone, as any clinical scenario that would result in PRA changes would also proportionately affect aldosterone.

Data on age, sex, race/ethnicity (when available), laboratory values, medication use, and comorbidities were extracted from the EHR, which included laboratory databases, disease registries, and electronic medical charts. Race/ethnicity information from the EHR was used to categorize individuals as white, black, Hispanic, Asian, or other. Individuals were categorized as other when they were not classified as any of the above or where no race data were available. The presence of comorbidities was assessed based on inpatient and outpatient diagnoses ICD-9 codes extracted from the EHR. In order to ensure that comorbidities were reliably captured, we required individuals to have had continuous enrollment in the health plan 3 months prior to and 3 months after the PRA measurement for inclusion in the study analyses.

Anti-hypertensive medication use was determined as those prescribed within 90 days prior to the PRA result date. Given the potential effects of anti-hypertensive medications on PRA, these medications were further categorized as either diuretics/natriuretic, RAS blockers, or

RAS suppressors (e.g., as beta-blockers). All laboratory results reported were those obtained within 3 months prior to or after the PRA measurement.

Analytic approach

The primary objective was to evaluate the likelihood of prevalent IHD, CHF, and CED based on PRA levels. These morbidities were captured based on ICD-9 diagnoses codes from the electronic health records. The rates of IHD, CHF, and CED and comparisons across PRA levels were reported.

Hypertensive individuals who had PRA measurements were categorized into population based PRA quartiles previously established and described [19] (Figure 1). The primary objective of the study was to determine whether higher levels of PRA were associated with increased likelihood of existing IHD, CHF, and CED. Each morbidity was treated separately for the analyses and thus the different morbidities were not treated as competing risks. Logistic regression models were employed to estimate odds ratios (OR) for IHD, CHF, and CED for each PRA quartile compared with the lowest quartile (quartile 1). Multivariable adjustments were performed to control for potential confounders of age older than 59 years, gender, black race, DM, and use of anti-hypertensive medication classes. PRA was also treated as a continuous variable. Medication classes and associations with morbidities were also evaluated.

Within each PRA quartile, rates of IHD, CHF, and CED and other comorbidities were determined for each quartile and comparisons were made by either chi-squared test or Cochran–Armitage test. Additional data on age, sex, race, and laboratory values were determined among each quartile and trends across the quartiles was investigated.

In secondary analyses, logistic regression models were used to estimate OR using ARR as the explanatory variable controlling for the same covariates as above.

All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

Results

Cohort characteristics

A total of 7,887 individuals were identified for inclusion in the study cohort. The distribution of the PRA cohort is shown in Figure 2. Overall, values ranged from undetectable to as high as 16.5 ng/ml per h. The median PRA value for the cohort was 1.30 ng/ml per h. The mean blood pressures in the subset of the cohort who had documented measurements (N=3709) were 141 systolic and 79 mm Hg diastolic [27].

The study population included 59.6% women and was comprised of 29% DM patients (Table 1). Whites had the greatest representation at 34.4% followed by blacks (22.7%) and Hispanics (19.0%). Blacks had the greatest proportion in the lowest PRA quartile and their proportion decreased across higher PRA quartiles (29.6 to 16.9%). Conversely, whites had the lowest representation in the lowest PRA quartile, which increased with each quartile and

had the highest proportion in the highest PRA quartile (31.2 to 38.4%). Higher PRA quartiles included younger individuals as demonstrated by a mean age of 55.7 years in the highest quartile compared with mean age of 60.4 years in the lowest quartile. No meaningful differences between genders were noted within different PRA quartiles.

Overall, the study population included 23% IHD, 9.8% CHF, and 10.5% CED patients. Cerebrovascular disease showed a trend toward higher rates with lower PRA (Table 1). Among the study cohort, 83% were on anti-hypertensive medications (Table 2). Diuretic/natriuretics were the most frequently used medication class accounting for 70% of the cohort (73% in the highest PRA quartile). RAS blockers (56%) and RAS suppressors (53%) accounted for the next two medication classes that were frequently used.

Regression analyses

The crude and multivariable OR for IHD, CHF, and CED using PRA and other explanatory variables are shown in Tables 3(A, B, C).

Ischemic Heart Disease

With adjustment for age, sex, black race, DM status, and type of anti-hypertension medication use, the OR's (95% CI) for IHD were 0.94 (0.80–1.10), 1.09 (0.92–1.29) and 1.18 (1.00–1.39) for PRA quartiles 2, 3, and 4 respectively compared to quartile 1. A linear trend was observed between increasing PRA and presence of IHD wherein each one-unit, five-unit and 10-unit increase in PRA was associated with OR of 1.01 (1.00–1.02), 1.05 (1.02–1.09) and 1.11 (1.04–1.18) respectively (table 3A). Age older than 59 years [2.46 (2.18–2.77)], male sex [1.28 (1.14–1.44)], and presence of DM [1.77 (1.56–1.99)] were associated with IHD. Black race had a lower IHD OR [0.88 (0.77–1.00)] compared to non-black race. Use of RAS suppressing medications was associated with higher OR for IHD [1.67 (1.47–1.90)] (Table 3A, Figure 3).

Congestive Heart Failure

The OR's (95% CI) for CHF were 1.23 (0.99–1.53), 1.27 (1.01–1.61) and 1.41 (1.13–1.77) for quartiles 2, 3 and 4 respectively compared to quartile 1. Each five-unit increase in PRA was associated with OR of 1.05 (1.00–1.09). Age older than 59 years [1.96 (1.66–2.33)], male gender [1.45 (1.24–1.70)] and presence of DM [2.19 (1.86–2.57)] were associated with CHF. In terms of medications, both RAS blocker and RAS suppressor agents were associated with CHF demonstrating OR's of 1.26 (1.05–1.52) and 1.62 (1.35–1.95) respectively (Table 3B, Figure 3).

Cerebrovascular Disease

The OR (95% CI) for CED were 0.95 (0.78–1.17), 0.77 (0.61–0.97) and (0.97 (0.78–1.20) for quartiles 2, 3 and 4 respectively compared to quartile 1. Older age [2.46 (2.08–2.91)] and presence of DM [1.27 (1.08–1.49)] were associated with CED. Black race and male gender showed no difference in CED. In terms of medication use, RAS suppressor use was associated with greater OR for CED [1.40 (1.18–1.65)] (Table 3C, Figure 3).

Secondary Analyses

The OR's for IHD, CHF, and CED across quartiles of PRA, serum aldosterone, and ARR are shown in Figure 3. The OR for the three morbidities using ARR as the predictor exhibited a similar trend as PRA but in an inverse manner. Higher ARR was associated with decreased OR for the three morbidities, though the values were not as pronounced as for PRA. Using serum aldosterone alone, there were no significant differences in OR across the ranges of aldosterone and risk of the IHD, CHF, or CED.

Discussion

Summary of findings

In our large ethnically diverse population of over seven thousand hypertensive individuals, we found that higher levels of PRA were associated with prevalent IHD and CHF. For each five-unit increase in PRA, there was a 5% increased likelihood for both IHD and CHF. Within our population, we initially observed increased associations at PRA values of 1.40 ng/ml per h and higher which represented the 3rd quartile. Traditional risk factors including older age, DM, and male gender also demonstrated higher OR's for IHD and CHF. Higher PRA, however, had no association with CED. Black race in our PRA cohort showed lower association with IHD but not CHF or CED. The lower IHD risk may be attributed to the fact that blacks were disproportionately represented in the lower PRA quartiles. When using ARR as the explanatory variable, a similar but inverse trend was observed for IHD and CHF but not CED throughout the study cohort. Our findings further support the contention that inappropriate up-regulation of the RAS may be involved in the pathophysiology and manifestation of cardiovascular disease. Our study seeks to examine the possible role of PRA as a biomarker for a sicker population such as those with prevalent cardiovascular disease.

Implications

PRA reflects the state of RAS and may represent a biomarker for adverse biology within certain populations. Physiologically, an increase in RAS maintains "normal blood pressure" by counteracting falls in circulatory volume via an increase in angiotensin II mediated vasoconstriction [1]. Reciprocally, states of volume excess or high blood pressure should lead to suppressed PRA levels. When elevated blood pressure does not suppress PRA, it may represent inappropriate up-regulation of renin secretion. The resultant excessive vasoconstriction may lead to vascular injury and poor clinical outcomes. In fact, PRA as a prognosticator for cardiovascular and mortality outcomes has been well described[2–5,9–11]. We have previously described that elevated PRA levels are also associated with renal disease amongst a hypertensive and non-hypertensive population [19]. Interventional studies that have shown the benefit of targeting RAS support the prominence of RAS's role in vascular diseases and in treatment[28–31]. Additionally, reactively high PRA levels induced by excessive diuretic usage are also associated with increased cardiovascular mortality [32]. Thus another treatment approach might be able to reduce PRA levels by restoring circulatory volume.

Renin and the use of PRA as a biomarker are more suitable in specific populations. Renin has been examined as a variable to explain various clinical outcomes such as myocardial infarction, stroke, and mortality. Alderman et al[4] and Blumenfeld et al[8] have found that elevated PRA was associated with higher myocardial infarction rates among hypertensive individuals. Muhlestein *et al.* [10] demonstrated that higher PRA was associated with greater rates of myocardial infarction, heart failure, and mortality among a population with known coronary artery disease. Sub analyses of the Heart Outcomes Prevention Evaluation (HOPE) Canadian population and the valsartan heart failure trial (Val-HeFT) studies both revealed that high PRA was a risk for cardiovascular mortality[9,17]. Populations with cerebrovascular disease have also been described where PRA were associated with worsened cardiovascular events risk[33]. Higher PRA among the Framingham offspring population were prone to greater rates of short-term mortality[7]. In contrast, Meade *et al.* [6] found no such relationship of PRA and cardiovascular outcomes. It is worthy to note that the study population was generally normotensive in the Meade *et al* study compared to previous observations on hypertensive and/or known cardiovascular disease populations. Similarly, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) on a hypertensive population did not demonstrate an association with higher baseline PRA and subsequent risk of cardiovascular disease and mortality [34]. However, the mean blood pressures at the end of the study were less than 140/80 mm Hg. Thus while past PRA outcomes studies appear to be inconsistent collectively, they have been consistently prognostic in those with known cardiovascular disease and risks while they have consistently shown lack of predictive value in those without elevated blood pressures or heart disease.

Potential Limitations

In our study, we attempted to evaluate the value of PRA as a biomarker for cardiovascular disease prevalence in a hypertensive population. We hypothesized that inappropriately elevated PRA levels in our hypertensive population would reflect both the existent vascular damage and the underlying role of renin angiotensin system in cardiovascular disease. We report our findings on the assumption that our hypertensive population had elevated blood pressures where RAS would be expected to be suppressed. Therefore, the fact that blood pressure data was missing on the majority of our study population (61%) confounds the interpretation of our findings and represents an important limitation of our study. While we feel confident in the accuracy of the hypertension cohort identified for our study, uncontrolled or elevated blood pressures actually represent a small proportion of the KPSC hypertension population[35,36]. Furthermore, causality cannot be inferred from our cross sectional observation as morbidities were captured both before and after the PRA measurement. It would be of interest to stratify the population by blood pressures and determine the prognostic value of PRA on longitudinal cardiovascular outcomes. We are currently working to obtain clinical information including blood pressures on hypertensive individuals with long term follow up in order to determine the utility of PRA on future cardiovascular risks in those with and without elevated blood pressures.

The potential limitations of our study should further be qualified due to its retrospective observational nature. The findings, though obtained from a real world practice environment, may not necessarily represent findings in the entire hypertensive population of KPSC or the

general population for that matter. Since PRA and aldosterone are not routine laboratory tests, there is a confounding by indication where PRA was measured selectively in certain individuals. The tests were likely ordered based upon clinical assessments deemed as necessary by practicing clinicians. In addition, the effects of medication use on PRA levels are somewhat underemphasized by our analysis. Most of the medication used to treat hypertension affect the level of PRA [37]. We did attempt to account for this by categorizing and controlling for medications according to how they effect on PRA levels [1]. It is also important to note that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers significantly lower the effective PRA in vivo [38] which would not be reflected in the measured PRA levels themselves. Given the fact that 54% of the study population was on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, the vasculopathic effects or manifestations of up-regulated RAS may have been ameliorated to some extent in our study population and thus lowered the actual cardiovascular disease rates. To that end, we cannot determine with certainty that all medications were prescribed for the purpose of treating hypertension as certain antihypertensive medications may have been used for other clinical indications such as heart failure, proteinuria, or prostatism.

Strengths

Among the strengths of our study is the large population of hypertensive individuals, which far exceeds any study evaluating PRA and cardiovascular disease to date. The study population was gender balanced and racially/ethnically representative in the fact that there were ample proportions of minorities including blacks, Hispanics, and Asians. Our findings were drawn from a real world practice environment and that aspect may increase the generalizability of our findings.

In conclusion, higher PRA were associated with greater risk for IHD and CHF among a large and ethnically diverse population of hypertensive individuals. However no association was found for CED. PRA status may reflect the presence of vascular disease in addition to the prognostic potential that has been previously described.

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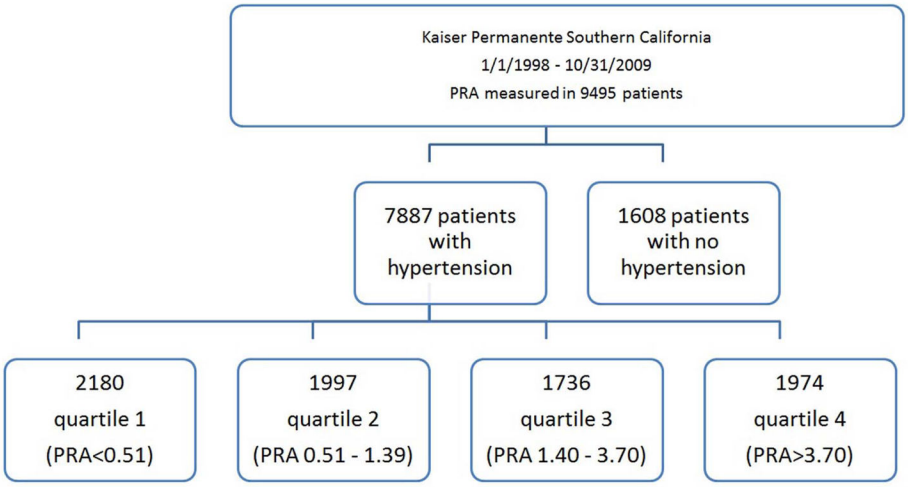

Figure 1.

The study cohort was identified from KPSC members age >/=18 years with diagnosed hypertension and a documented PRA and aldosterone measurements. The 7887 individuals who met the inclusion criteria were further categorized by population based quartiles based on their PRA measurement values.

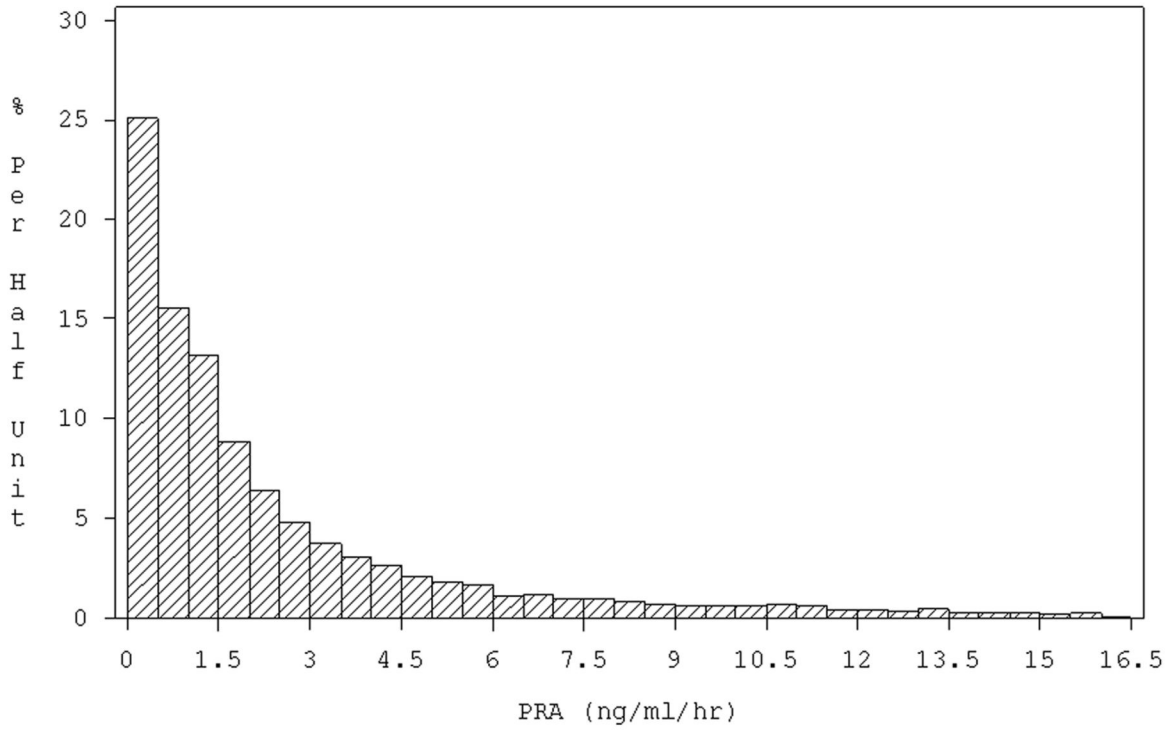

Figure 2.

Plasma renin activity (PRA) distribution among the study cohort (*N* = 7887). The median PRA was 1.30 ng/ml per h with values ranging from undetectable to as high as 16.5 ng/ml per h.

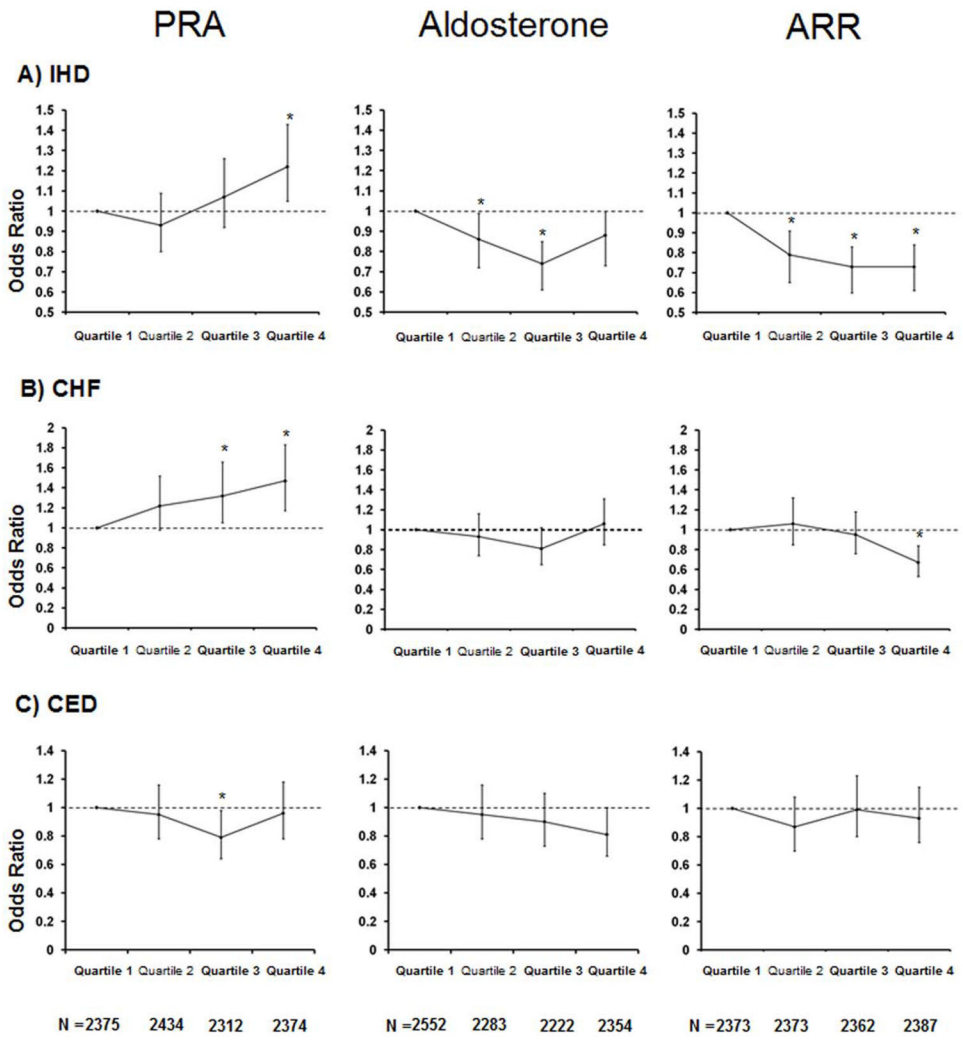

Figure 3.

Adjusted Odds Ratios based on column 1) Plasmin Renin Activity (PRA), column 2) Aldosterone, and column 3) Aldosterone:Renin Ratio (ARR). Rows describe the quartiles for a) Ischemic Heart Disease (IHD), b) Chronic Heart Failure (CHF), and c) Cerebrovascular Disease (CVD). The results demonstrate a relationship between higher PRA with IHD and CHF but not CED. ARR demonstrated a similar pattern of association but in an inverse manner. *$p<0.05$

Table 1

Characteristics of study cohort by plasma renin activity distribution

Characteristics	All (*N*=7887)	Quartile 1 (< 0.51) (*N*=2180)	Quartile 2 (0.51 – 1.39) (*N*=1997)	Quartile 3 (1.40 – 3.70) (*N*=1736)	Quartile 4 (> 3.70) (*N*=1974)	*P*
Aldosterone ng/dl [median (Q1-Q3)]	10.40 (5.00–19.00)	11.00 (5.65–19.00)	9.00 (5.00–16.00)	10.00 (5.00–18.00)	12.00 (6.00–23.10)	
PRA ng/ml per h [median (Q1-Q3)]	1.30 (0.43–3.70)	0.20 (0.19–0.32)	0.90 (0.74–1.14)	2.20 (1.80–2.80)	7.82 (5.10–13.60)	
ARR [median (Q1-Q3)]	7.14 (2.40–23.38)	46.88 (22.11– 92.12)	10.00 (4.62–17.86)	4.66 (2.27–8.43)	1.40 (0.56–3.11)	
Age [(years, mean (SD)]	58.0 (15.1)	60.4 (12.8)	58.8 (14.8)	56.8 (16.1)	55.7 (16.5)	<.001 *a*
Sex						
Female (%)	59.6	58.2	61.2	59.0	60.0	0.237 *b*
Male (%)	40.4	41.8	38.8	41.0	40.0	
Race						
White (%)	34.4	31.2	32.9	35.8	38.4	<.001 *C*
Black (%)	22.7	29.6	24.2	18.7	16.9	
Hispanic (%)	19.0	18.6	19.0	19.4	19.0	
Asian/Pacific (%)	9.3	8.3	10.6	10.4	8.1	
Other (%)	14.6	12.2	13.3	15.8	17.6	
Diabetes (%)	29.1	29.4	29.3	27.9	29.6	0.678 *b*
Ischemic Heart Disease (%)	22.9	24.7	21.4	22.4	22.9	0.080 *b*
Congestive Heart Failure (%)	9.8	9.3	9.9	9.5	10.4	0.645 *b*
Cerebrovascular Disease (%)	10.5	12.2	10.9	8.6	9.9	0.003 *b*

PRA=plasma renin activity

ARR= aldosterone:PRA ratio

eGFR= estimated glomerular filtration rate

a Test for linear trend.

b Cochran-Armitage trend test.

C Chi-squared test

Table 2

Antihypertensive medication usage

	All (*N*=7887)	Quartile 1 (< 0.51) (*N*=2180)	Quartile 2 (0.51 – 1.39) (*N*=1997)	Quartile 3 (1.40 – 3.70) (*N*=1736)	Quartile 4 (> 3.70) (*N*=1974)	*P*
[a] Diuretics/Natriuretic (%)	68	70	65	65	70	<0.001
[b] RAS blocker (%)	54	59	50	48	58	<0.001
[c] RAS suppressor (%)	51	68	54	41	39	<0.001
Any Medication (%)	83	88	81	80	84	<0.001

RAS, renin-angiotensin system.

[a]Diuretics/natriuretic: aldosterone receptor blockers, thiazide diuretics, calcium channel blockers, alpha-blockers, loop diuretics.

[b]RAS blockers: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

[c]RAS suppressors: beta-receptor blockers, centrally acting alpha-antagonists (guanfacine, clonidine) reserpine, methyl DOPA, direct renin inhibitors.

The majority of the PRA cohort was on antihypertensive medicines (83%). Diuretic/natriuretics were the most frequently used medicines which were consistent with the KPSC hypertension treatment guidelines during the observation period.

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Table 3A

Ischemic Heart Disease

PRA	Crude OR (95% CI)		*P*	Adjusted OR (95% CI)		*P*
Quartile 1	-		-	-		-
Quartile 2	0.83	(0.72–0.96)	0.012	0.94	(0.80–1.10)	0.410
Quartile 3	0.88	(0.76–1.02)	0.097	1.09	(0.92–1.29)	0.314
Quartile 4	0.90	(0.78–1.04)	0.166	1.18	(1.00–1.39)	0.047
Every 1 unit increase in PRA	1.00	(1.00–1.01)	0.173	1.01	(1.00–1.02) [a]	0.002
Every 5 units increase in PRA	1.02	(1.00–1.05)	0.173	1.05	(1.02–1.09) [a]	<.001
Every 10 units increase in PRA	1.04	(1.00–1.10)	0.173	1.11	(1.04–1.18) [a]	<.001
Diabetes	2.30	(2.06–2.57)	<.001	1.77	(1.56–1.99) [a]	<.001
Age >59 vs. 18–59 years	3.05	(2.72–3.40)	<.001	2.46	(2.18–2.77) [a]	<.001
Male	1.18	(1.06–1.31)	0.003	1.28	(1.14–1.44) [a]	<.001
Black vs. non-black	0.82	(0.72–0.93)	0.002	0.88	(0.77–1.00) [a]	0.054
Diuretics/Natriuretic	1.37	(1.21–1.54)	<.001	0.91	(0.79–1.05) [a]	0.192
Blocker	1.58	(1.42–1.76)	<.001	1.08	(0.95–1.23) [a]	0.241
Suppressor	1.96	(1.76–2.19)	<.001	1.67	(1.47–1.90) [a]	<.001

CI, confidence interval; OR, odds ratio; PRA, plasma renin activity.

[a] Modeling with PRA as a continuous variable

Estimated odds ratios (OR) for ischemic heart disease using logistic regression analysis. Crude OR's are listed in column one and OR's with adjustment for age, sex, black race, diabetes, medication use are described in the second column.

Table 3B

Congestive Heart Failure

PRA	Crude OR (95% CI)		*P*	Adjusted OR (95% CI)		*P*
Quartile 1	-		-	-		-
Quartile 2	1.08	(0.88–1.32)	0.477	1.23	(0.99–1.53)	0.066
Quartile 3	1.03	(0.83–1.28)	0.799	1.27	(1.01–1.61)	0.042
Quartile 4	1.14	(0.93–1.39)	0.226	1.41	(1.13–1.77)	0.003
Every 1 unit increase in PRA	1.01	(1.00–1.02)	0.052	1.01	(1.00–1.02) [a]	0.030
Every 5 units increase in PRA	1.04	(1.00–1.08)	0.052	1.05	(1.00–1.09) [a]	<.001
Every 10 units increase in PRA	1.08	(1.00–1.16)	0.052	1.09	(1.01–1.18) [a]	<.001
Diabetes	2.98	(2.56–3.46)	<.001	2.19	(1.86–2.57) [a]	<.001
Age >59 vs. 18–59 years	2.70	(2.30–3.17)	<.001	1.96	(1.66–2.33) [a]	<.001
Male	1.38	(1.19–1.60)	<.001	1.45	(1.24–1.70) [a]	<.001
Black vs. non-black	0.97	(0.82–1.16)	0.742	1.02	(0.85–1.22) [a]	0.851
Diuretics/Natriuretic	1.77	(1.48–2.13)	<.001	1.16	(0.95–1.42) [a]	0.156
Blocker	2.00	(1.70–2.35)	<.001	1.26	(1.05–1.52) [a]	0.012
Suppressor	1.95	(1.66–2.28)	<.001	1.62	(1.35–1.94) [a]	<.001

CI, confidence interval; OR, odds ratio; PRA, plasma renin activity.

[a] Modeling with PRA as a continuous variable

Estimated odds ratios (OR) for congestive heart failure using logistic regression analysis. Crude OR's are listed in column one and OR's with adjustment for age, sex, black race, diabetes, medication use are described in the second column.

Table 3C

Cerebrovascular Disease

PRA	Crude OR (95% CI)		*P*	Adjusted OR (95% CI)		*P*
Quartile 1	-		-	-		-
Quartile 2	0.88	(0.73–1.06)	0.178	0.95	(0.78–1.17)	0.638
Quartile 3	0.68	(0.55–0.84)	0.003	0.77	(0.61–0.97)	0.024
Quartile 4	0.79	(0.65–0.96)	0.020	0.97	(0.78–1.20)	0.759
Every 1 unit increase in PRA	0.99	(0.98–1.00)	0.036	1.00	(0.99–1.01) [a]	0.443
Every 5 units increase in PRA	0.94	(0.89–0.99)	0.036	0.98	(0.93–1.03) [a]	0.005
Every 10 units increase in PRA	0.89	(0.80–0.99)	0.036	0.96	(0.86–1.06) [a]	<.001
Diabetes	1.63	(1.40–1.89)	<.001	1.27	(1.08–1.49) [a]	0.004
Age >59 vs. 18–59 years	2.82	(2.41–3.29)	<.001	2.46	(2.08–2.91) [a]	<.001
Male	0.90	(0.77–1.04)	0.153	0.92	(0.78–1.08) [a]	0.290
Black vs. non-black	0.88	(0.74–1.04)	0.133	0.92	(0.77–1.10) [a]	0.350
Diuretics/Natriuretic	1.17	(1.00–1.37)	0.057	0.84	(0.70–1.01) [a]	0.067
Blocker	1.46	(1.25–1.69)	<.001	1.11	(0.93–1.31) [a]	0.252
Suppressor	1.66	(1.43–1.92)	<.001	1.40	(1.18–1.65) [a]	0.001

CI, confidence interval; OR, odds ratio; PRA, plasma renin activity.

[a] Modeling with PRA as a continuous variable

Estimated odds ratios (OR) for cerebrovascular disease using logistic regression analysis. Crude OR's are listed in column one and OR's with adjustment for age, sex, black race, diabetes, medication use are described in the second column.