The Enduring Association of Plasma Renin Activity to All-Cause Mortality

Maday C. Gonzalez, Hillel W. Cohen, Jean E. Sealey, John H. Laragh, Michael H. Alderman

Albert Einstein College of Medicine and Weill Cornell Medical Center

BACKGROUND

Plasma Renin Activity (PRA) has been independently associated with all-cause and cardiovascular disease (CVD) mortality in a broad range of patient groups. The incidence of CVD is directly proportional to arterial blood pressure (BP). In hypertensive individuals, plasma renin activity levels are expected to remain low due to a physiological negative feedback loop in response to higher blood pressure by which angiotensin II inhibits renin release from the juxtaglomerular cells in the kidney. However, some hypertensive patients have plasma renin levels abnormally elevated. In 1997, we showed that PRA was an independent predictor of myocardial infarction (MI), total CVD (but not stroke) and all-cause mortality in a cohort of 1,717 hypertensive patients with 3.6 years of average follow-up. We now report the long-term association of PRA to all-cause mortality, as well as an interaction with systolic blood pressure, in a cohort of 3323 subjects after a mean follow-up time of 17 years.

OBJECTIVES

- To assess whether baseline plasma renin activity predicts future all-cause and CVD mortality after a long-term follow-up time.
- To explore possible interactions between PRA and baseline systolic blood pressure among hypertensive patients.
- To determine whether PRA is associated to CVD mortality independently of the Framingham risk score.

METHODS

Participants with BP ≥140/90 and aged from 22 to 83 in a worksite-based, hypertension treatment program were included. All-cause mortality was ascertained from the National Death Index. PRA, not normally distributed, was log transformed to explore its continuous relation to all-cause mortality. PRA was also categorized by tertiles: 0.05-0.72 (L = low), 0.73-1.99 (LM = low/medium), and ≥ 2.0 (MH = medium/high) ng/mL/h. Framingham risk scores were calculated for men and women using the Framingham 10-year Risk Score for General Cardiovascular Disease formula. Potential interactions of systolic BP (SBP) were assessed with product terms. Baseline SBP was dichotomized at the mean of 150 mmHg for stratified analysis. A stepwise backward elimination approach was used to arrive at the best fit Cox model.

RESULTS

Mean follow-up was 17 years. Those with higher renin (MH vs. L) were younger (mean: 51 vs. 54 years, P<0.001), more likely to be Caucasian [40% (428/1079) vs. 20% (223/1122), P<0.001], males [72% (776/1079) vs. 53% (590/1122, P<0.001), and have a higher serum cholesterol [226 vs. 213 mm/dL, P<0.001]. Of 3323 subjects, 896 died. Although MH v. L had lower mean baseline and follow-up systolic BP [150 vs. 153 mmHg (P < 0.001) and 117 vs. 124 mmHg (P = 0.002), respectively], in a Cox model, MH had a 20% increased risk of all-cause mortality after adjusting for age, gender, race, BMI, cGFR, blood glucose, smoking, family history of CVD, history of diabetes, and baseline systolic BP (HR: 1.20, 95%CI: 1.01 - 1.42, P = 0.04). Moreover, while MH v. L hypertensives with systolic BP ≥ 150 mmHg (n = 1726) had increased risk of all-cause mortality (HR: 1.26, 95% CI: 1.02 - 1.56, P = 0.03) those with systolic BP < 150 mmHg (n = 1530) showed the same trend, but it was not significant after adjusting for the same covariates (HR: 1.11, 95%CI: 0.83 - 1.48, P = 0.34). Those in MH vs L had also an increased risk of CVD (HR: 1.48, 95%CI: 1.13 - 1.95, P=0.01) mortality after adjusting for age, sex and Framigham risk score.

ABSTRACT

Title: The Enduring Association of Plasma Renin Activity to All-Cause Mortality.

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Introduction: The incidence of Cardiovascular Disease (CVD) is directly proportional to arterial blood pressure (BP). Plasma Renin Activity (PRA) has also been independently associated with CVD, especially MI, among hypertensive patients. We now extend those findings to show an enduring association of PRA to all-cause mortality, as well as an interaction with systolic blood pressure.

Methods: Participants with BP ≥140/90 and aged from 22 to 83 in a worksite-based, hypertension treatment program were included. All-cause mortality was ascertained from the National Death Index. PRA was log transformed to explore its continuous relation to all-cause mortality. PRA was also categorized by tertiles: 0.05-0.72 (L = low), 0.73-1.9 (LM = low/medium), and ≥ 2.0 (MH = medium/high) ng/mL/

Results: Mean follow-up was 17 years. Those with higher renin (MH vs. L) were younger (mean: 51 vs. 54 years, P<0.001), more likely to be Caucasian [40% (428/1079) vs. 20% (223/1122), P<0.001], males [72% (776/1079) vs. 53% (590/1122, P<0.001), and have a higher serum cholesterol [226 vs. 213 mm/dL, P<0.001]. Of 3323 subjects, 896 died. Although MH v. L had lower mean baseline and follow-up systolic BP [150 vs. 153 mmHg (P = 0.0001) and 117 vs. 124 mmHg (P = 0.0024), respectively], in a Cox model, MH had a 20% increased risk of all-cause mortality after adjusting for age, gender, race, BMI, cGFR, blood glucose, smoking, family history of CVD, history of diabetes, and baseline systolic BP (HR: 1.20, 95%CI: 1.01 - 1.42, P = 0.037). Moreover, while MH v. L hypertensives with systolic BP ≥ 150 mmHg (n = 1726) had increased risk of all-cause mortality (HR: 1.26, 95% CI: 1.02 - 1.56, P = 0.034) those with systolic BP < 150 mmHg (n = 1530) showed the same trend, but it was not significant after adjusting for the same covariates (HR: 1.11, 95%CI: 0.83 - 1.48, P = 0.344).

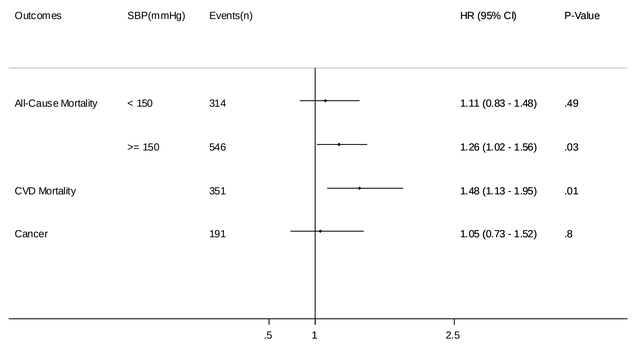
Conclusions: The plasma renin activity level is an independent predictor of all-cause mortality. This risk of death is exacerbated at higher levels of systolic blood pressure.

Table 1 | Demographic, clinical and laboratory characteristics by tertiles of PRA.

Characteristic (n=3323)	T1 (n=1122)	T2 (n=1122)	T3 (n=1079)	P-value
Age (years)	54 ± 8.2	54 ± 9	52 ± 10	<0.001
Males	590 (52.6)	708 (63.1)	776 (71.9)	<0.001
Race				<0.001
White	223 (20.0)	369 (32.9)	428 (39.7)	
Black	525 (46.8)	275 (24.5)	185 (17.2)	
Hispanic	337 (30.0)	430 (38.3)	431 (39.9)	
Other	37 (3.3)	48 (4.3)	35 (3.2)	
BMI (kg/m^2)	28.5 ± 4.6	28.5 ± 4.5	28.1 ± 4.8	0.09
LVH by ECG	164 (14.6)	133 (11.9)	132 (12.2)	0.11
eGFR (mL/min/1.73 m^2)	78.4 ± 16.3	77.0 ± 16.6	76.8 ± 17.8	
Cholesterol (mg/dL)	213 ± 42	224 ± 44	226 ± 43	<0.001
Serum Glucose (mg/dL)	102 ± 28	105 ± 35	105 ± 33	0.05
Non-Smokers	900 (80.0)	939 (83.7)	856 (79.3)	
History of:				
Diabetes	59 (5.3)	63 (5.6)	58 (5.4)	0.93
MI	14 (1.3)	12 (1.1)	14 (1.3)	0.88
CKD	17 (1.5)	39 (3.5)	35 (3.2)	0.01
No Alcohol Use	433 (38.7)	423 (38.0)	321 (29.9)	<0.001
Baseline SBP (mmHg)	153 ± 23	151 ± 16	150 ± 16	<0.001
Baseline DBP (mmHg)	95 ± 11	94 ± 10	95 ± 11	0.07
Final SBP (mmHg)	138 ± 15	137 ± 16	137 ± 16	0.08
Final DBP (mmHg)	84 ± 10	84 ± 10	84 ± 10	0.91
Last Program Treatment				<0.001
V but not R drug	414 (44.5)	346 (37.2	172 (20.2)	
R but not V drug	167 (18.0)	280 (37.2)	442 (51.8)	
R + V Combination	321 (34.5)	280 (30.1)	206 (24.2)	
Neither V not R drugs	28 (3.0)	38 (4.1)	33 (3.9)	

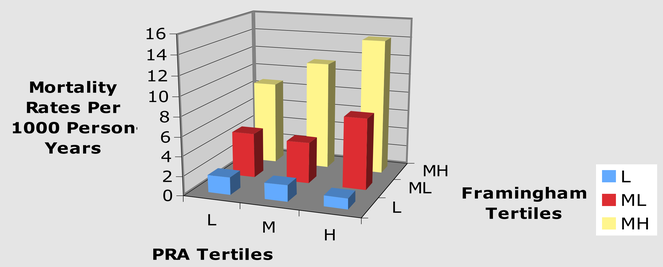
a-Results for continuous variables are presented as mean ± s.d. or median (interquartile range) with *P* values calculated by ANOVA *F* test between PRA tertiles. Categorical variables are reported as n (%) of the column *N* with *P* values calculated by χ2.
PRA, plasma renin activity; T1, tertile 1 (lowest); T2, tertile 2 (middle); T3, tertile 3 (highest); BMI, body mass index; cGFR, calculated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; MI, myocardial infarction; CKD, chronic kidney disease; V drug, natriuretic drugs (diuretics and calcium-channel blockers); R drug, antirenin drugs (β blockers and angiotensin-converting enzyme inhibitors).

Figure 1. Adjusted Hazard Ratios and 95% Confidence Intervals Comparing MH vs. L for All-Cause*, CVD† and Cancer^ Mortality by Baseline Systolic BP.



*Hazard ratios adjusted for age, sex, race, BMI, cGFR, glucose, smoking, family history of CVD, history of diabetes and baseline SBP.
†Hazard ratio adjusted for age, sex and Framingham risk score.
^Hazard ratio adjusted for age, sex, race, smoking, and baseline SBP.

Figure 2. CVD Mortality Rates Adjusted for Age-Sex by Tertiles of Framingham and PRA



	L	M	H
L	1.8	1.7	1.1
ML	4.7	4.3	7.4
MH	8.7	11.3	14.1

a Column values represent actual age- and sex- adjusted mortality rates in each tertile of PRA and Framingham scores.

CONCLUSIONS

1. Plasma renin activity level is significantly associated to all-cause and CVD mortality.
2. The risk of death associated with higher PRA is greater at higher levels of systolic blood pressure.
3. PRA is an independent predictor of CVD mortality in addition to the Framingham risk score.