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Original Article

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

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Abstract

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) ≥ 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 (≥ 18 years) within an integrated health system was conducted. Subjects were categorized by SBP into 2 groups: SBP < 140 mmHg and SBP ≥ 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 ≥ 140 mmHg. Multivariable hazard ratios for PRA tertiles T2 and T3 compared to T1 in subjects with SBP ≥ 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 ≥ 140 mmHg but not among those with SBP < 140 mmHg.

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 m^2 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

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