Plasma Renin Activity Is a Predictive Biomarker of Blood Pressure Response in European but not in African Americans With Uncomplicated Hypertension

Mai Mehanna,^{1,✉} Zhiying Wang,² Yan Gong,¹ Caitrin W. McDonough,¹ Amber L. Beitelshes,³ John G. Gums,¹ Arlene B. Chapman,⁴ Gary L. Schwartz,⁵ Kent R. Bailey,⁶ Julie A. Johnson,¹ Stephen T. Turner,⁵ and Rhonda M. Cooper-DeHoff¹

BACKGROUND

Interindividual variability in blood pressure (BP) response to antihypertensives has been reported. Although plasma renin activity (PRA) is a potential biomarker for personalizing antihypertensive therapy in European American (EA) and African American (AA) hypertensives, clinical utility of PRA-guided prescribing is incompletely understood.

METHODS

Using systematic-phased approach, PRA's clinical utility was assessed. After categorizing by baseline PRA, clinic systolic BP (SBP) responses to metoprolol and chlorthalidone were compared in 134 EAs and 102 AAs enrolled in the Pharmacogenomics Evaluation of Antihypertensive Responses-2 (PEAR-2) trial. Receiver operating characteristic (ROC) analysis was conducted in EAs. Data from PEAR-2 AAs were used to estimate an optimal PRA cut point using multivariable linear regression models. The derived cut point in AAs was tested in a meta-analysis of 2 independent AA cohorts, and its sensitivity and specificity were assessed.

RESULTS

EAs with PRA < 0.65 ng/ml/hour had a greater decrease in SBP to chlorthalidone than metoprolol (by −15.9 mm Hg, adjusted $P < 0.0001$),

whereas those with PRA ≥ 0.65 ng/ml/hour had a greater decrease in SBP to metoprolol than chlorthalidone (by 3.3 mm Hg, adjusted $P = 0.04$). Area under ROC curve (0.69, $P = 0.0001$) showed that PRA can predict SBP response among EAs. However, we observed no association between PRA and SBP response in PEAR-2 AAs. Among independent AA cohorts, those with PRA ≥ 1.3 ng/ml/hour (PEAR-2-derived cut point) responded better to atenolol/candesartan than hydrochlorothiazide (meta-analysis $P = 0.01$). However, sensitivity of the derived cut point was 10%.

CONCLUSIONS

PRA at the previously established 0.60–0.65 ng/ml/hour cut point is an effective predictive biomarker of BP response in EAs. However, we were unable to identify PRA cut point that could be used to guide antihypertensive selection in AAs.

TRIAL REGISTRATION

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Keywords: African Americans; blood pressure; European Americans; hypertension; plasma renin activity.

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Hypertension (HTN) is one of the most common chronic diseases, with a prevalence of 45.6% among US adults aged 20 years and older.¹ It is a primary risk factor for multiple adverse cardiovascular outcomes, including angina, myocardial infarction, heart failure, and stroke.² Use of antihypertensive drugs to control high blood pressure (BP), particularly high systolic BP (SBP), has been proven to reduce cardiovascular risks and prevent target organ damage.^{3,4}

However, recent data demonstrate that among hypertensives taking antihypertensive medications, approximately half of European Americans (EAs) and almost two-thirds of African Americans (AAs) have poorly controlled BP.^{1,5,6} In addition to increased cardiovascular risk, poorly controlled BP often results in prescribing additional antihypertensive drugs, which may lead to poor adherence, increased risk for adverse events, and additional treatment costs.⁷ Inter-patient

Correspondence: Rhonda M. Cooper-DeHoff (dehoff@cop.ufl.edu).

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¹Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, College of Pharmacy, University of Florida, Gainesville, Florida, USA; ²Human Genetics and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA; ³Department of Medicine, University of Maryland, Baltimore, Maryland, USA; ⁴Department of Medicine, University of Chicago, Chicago, Illinois, USA; ⁵Department of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; ⁶Department of Statistics, Mayo Clinic, Rochester, Minnesota, USA.

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variability in BP response to antihypertensive medications is likely a contributor to poorly controlled BP and is primarily a result of heterogeneity in the pathophysiological pathways underlying HTN.⁸

Renin–angiotensin–aldosterone system (RAAS) is one of the physiologic mechanisms that regulate BP. Renin produces angiotensin-I, which is converted by angiotensin-converting enzyme into angiotensin-II, which causes vasoconstriction and stimulates aldosterone release, leading to sodium retention and elevated BP.⁹ Activity of this system can be assessed by measuring renin activity from plasma samples.¹⁰ Published literature suggests that plasma renin activity (PRA) could be used as a predictive biomarker of BP response that can differentiate between patients with predominantly volume-mediated HTN (PRA < 0.65 ng/ml/hour) and those with predominantly vasoconstriction-mediated HTN (PRA ≥ 0.65 ng/ml/hour), thus inform antihypertensive treatment selection to optimize BP response.^{9,11–13} However, PRA's clinical utility is still questionable.^{14–18}

A biomarker's clinical utility can be evaluated through 3 phases: investigating association between the biomarker and the outcome of interest (early-phase evidence), measuring its predictive performance (mid-phase evidence), and studying health impact of biomarker measurement by conducting randomized controlled clinical trials (RCTs; late-phase evidence).¹⁹ Because of the current conflicting findings and lack of studies evaluating PRA's clinical utility in a systematic way, our objective was to assess clinical utility of PRA as a biomarker for predicting BP response to antihypertensive drugs—using the early- and mid-phases of a systematic-phased approach—in EAs and AAs with essential uncomplicated HTN.

METHODS

Study populations

The studies described later were conducted in accordance with the Declaration of Helsinki and their protocols were approved by the institutional review boards at the participating sites. All participants provided voluntary, written informed consent before participation. In all studies, clinic BP at baseline and posttreatment was recorded, and baseline blood samples were collected for multiple biomarker analyses. Further details about study designs are described later and in [Supplementary Data](#).

The Pharmacogenomics Evaluation of Antihypertensive Responses-2

The Pharmacogenomics Evaluation of Antihypertensive Responses-2 (PEAR-2) study was a prospective, multicenter, open-label, sequential trial (clinicaltrials.gov identifier: NCT01203852), in which participants with uncomplicated essential HTN, aged 17–65 years, were sequentially treated with metoprolol (β-blocker, renin–angiotensin system (RAS) blocker) monotherapy followed by chlorthalidone (thiazide-like diuretic) monotherapy.²⁰ Participants with cardiovascular disease, diabetes mellitus, renal, or hepatic dysfunction were excluded. To assess PRA's clinical utility,

PEAR-2 EAs were included in both the early- and mid-phase analyses, whereas PEAR-2 AAs were only included in the early-phase analysis. Because we were unable to successfully predict AA antihypertensive drug responders based on the 0.65 ng/ml/hour PRA cut point, which was from EA cohort, we used the PEAR-2 AAs as a discovery cohort to estimate an optimal PRA cut point in AAs.

The PEAR-1 and the Genetic Epidemiology of Responses to Antihypertensives (GERA-1 and -2) studies

The PEAR-1 study was a prospective, multicenter, randomized, open-label, crossover trial (clinicaltrials.gov identifier: NCT00246519), in which participants with uncomplicated essential HTN, aged 17–65 years, were randomized to either atenolol (β-blocker, RAS-blocker) followed by hydrochlorothiazide (HCTZ; thiazide-like diuretic) or HCTZ followed by atenolol.^{21,22}

In the Genetic Epidemiology of Responses to Antihypertensive (GERA) studies, participants were treated with either HCTZ (GERA-1) or candesartan (angiotensin-II receptor blocker (ARB), RAS-blocker; GERA-2; clinicaltrials.gov identifier: NCT00005520).^{15,23} Primary participants with hypertension aged 30–59 years were included. PEAR-1 and GERA exclusion criteria were the same as described earlier for PEAR-2.

The PEAR-1 and GERA AAs were used as independent validation cohorts to test the PRA PEAR-2-derived cut point (early- and mid-phase analyses).

Laboratory analysis

Baseline PRA was determined from plasma samples obtained before treatment with each drug monotherapy in PEAR and GERA studies. All PRA samples were assayed in duplicate or triplicate, and the mean value for each participant was used in all analyses. Further details about PRA measurement are described in [Supplementary Data](#).

Statistical analyses

The analytic steps undertaken in this study are summarized in [Figure 1](#). Our analysis is predicated on data suggesting that patients with hypertension with PRA < 0.65 ng/ml/hour respond better to diuretics, whereas those with PRA ≥ 0.65 ng/ml/hour respond better to RAS-blockers.¹¹ In brief, using PEAR-2 EA data, we first estimated the adjusted mean differences in SBP response to metoprolol vs. chlorthalidone using multivariable mixed-effects linear regression models, after categorizing participants by PRA subgroups (<0.65 and ≥0.65 ng/ml/hour; early-phase). We then conducted a receiver operating characteristic (ROC) analysis to evaluate PRA's predictive performance using MedCalc statistical software,²⁴ version 16.8.4 (Mariakerke, Belgium; <http://www.medcalc.org>; mid-phase).

As illustrated earlier for EAs, we conducted the early-phase analysis in PEAR-2 AAs. Because we observed no association between PRA cut point of 0.65 ng/ml/hour and SBP response in PEAR-2 AAs, we used the PEAR-2 AA as a discovery cohort to derive an optimal cut point, which was defined as PRA level at which both metoprolol and chlorthalidone were associated with

Figure 1. Flow chart showing the analytic steps undertaken in this study according to Pletcher's systematic-phased approach.¹⁹ Abbreviations: AA, African American; EA, European American; GERA, Genetic Epidemiology of Responses to Antihypertensives; NPV, negative predictive value; PEAR, Pharmacogenomics Evaluation of Antihypertensive Responses; PPV, positive predictive value; PRA, plasma renin activity; RCTs, randomized controlled clinical trials; ROC, receiver operating characteristic; SBP, systolic blood pressure.

Table 1. Baseline and posttreatment BP of PEAR-2 EAs and AAs

Metoprolol tartrate 100 mg twice daily				Chlorthalidone 25 mg once daily		
		Pre-BP mm Hg (SD)	Post-BP mm Hg (SD)	Delta-BP mm Hg (SD)	Pre-BP mm Hg (SD)	Post-BP mm Hg (SD)
EA	SBP	149.9 (12.5)	137.1 (15.6)	−12.8 (14.7)	150.9 (13.0)	134.9 (12.3)
	DBP	97.6 (4.7)	86.5 (8.0)	−11.1 (8.5)	98.6 (5.4)	90.0 (7.9)
AA	SBP	150.6 (11.9)	144.1 (15.7)	−6.5 (14.3)	148.8 (12.0)	133.2 (11.5)
	DBP	98.9 (6.1)	92.2 (8.0)	−6.7 (7.9)	97.9 (5.1)	88.9 (8.0)

Data are summarized as mean (SD). Abbreviations: AA, African Americans; BP, blood pressure; EA, European Americans; DBP, diastolic blood pressure; PEAR, Pharmacogenomics Evaluation of Antihypertensive Responses; SBP, systolic blood pressure.

a similar SBP response. Details on the variables included in the models constructed to determine the optimal PRA cut point are provided in [Supplementary Data](#). Then, we tested the derived PRA cut point in a meta-analysis of PEAR-1 and GERA AAs to assess the association between the PEAR-2-derived PRA cut point and SBP responses to atenolol/candesartan and HCTZ. This was done using metafor R package (<https://cran.r-project.org/web/packages/metafor/metafor.pdf>). We then progressed to the mid-phase analysis by assessing sensitivity, specificity, positive and negative predictive values of the derived cut point in atenolol-treated PEAR-1 and GERA-2 AAs using epiR R package (<https://cran.r-project.org/web/packages/epiR/epiR.pdf>). In addition, an ROC analysis was conducted in atenolol-treated PEAR-1 AAs using MedCalc statistical software, version 16.8.4. All statistical analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC) unless otherwise specified. More details about statistical analytic steps are illustrated in [Supplementary Data](#).

RESULTS

PEAR-2 study population

The final PEAR-2 population included 134 EAs and 102 AAs ([Supplementary Figure 1A](#)). Their baseline and posttreatment BPs are presented in [Table 1](#). Both EA and AA populations had a similar mean age of approximately 50 years and comprised 59 (44.0%) and 53 (52.0%) women, respectively ([Supplementary Table 2](#)).

Clinical utility of PRA in EA

Early-phase: association between PRA and SBP response in PEAR-2 EAs PEAR-2 EAs with PRA < 0.65 ng/ml/hour had a greater reduction in SBP of −15.9 mm Hg to chlorthalidone than to metoprolol (95% confidence interval (CI) = −20.5 to −11.3 mm Hg, adjusted

Figure 2. Adjusted mean differences in systolic blood pressure (SBP) response (mean, 95% confidence interval (CI)) to chlorthalidone vs. metoprolol by plasma renin activity (PRA) subgroup in PEAR-2 EA and AA participants. All values are adjusted for baseline SBP. A positive value in the adjusted SBP response difference indicates a participant had a better response to metoprolol than to chlorthalidone, whereas a negative value in the adjusted SBP response difference indicates a participant had a better response to chlorthalidone than to metoprolol. Abbreviations: AA, African American; EA, European American; PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses.

$P < 0.0001$), whereas those with $PRA \geq 0.65$ ng/ml/hour had a greater reduction in SBP of 3.3 mm Hg to metoprolol than to chlorthalidone (95% CI = 0.1 to 6.5 mm Hg, adjusted $P = 0.04$; [Figure 2](#)).

Mid-phase: predictive performance of PRA in PEAR-2 EAs Area under ROC curve was 0.69 (95% CI = 0.60 to 0.76, $P = 0.0001$; [Figure 3](#)). PRA of 0.6 ng/ml/hour was the optimal cut point value based on the highest Youden index and had a sensitivity of 48.3% and a specificity of 85.1% to predict SBP response to chlorthalidone vs. metoprolol among PEAR-2 EAs.

Clinical utility of PRA in AAs

Early-phase: association between PRA and SBP response in PEAR-2AAs PEAR-2 AAs with $PRA < 0.65$ ng/ml/hour had a greater reduction in SBP of -12.4 mm Hg (95% CI = -16.4 to -8.4 mm Hg, adjusted $P < 0.0001$) to chlorthalidone than to metoprolol, whereas those with $PRA \geq 0.65$ ng/ml/hour had a similar response to both drugs (adjusted $P = 0.8$; [Figure 2](#)).

Determination of the PRA cut point in PEAR-2 AA cohort On the basis of our prespecified criteria for selecting covariates to be retained in the final 2 models constructed to determine the PRA cut point in PEAR-2 AAs (discovery cohort), only baseline SBP was retained along with log-transformed PRA ([Table 2](#)). After solving the 2 regression equations, the estimated PRA cut point was 1.3 ng/ml/hour ([Supplementary Figure 2](#)).

Early-phase (derived cut point): association between PRA (based on PEAR-2-derived cut point of 1.3 ng/ml/hour) and SBP response in PEAR-1, GERA-1, and -2 AA cohorts PEAR-1 and GERA AAs included in final analysis are shown in [Supplementary Figure 1B](#) and [C](#), respectively. In both cohorts, baseline characteristics did not differ by drug

Figure 3. Receiver operating characteristic curve of plasma renin activity (PRA) biomarker in PEAR-2 EA participants ($n = 134$), where the vertical axis shows whether or not the difference in systolic blood pressure response to chlorthalidone than that to metoprolol was at least 5 mm Hg better. The area under the curve (AUC) was 0.69 (95% confidence interval (CI) = 0.60 to 0.76, $P = 0.0001$); the optimal cut point value with the highest Youden index (0.33) was 0.6 ng/ml/hour with a sensitivity of 48.3% and a specificity of 85.1%. Abbreviations: EA, European American; PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses.

treatment. However, in GERA cohort, median baseline PRA of AAs given candesartan (GERA-2) was significantly lower than that of those given HCTZ (GERA-1), which may be due to the different assays used as described in [Supplementary Table 2](#). Clinic SBP was similar in AAs before treatment with each drug in both PEAR-1 and GERA cohorts ([Table 3](#)).

PEAR-1 AAs with $PRA \geq 1.3$ ng/ml/hour had a similar SBP response to both HCTZ and atenolol (7.7 mm Hg (95% CI = -5.9 to 21.2 mm Hg) adjusted $P = 0.3$), whereas GERA

AAs with PRA ≥ 1.3 ng/ml/hour given candesartan had a greater reduction in SBP of 7.5 mm Hg (95% CI = 0.8 to 14.2 mm Hg, adjusted $P = 0.028$) than those given HCTZ (Supplementary Figures 3 and 4).

In the meta-analysis of PEAR-1 and GERA, AAs with PRA < 1.3 ng/ml/hour had a better SBP response to HCTZ than to atenolol or candesartan (meta-analysis $P < 0.0001$), whereas those with PRA ≥ 1.3 ng/ml/hour had a greater reduction in mean SBP of 7.6 mm Hg to atenolol or candesartan than to HCTZ (95% CI = 1.8 to 13.3 mm Hg, meta-analysis $P = 0.01$; Figure 4).

Mid-phase: predictive performance of the PEAR-2-derived PRA cut point (1.3 ng/ml/hour) using PEAR-1 atenolol-treated and GERA-2 AA cohorts Our derived 1.3 ng/ml/hour PRA cut point had a specificity of 97% (95% CI = 93% to 99%) and a positive predictive value of 88% (95% CI = 71% to 96%), yet a sensitivity of 10% (95% CI = 7% to 15%) and a negative **Table 2.** Multivariable linear regression models for SBP responses to metoprolol and to chlorthalidone in PEAR-2 AAs

Predictors	Model for SBP response post-metoprolol		Model for SBP response post-chlorthalidone	
	Beta $\pm$ SE	P	Beta $\pm$ SE	P
Intercept	55.4 $\pm$ 17.0	0.0015	85.5 $\pm$ 13.5	<0.0001
Log ₁₀ PRA	-12.5 $\pm$ 4.1	0.0028	8.8 $\pm$ 3.1	0.0057
Baseline SBP	-0.4 $\pm$ 0.1	0.0002	-0.7 $\pm$ 0.1	<0.0001

The negative coefficient of the log-transformed PRA (-12.5 ± 4.1) indicates a greater reduction in SBP in response to metoprolol when baseline PRA values were higher, whereas the positive coefficient (8.8 ± 3.1) indicates a greater reduction in SBP in response to chlorthalidone when baseline PRA values were lower. Abbreviations: AA, African American; Beta, regression coefficient; PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses; PRA, plasma renin activity; SBP, systolic blood pressure; SE, standard error of the regression coefficient.

predictive value of 38% (95% CI = 33% to 43%). This low sensitivity indicates many false negatives, reflecting a high proportion (62.1%) of AAs with PRA < 1.3 ng/ml/hour who had a fall in SBP ≥ 5 mm Hg from baseline (good response) to PEAR-1-atenolol and GERA-2-candesartan (Supplementary Table 3). It also reflects a high variability in SBP response to PEAR-1-atenolol and GERA-2-candesartan, especially in AAs with PRA < 1.3 ng/ml/hour, and suggests there are likely additional important biomarkers contributing to the response of RAS-blockers that warrant further investigation in AAs (Supplementary Figure 5).

In addition, area under ROC curve (0.59 (95% CI = 0.51 to 0.67, $P = 0.06$)) indicates that PRA cannot discriminate between the PEAR-1 AAs based on their SBP response to atenolol (Supplementary Figure 6).

DISCUSSION

To our knowledge, this is the first study undertaken to assess PRA biomarker clinical utility among a cohort of EA and AA hypertensives using a systematic-phased approach. We demonstrated that a previously identified PRA cut point of 0.60–0.65 ng/ml/hour is a useful predictive biomarker of SBP response and could be used to guide antihypertensive selection in EAs with uncomplicated HTN. However, based on our datasets, we were unable to identify a PRA cut point, which is predictive of SBP response in AAs with uncomplicated HTN. Importantly, our findings demonstrate that β -blockers and ARBs are effective BP-lowering agents in some AA hypertensives.

High interindividual variability in BP response to different antihypertensive drug classes has been reported previously,^{25,26} thus identifying biomarkers that can predict BP response is an important key to personalizing antihypertensive therapy and reducing the long-term cardiovascular risks. PRA is one of the most promising biomarkers studied to date. Laragh and associates advocate that patients with hypertension with PRA < 0.65 ng/ml/hour

Table 3. Baseline and posttreatment BP of PEAR-1 and GERA AAs

PEAR-1 AA					
HCTZ 25 mg once daily (n = 151)			Atenolol 100 mg once daily (n = 152)		
	Pre-BP mm Hg (SD)	Post-BP mm Hg (SD)	Delta-BP mm Hg (SD)	Pre-BP mm Hg (SD)	Post-BP mm Hg (SD)
SBP	151.6 (13.5)	135.9 (14.4)	-15.7 (14.3)	151.2 (12.1)	142.2 (16.6)
DBP	99.3 (6.2)	90.0 (8.6)	-9.3 (8.6)	98.9 (6.8)	90.9 (10.2)
GERA AA					
HCTZ 25 mg once daily (n = 286)			Candesartan 32 mg once daily (n = 265)		
	Pre-BP mm Hg (SD)	Post-BP mm Hg (SD)	Delta-BP mm Hg (SD)	Pre-BP mm Hg (SD)	Delta-BP mm Hg (SD)
SBP	150.0 (15.4)	132.4 (15.8)	-17.6 (13.4)	147.6 (12.4)	137.7 (14.8)
DBP	96.8 (5.3)	87.4 (9.3)	-9.4 (8.5)	95.6 (5.2)	88.5 (9.3)

Data are summarized as mean (SD). Abbreviations: AA, African Americans; BP, blood pressure; DBP, diastolic blood pressure; GERA, Genetic Epidemiology of Responses to Antihypertensives; HCTZ, hydrochlorothiazide; PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses; SBP, systolic blood pressure.

Figure 4. Pooled adjusted mean differences in systolic blood pressure (SBP) response (mean, 95% confidence interval (CI)) to hydrochlorothiazide (HCTZ) vs. atenolol/candesartan in a meta-analysis of PEAR-1 and GERA AA cohorts by the different PRA subgroups based on the PEAR-2-derived plasma renin activity (PRA) cut point. All the values are adjusted for baseline SBP. A positive value in the pooled adjusted SBP response difference indicates AA participant had a better response to atenolol/candesartan than to HCTZ, whereas a negative value in the pooled adjusted SBP response difference indicates AA participant had a better response to HCTZ than to atenolol/candesartan. Abbreviations: AA, African American; GERA, Genetic Epidemiology of Responses to Antihypertensives; PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses.

have predominantly volume-dependent HTN and would likely respond better to diuretics, whereas those with PRA ≥ 0.65 ng/ml/hour have predominantly vasoconstriction-dependent HTN and would likely respond better to RAS-blockers that either block angiotensin-II formation (angiotensin-converting enzyme inhibitors), block its action (ARBs), or decrease renal renin release (β -blockers).¹¹ As published literature has yielded conflicting results regarding PRA's role as a potential predictive biomarker of BP response,^{14–17} we sought to evaluate its clinical utility in EA and AA hypertensives using a systematic-phased approach.¹⁹

In this study, we demonstrated that PRA is significantly associated with SBP responses to both metoprolol and chlorthalidone in PEAR-2 EAs (early-phase evidence). We observed that EAs with lower PRA (<0.65 ng/ml/hour) had a greater SBP response to chlorthalidone than to metoprolol. Previously, we demonstrated that regardless of age, PEAR-1 EAs with lower PRA had similar BP responses to both atenolol and HCTZ,¹⁴ whereas GERA EAs with lower PRA had a greater BP response to candesartan than to HCTZ.¹⁵ This inconsistency could be due to the HCTZ lower potency, compared with chlorthalidone.^{27,28} In contrast, we observed that PEAR-2 EAs with higher-PRA (≥ 0.65 ng/ml/hour) had a greater response to metoprolol than to chlorthalidone, which is consistent with other studies.^{14,15}

In accordance with a systematic-phased approach,¹⁹ we further tested PRA's predictive performance in EAs and demonstrated, for the first time, that PRA at cut point of 0.60–0.65 ng/ml/hour, derived in Caucasians decades ago, can discriminate between EAs based on their SBP responses (mid-phase evidence). An RCT has been conducted to test the PRA-guided treatment approach in EA;²⁹ however, additional trials investigating multiple antihypertensive agents and assessing BP response and BP control are needed to fully elucidate PRA's role in HTN treatment.^{27,28}

Among PEAR-2 AAs, we observed that PRA is significantly associated with SBP response to chlorthalidone, but not metoprolol, which is consistent with previous studies.^{14,15} Thus, it is unclear whether PRA is an unreliable predictive biomarker, or the 0.65 ng/ml/hour, originally derived in EAs,^{30,31} is not the optimal cut point in AAs. Accordingly, we investigated whether an optimal PRA cut point could be identified among a cohort of AA hypertensives. Using a systematic approach, we derived a PRA cut point of 1.3 ng/ml/hour, which was then tested in a meta-analysis of 2 independent validation cohorts, where we found that PRA at the 1.3 ng/ml/hour cut point is significantly associated with SBP responses to HCTZ and atenolol or candesartan (early-phase evidence).

However, when we moved to the mid-phase evidence to further assess clinical impact of these findings, we found that PRA at the 1.3 ng/ml/hour cut point had only 10% sensitivity to identify the subset of AAs who could be effectively treated with either atenolol or candesartan, and this was also confirmed by an ROC analysis. The PRA's low sensitivity reflects many false negatives, and we, in fact, observed a high percentage (62.1%) of AAs with PRA <1.3 ng/ml/hour who had a good response to atenolol or candesartan. A possible explanation for this observation is that these individuals might have an activated RAAS at tissue level that may not be correlated with renin plasma levels as observed in a previous study.³² In addition, the good response we observed to atenolol could be due to other β -blockers' well-known mechanisms such as decreasing heart rate, rather than solely inhibition of renal renin secretion.³³ Moreover, the good response to candesartan could be due to blocking the action of the vasoconstrictor angiotensin-II, thus decreasing aldosterone release and enhancing sodium excretion.³⁴

Our study has several strengths. Among studies investigating PRA's role in personalizing antihypertensive therapy, this is the first study to use the more potent thiazide-like diuretic,

chlorthalidone. To our knowledge, data pertaining to PRA from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, one of the largest RCTs to include chlorthalidone, has not collected PRA data.³⁵ In addition, ours is the first study to confirm the predictive value of the 0.65 ng/ml/hour PRA cut point among uncomplicated EA hypertensives and to report a high percentage of AA hypertensives having a good response to RAS-blockers. On the other hand, results of this study should be considered in light of its limitations. First, this study is an analysis from 3 independent cohorts with a relatively short observation period. However, we assume that inferences from this analysis are unlikely to be biased since the populations used, and inclusion and exclusion criteria were very similar among these studies, and it is highly likely that all drugs tested achieved steady state in the follow-up period. Another limitation is that we estimated the 1.3 ng/ml/hour PRA cut point in AAs based on the average SBP response of the PEAR-2 AAs. Although this might have introduced some potential error, using PEAR-2 data, where all participants were sequentially exposed to the same antihypertensive agents is expected to be associated with a minimal inter-patient variability. We were unable to assess whether the 1.3 ng/ml/hour PRA cut point predicts a better BP response to a diuretic vs. a RAS-blocker in AAs as we did not have a validation cohort where AA participants received both drug classes. Further research is needed to complete this assessment. Also, the use of HCTZ in the validation AA cohorts (instead of the more potent diuretic chlorthalidone used in the discovery cohort) is considered a limitation. In addition, PRA was measured using 2 different assays: DiaSorin assay (PEAR-2, PEAR-1, and GERA-2) was associated with lower-PRA values than DuPont assay (GERA-1). An analysis using GERA samples from which PRA was measured by both assays suggests that 7% AAs would have been categorized differently using the 1.3 ng/ml/hour cut point (data not shown). Using PEAR-1 and GERA data, we expect that differences in PRA categorization may have had a small effect on the meta-analysis results and had no effect on the sensitivity and ROC results. In addition, our conclusions are limited to patients aged < 65 years. PRA's predictive value in patients aged > 65 years warrants further investigation.

In conclusion, our data suggest that PRA cut point of 0.60–0.65 ng/ml/hour could be used in EAs for a personalized antihypertensive treatment, especially when chlorthalidone is the diuretic of choice. In contrast, PRA is not a useful biomarker in hypertensive AAs. In addition, our observations emphasize that thiazides' use as first-line treatment in uncomplicated AA hypertensives—based on the recent recommendations—³⁶ should be reconsidered as we found that β -blockers and ARBs had a BP-lowering effect in a proportion of these patients and may be beneficial for those having other comorbid conditions such as coronary artery disease where RAAS blockade is favorable.^{37,38}

SUPPLEMENTARY DATA

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflicts of interest.

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