ORIGINAL ARTICLE

Comparison of Blood Pressure Control Rates Among Recommended Drug Selection Strategies for Initial Therapy of Hypertension

Kamel A. Gharaibeh[1], Stephen T. Turner[1], Abdurrahman M. Hamadah[1], Arlene B. Chapman[2], Rhonda M. Cooper-Dehoff[3], Julie A. Johnson[3], John G. Gums[3], Kent R. Bailey[4], and Gary L. Schwartz[1]

BACKGROUND
Several approaches to initiation of antihypertensive therapy have been suggested. These include thiazide diuretics (TDs) as the first drug in all patients, initial drug selection based on age and race criteria, or therapy selection based on measures of plasma renin activity (PRA). It is uncertain which of these strategies achieves the highest control rate with monotherapy in Stage-I hypertension. We sought to compare control rates among these strategies.

METHODS
We used data from the Pharmacogenomic Evaluation of Antihypertensive Responses study (PEAR) to estimate control rates for each strategy: (i) TD for all, (ii) age- and race-based strategy: Hydrochlorothiazide (HCTZ) for all blacks and for whites ≥50 years and a renin-angiotensin system inhibitor (atenolol) for whites <50 years) or (iii) a PRA based strategy: HCTZ for suppressed PRA (<0.6 ng/ml/h) and atenolol for non-suppressed PRA (≥0.6 ng/ml/h) despite age or race. Hypertension was confirmed prior to treatment with HCTZ (148 blacks and 218 whites) or with atenolol (146 blacks and 221 whites).

RESULTS
In the overall sample, using clinic blood pressure (BP) response, the renin-based strategy was associated with the greatest control rate (48.9% vs. 40.8% with the age and race-based strategy ($P = 0.0004$) and 31.7% with the TD for all strategy ($P < 0.0001$)). The findings were similar using home or by 24-hour ambulatory BP responses and within each racial subgroup.

CONCLUSIONS
A strategy for selection of initial antihypertensive drug therapy based on PRA was associated with greater BP control rates compared to a thiazide-for-all or an age and race-based strategy.

Keywords: antihypertensive drug therapy; atenolol; beta-blocker; blood pressure; hydrochlorothiazide; hypertension; plasma renin activity; thiazide diuretic.

doi:10.1093/ajh/hpw067

INTRODUCTION

Elevated blood pressure (BP) is the most important risk factor for death and disability worldwide, affecting more than one billion individuals and causing an estimated 9.4 million deaths every year. Hypertension (HTN) is a major independent risk factor for stroke, chronic kidney disease, coronary artery disease, and heart failure. In the United States, more than $47.5 billion is spent each year on high-BP management.[1]

Despite the availability of numerous drug options, the overall control rate among adults with HTN in the United States remains low at 52%.[2,3] The percentage of hypertensives in the optimal BP range is 18.6%.[2] Non-adherence, which increases as the number of drugs required increases[4] is the major reason for low-BP control rate.[5] Thus, for initial therapy, identification of the drug most likely to be effective in BP reduction is important.

HTN treatment guidelines suggest a thiazide diuretics (TDs) as the agent of first choice for initial therapy of most people with uncomplicated HTN (TD strategy).[6] However, BP response to any single antihypertensive drug is characterized by significant interindividual variation.[7,8] This variation in response is believed to be secondary to variation in the pathophysiologic mechanisms causing HTN and heterogeneity in the counterregulatory physiological responses to BP reduction.[9,10] The renin-angiotensin-aldosterone system (RAAS) plays a major role in BP regulation and the activity of this system varies among individuals with HTN.[11,12]

Initial drug selection based on an estimation of the activity of the RAAS has been extensively supported by Laragh and colleagues.[13,14] This strategy is based on the hypothesis that individuals with high (non-suppressed) plasma renin activity (PRA) have vasoconstriction-dependent HTN mediated by angiotensin II, directing initial therapy to drugs

Correspondence: Kamel Gharaibeh (kamelgharaibeh@yahoo.com).

Initially submitted April 18, 2016; date of first revision May 2, 2016; accepted for publication June 7, 2016; online publication June 30, 2016.

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [2]Section of Nephrology, University of Chicago, Chicago, IL, USA; [3]College of Pharmacy, University of Florida, Gainesville, FL, USA; [4]Divisions of Biostatistics and Biomedical Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

that directly block renin release or the formation or action of angiotensin II (RAS inhibitors), while individuals with low (suppressed) PRA are hypothesized to have sodium volume–dependent HTN, directing initial therapy to a diuretic.[14]

Others have suggested that age and race criteria can serve as useful surrogates for PRA. In this strategy, a TD is recommended for older whites or blacks of any age and a RAS blocker is recommended for younger whites.

In a previous study of adults with stage 1 HTN, we demonstrated that initial drug selection based on PRA was associated with higher BP control rates compared to drug selection based on age and race criteria or TD as the initial drug of choice for all.[15] In this previous study, the angiotensin receptor blocker candesartan was used as the RAS blocker and BP response was based on change in office BP. The objective of the present study is to confirm our previous findings in a separate cohort using a different RAS blocking drug (atenolol) and using more comprehensive measures of BP response including both home and 24-hour ambulatory BP in addition to office measures.

METHODS

Study population

This study is a retrospective analysis of data previously collected in the PEAR-1 study. The PEAR-1 study was a prospective, multicenter, randomized, open-label, parallel group study with a primary focus on identifying the genetic determinants of antihypertensive and adverse metabolic responses to a TD (hydrochlorothiazide (HCTZ)), a beta-blocker (atenolol) and their combination. Full details of the PEAR study methodology have been reported elsewhere.[16]

Briefly, the study cohort consisted of males and females, of any race and ethnicity, aged 17 to 65 at enrollment who had newly diagnosed, untreated, or known mild-to-moderate essential HTN (stage 1–2 primary HTN defined by average home diastolic BP (DBP) >85 mm Hg and office DBP >90 mm Hg) treated with two or fewer antihypertensive medications. Study participants were enrolled at the University of Florida (Gainesville, FL), Emory University (Atlanta, GA) and Mayo Clinic (Rochester, MN). Following enrolment, all antihypertensive therapy was discontinued in treated participants. After an average washout period of 4 weeks, HTN was confirmed and participants were randomly assigned to receive monotherapy with either atenolol or HCTZ. Participants received 50 mg of atenolol daily or 12.5 mg of HCTZ daily, titrated to 100 mg daily or 25 mg daily respectively, if BP remained above 120/70 mm Hg after 3 weeks. Participants remained on drug monotherapy for a total of 9 weeks. Home BP was monitored throughout the 9-week treatment period and 24-hour ambulatory BP was measured at the end of the washout period and repeated at the end of the treatment period. All individuals provided written informed consent to participate. The study was approved by the institutional review board at each study site.

Patients were excluded if they had an office or average home SBP >180 mm Hg or DBP >110 mm Hg, secondary forms of HTN (including sleep apnea), isolated systolic HTN, known cardiovascular disease, heart rate <55 beats per minute (bpm) in the absence of beta-blocker therapy, diabetes mellitus (type 1 or 2) or screening fasting blood glucose >126 mg/dl, primary renal disease, concomitant diseases treated with BP-lowering medications, or chronic treatment with BP-elevating drugs

Laboratory analyses

Plasma samples were assayed in duplicate or triplicate, and participant's average values were used in the analyses. Plasma analytes were measured on a Hitachi 911 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). PRA was measured by radioimmunoassay of angiotensin I according to the method of Sealey using reagents purchased from DiaSorin (Stillwater, MN). The incubation period for angiotensin I generation was 3 hours.[17]

Statistical analyses

Data were summarized by calculating means and SDs or medians and upper and lower quartiles for quantitative variables and percentages for categorical variables. *P* values for differences in quantitative variables were calculated using analysis of variance for variables that were normally distributed and the Mann–Whitney rank sum test for quantitative variables that were not normally distributed. In all analyses, statistical significance was inferred when $P < 0.05$. Office BP was considered controlled if it was <140 mm systolic and <90mm Hg diastolic at the end of drug therapy. The corresponding values indicating control for home BP were <135 mm Hg systolic and <85 mm Hg diastolic and for 24-hour ABMP were <130 mm Hg systolic and <80 mm Hg diastolic. Control rates were calculated for the following three strategies: (i) HCTZ for all subjects (TD strategy); (ii) HCTZ for all black subjects and for white subjects aged ≥50 years, with atenolol for white subjects aged <50 years (age and race strategy); and (iii) HCTZ if PRA < 0.6 ng/ml/h (suppressed PRA) and atenolol if PRA ≥ 0.6 ng/ml/h (non-suppressed PRA; PRA strategy).

A formal test of the null hypothesis of equality of BP control rates between two strategies was because each strategy involves a choice between one of two antihypertensive drugs within each of eight age, race, and PRA strata. Within each of these eight strata, the difference in BP control rates was calculated as the difference between two binomial proportions as previously described.[15]

RESULTS

Sample description

The overall sample consisted of 294 (40%) black subjects and 439 (60%) white subjects; 391 (53.3%) were women. On average, subjects were overweight or obese (body mass index = 30.8 ± 5.6 kg/m^2), had a clinic SBP of 151.7 (±12.6) mm Hg and clinic DBP of 98.5 (±6.1) mm Hg (Table 1). There were no significant differences between the treatment groups (atenolol vs. HCTZ) in mean age, gender, BMI, baseline BP (in all settings/measures), heart rate, and baseline PRA. This was true between the overall treatment groups and between treatment groups within each racial subgroup.

Table 1. Subject characteristics

		Black			White		
	Overall	Atenolol	HCTZ	*P* value	Atenolol	HCTZ	*P* value
No (%)	733 (100%)	146	148		221	218	
Age, years	49.0 (9.2)	47.3 (8.5)	47.4 (8.7)	0.8795	49.9 (9.5)	50.4 (9.3)	0.5793
Female No. (%)	391 (53.3%)	104 (71.2%)	92 (62.2%)	0.0990	105 (47.5%)	90 (41.3%)	0.1892
BMI kg/m^2	30.8 (5.6)	31.4 (6.3)	31.5 (5.4)	0.8990	30.4 (5.7)	30.3 (5.0)	0.8923
Baseline Clinic SBP	151.7 (12.6)	151.2 (12.2)	151.8 (13.4)	0.6627	151.5 (12.4)	152.2 (12.5)	0.5668
Post-treatment Clinic SBP	138.9 (15.0)	142.6 (16.7)	136.2 (14.5)	0.0005	136.1 (14.8)	141.0 (13.6)	0.0003
Systolic Clinic BP (End − Baseline)	−12.8 (14.9)	−8.6 (16.8)	−15.6 (14.4)	0.0001	−15.4 (15.0)	−11.2 (13.0)	0.0017
Baseline Clinic DBP	98.5 (6.1)	98.9 (6.8)	99.4 (6.2)	0.5042	98.0 (5.8)	98.1 (5.9)	0.8369
Post-treatment Clinic DBP	90.1 (9.4)	91.4 (10.2)	90.1 (8.6)	0.2667	86.1 (9.0)	93.1 (8.4)	<0.0001
Diastolic Clinic BP (End − Baseline)	−8.4 (9.1)	−7.5 (9.7)	−9.3 (8.7)	0.1086	−11.9 (9.2)	−5.0 (7.3)	<0.0001
Baseline Home SBP	145.8 (10.4)	145.0 (10.5)	147.3 (11.6)	0.0692	145.1 (9.6)	146.2 (10.1)	0.2430
Post-treatment Home SBP	137.2 (12.5)	141.9 (13.1)	135.6 (13.3)	0.0001	134.0 (12.5)	138.4 (10.2)	0.0001
Systolic Home BP (End − Baseline)	−8.7 (9.9)	−3.1 (10.4)	−11.7 (9.7)	<0.0001	−11.1 (9.5)	−7.8 (8.5)	0.0002
Baseline Home DBP	93.8 (6.0)	94.0 (6.4)	95.2 (6.5)	0.1109	92.9 (5.6)	93.6 (5.5)	0.1663
Post-treatment Home DBP	87.3 (8.2)	89.8 (8.5)	88.3 (8.3)	0.1239	83.0 (7.4)	89.3 (6.9)	<0.0001
Diastolic Home BP (End − Baseline)	−6.5 (6.7)	−4.2 (6.6)	−6.9 (6.6)	0.0004	−9.9 (6.5)	−4.3 (5.4)	<0.0001
Baseline 24-hour ambulatory SBP	138.5 (11.0)	137.5 (10.1)	139.0 (12.3)	0.2715	138.1 (10.5)	139.2 (11.2)	0.3040
Post treatment 24-hour ambulatory SBP	127.6 (11.5)	130.4 (12.4)	126.2 (10.8)	0.0036	123.7 (10.8)	130.6 (10.8)	<0.0001
Systolic 24-hour ambulatory (End − Baseline)	−10.9 (10.7)	−6.4 (10.7)	−13.0 (9.5)	<0.0001	−14.3 (10.6)	−8.9 (10.3)	<0.0001
Baseline 24-hour ambulatory DBP	87.3 (8.0)	87.0 (8.1)	87.8 (7.8)	0.4310	87.0 (7.3)	87.5 (8.7)	0.5228
Post treatment 24-hour ambulatory DBP	79.9 (8.4)	81.0 (8.7)	79.9 (7.7)	0.2742	76.3 (7.2)	82.7 (8.6)	<0.0001
Diastolic 24-hour ambulatory (End − Baseline)	−7.2 (7.8)	−5.5 (7.3)	−7.8 (7.2)	0.0105	−10.5 (8.0)	−4.7 (7.2)	<0.0001
Baseline Renin	1.0 (1.1)	0.6 (0.6)	0.6 (0.8)	0.6705	1.3 (1.3)	1.2 (1.2)	0.7074
Post treatment Renin	1.3 (1.7)	0.3 (0.4)	1.5 (1.7)	<0.0001	0.5 (0.6)	2.5 (2.1)	<0.0001
P value (change in renin after treatment)	0.0076	0.0001	0.0001		0.0001	0.0001	
Number of Baseline Renin < 0.6	335 (47.1%)	95 (66.4%)	99 (70.2%)	0.4937	67 (31.0%)	74 (34.9%)	0.3935
Number of End Renin < 0.6	327 (52.2%)	113 (89.0%)	50 (38.8%)	<0.0001	146 (78.9%)	18 (9.7%)	<0.0001
Renin (End − Baseline)	0.3 (1.6)	−0.2 (0.5)	0.9 (1.5)	<0.0001	−0.8 (1.2)	1.3 (1.7)	<0.0001
Heart rate, bpm (end of washout)	77.6 (9.4)	79.7 (9.1)	78.9 (9.6)	0.5141	76.7 (9.2)	76.3 (9.5)	0.6599
Heart rate, bpm after treatment	72.5 (11.4)	68.7 (9.7)	81.0 (9.5)	<0.0001	63.9 (7.7)	77.8 (9.6)	<0.0001
P value (change in heart rate with treatment)	0.0001	0.0001	0.0001		0.0001	0.0001	

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; HCTZ, Hydrochlorothiazide; SBP, systolic blood pressure. Continuous variables were summarized as mean (standard deviation) with *P* values for the differences between groups calculated using the analysis of variance test. Discrete variables were summarized as frequency (group percentage) with *P* values for the differences between groups calculated using the χ^2 test. Statistical significance was inferred when $P < 0.05$. SAS version 9.3 (SAS Institute, Cary, NC) or higher was used for analyses.

Heart rate and PRA decreased significantly in both racial subgroups treated with atenolol ($P < 0.0001$ for both). In contrast, heart rate and PRA increased significantly in both racial subgroups treated with HCTZ ($P < 0.0001$ for both).

In black subjects overall: clinic, home and 24-hour ambulatory SBP and DBP responses were greater with HCTZ than with atenolol ($P = 0.0001$ and $P = 0.109$ for clinic BP, $P < 0.0001$ and $P = 0.0004$ for home BP and $P < 0.0001$ and $P = 0.01$ for 24-hour ambulatory BP). In white subjects

overall, the reverse was true—clinic, home and 24-hour ambulatory SBP and DBP responses were greater with atenolol than with HCTZ ($P = 0.0017$ and $P < 0.0001$ for clinic BP, $P = 0.0002$, and $P < 0.0001$, for home BP and $P < 0.0001$ and <0.0001 for 24-hour ambulatory BP).

BP control rate by treatment strategy

In the overall sample, the strategy of drug selection based on pretreatment PRA was associated with the highest control rate for all BP response measures: clinic BP (48.9% with the PRA strategy vs. 40.8% with the age and race strategy [$P = 0.0004$] and 31.7% with the TD strategy ($P < 0.0001$), home BP 42.6% with the PRA strategy vs. 36.1% with the age and race strategy ($P = 0.0026$) and 26.4% with the TD strategy ($P < 0.0001$)) and 24-hour ambulatory BP (61.3% with the PRA strategy vs. 51.6% with the age and race strategy ($P < 0.0001$) and 43.9% with the TD strategy ($P < 0.0001$, Table 2).

In blacks, the strategy of drug selection based on pretreatment PRA was also associated with a higher control rate than drug selection based on the other two strategies, both of which directed the use of a TD for all subjects: clinic BP 46.7% with the PRA strategy vs. 41.4% for both the age and race strategy and TD strategy ($P = 0.08$ for both), home BP 37% with the PRA strategy vs. 33.6% for both the age and race strategy and TD strategy ($P = 0.25$ for both) and 24-hour ambulatory BP 57.9% with the PRA strategy vs. 52.6% for both the age and race strategy and TD strategy ($P = 0.099$ for both; Table 3). The higher control with the PRA strategy was largely due to a higher control rate with atenolol than HCTZ in blacks with non-suppressed PRA (clinic BP 54.2% vs. 35.7%; $P = 0.08$, home BP 37.5% vs. 26.8% $P = 0.25$ and 24-hour ambulatory BP 62.5% vs. 45.2%, $P = 0.1$; Table 4). In blacks with suppressed PRA, the control rate was higher with HCTZ than with atenolol (clinic BP 43.4% vs. 14.3%, $P < 0.0001$, home BP 36.8% vs. 17.4%, $P = 0.002$ and 24-hour ambulatory BP 55.7% vs. 37.8%, $P = 0.011$; Table 4).

In white subjects, the strategy of drug selection based on pretreatment PRA was also associated with a higher control rate than drug selection based on either of the other 2 strategies for all BP measures: clinic BP 50.3% with the PRA strategy vs. 40.6% with the age and race strategy ($P = 0.002$) and 25.4% with the TD strategy ($P < 0.0001$), home BP 46.3% with the PRA strategy vs. 37.7% with the age and race strategy ($P = 0.004$) and 21.6% with the TD strategy ($P < 0.0001$) and 24-hour ambulatory BP 63.5% with the PRA strategy vs. 50.9% with the age and race strategy ($P < 0.0001$) and 38.2% with the TD strategy ($P < 0.0001$; Table 3).

Consistent with the findings in blacks with non-suppressed PRA, control rates were higher with atenolol than with HCTZ in whites with non-suppressed PRA—clinic

Table 2. Overall blood pressure control rates by treatment strategy

Treatment strategy	Clinic BP (<140/90)	Home BP (<135/85)	24-hour ambulatory BP (<130/80)
TD	31.7	26.4	43.9
Age–Race	40.8	36.1	51.6
PRA	48.9	42.6	61.3
Age–Race vs. TD *P* value	<0.0001	<0.0001	<0.0001
PRA vs. TD *P* value	<0.0001	<0.0001	<0.0001
PRA vs. Age–Race *P* value	0.0004	0.0026	<0.0001

Blood pressure control rate defined as percentage of subjects with BP < 140/90 mm Hg for clinic, < 135/85 for home BP and < 130/80 for 24-hour ambulatory BP. Thiazide diuretic (TD) strategy was hydrochlorothiazide in all subjects. Age/race strategy was hydrochlorothiazide in all black subjects and in white subjects aged ≥50 years and atenolol in white subjects aged <50 years. Plasma renin activity (PRA) strategy was hydrochlorothiazide for pretreatment PRA < 0.6 ng/ml/h and atenolol for pretreatment PRA ≥ 0.6ng/ml/h.

Table 3. Comparing blood pressure control between black and white based on the location and treatment strategy

	Clinic blood pressure		Home blood pressure		24-hour ambulatory blood pressure	
	Black	White	Black	White	Black	White
TD	41.1	25.4	33.6	21.6	52.6	38.2
Age–race	41.1	40.6	33.6	37.7	52.6	50.9
PRA	46.7	50.3	37	46.3	57.9	63.5
Age–race vs. TD *P* value	—	<0.0001	—	<0.0001	—	<0.0001
PRA vs. TD *P* value	0.08	<0.0001	0.2530	<0.0001	0.0994	<0.0001
PRA vs. age–race *P* value	0.08	0.0020	0.2530	0.0044	0.0994	<0.0001

Control rates were calculated for the following four strategies: (i) hydrochlorothiazide (HCT) for all subjects (TD strategy); (ii) HCT for all black subjects and for white subjects aged ≥50 years, with atenolol for white subjects aged <50 years (age/race strategy); and (iii) HCT if plasma renin activity (PRA) < 0.6 ng/ml/h (suppressed PRA) and atenolol if PRA ≥ 0.6 ng/ml/h (non-suppressed PRA; PRA strategy).

BP 65.1% vs. 26.8%; $P < 0.0001$, home BP 55 % vs. 16.7%; $P < 0.0001$ and 24-hour ambulatory BP 73.8% vs. 34.8%, $P < 0.0001$; Table 4). However, in contrast to the findings in blacks, control rates in whites with suppressed PRA were not significantly different between atenolol and HCTZ. In addition, in whites control rates were also higher with atenolol than with HCTZ in both age strata (aged <50 years: clinic BP: 63.5 % vs. 26.1%, $P < 0.0001$, home BP: 59.4% vs. 21.7% $P < 0.0001$ and 24-hour ambulatory BP: 71.9% vs. 42.4%, $P < 0.0001$; aged ≥50 years: clinic BP: 46.4% vs. 25.4 %, $P = 0.0005$, home BP: 36.8% vs. 22.2% $P = 0.01$ and 24-hour ambulatory BP: 64.8% vs. 35.7%, $P < 0.0001$.

Effect of race and age on PRA

Within each age stratum (< or ≥50 years of age), the proportion in each PRA stratum differed significantly by race ($P < 0.0001$ for all comparisons; Table 5). The majority of blacks were in the suppressed PRA stratum (PRA < 0.6ng/ml/h) with no difference in the proportion within each PRA stratum across age strata. In contrast, the majority of whites were in the non-suppressed PRA stratum (PRA ≥ 0.6ng/ml/h) with an increase in the proportion of suppressed PRA subjects in the aged ≥50 year stratum. Therefore, age influenced PRA status in whites more than in blacks.

Effects of race, age, and renin classification on differences in response to HCTZ vs. atenolol

Differences in office systolic and DBP responses (mean, 95% confidence interval (CI)) with HCTZ vs. atenolol for each racial subgroup overall and by age/PRA strata within each racial subgroup are shown in Figure 1. All values were adjusted for baseline BP, age, and sex.

Overall in blacks, compared to treatment with atenolol, treatment with HCTZ was associated with a greater decrease in both mean SBP response (by −7 mm Hg (95% CI = −3.4 to −10.7 mm Hg; $P = 0.0001$)) and mean DBP response (by −1.7 mm Hg (95% CI = −0.42 to −3.88 mm Hg; $P = 0.11$)).

In blacks with suppressed PRA, compared to treatment with atenolol, treatment with HCTZ was associated with a greater decrease in both mean SBP response (by −10.6 mm Hg (95% CI = −6.3 to −14.9 mm Hg; $P < 0.0001$)) and mean DBP response (by −4.26 mm Hg (95% CI −1.9 to −6.6; $P = 0.0005$)) and this response difference was consistent across age strata.

In young blacks with non-suppressed PRA, compared to treatment with HCTZ, treatment with atenolol was associated with a greater decrease in both mean SBP response (by −6.12 mm Hg (95% CI −1.8 to 14, $P = 0.13$) and mean DBP response (by −6.78 mm Hg (95% CI −1.3 to −12.3; $P = 0.015$)). However, in older blacks with non-suppressed PRA, there were no differences in responses between HCTZ and atenolol.

Overall, in whites, compared to treatment with HCTZ, treatment with atenolol was associated with a greater decrease in both mean SBP response (by −4.22 mm Hg [95% CI = -1.5 to −6.9 mm Hg]; $P = 0.0017$) and DBP response (by −6.9 mm Hg [95% CI = −5.3 to −8.5 mm Hg]; $P < 0.0001$).

In whites with suppressed PRA, there was no difference in response with atenolol compared to HCTZ for either SBP

Table 4. Clinic blood pressure control rates for each drug by PRA and age criteria

		Blood pressure control rate, %									
		Overall sample		Black subjects				White subjects			
	Drug	PRA < 0.6 ng/ml/h	PRA ≥ 0.6 ng/ml/h	PRA < 0.6 ng/ml/h	PRA ≥ 0.6 ng/ml/h	Aged <50 years	Aged ≥50 years	PRA < 0.6 ng/ml/h	PRA ≥0.6 ng/ml/h	Aged <50 years	Aged ≥50 years
Clinic	HCT	35	28.9	43.4	35.7	40.5	42.2	23.8	26.8	26.1	25.4
	Atenolol	21.2	62.4	14.3	54.2	25.3	30.5	30.6	65.1	63.5	46.4
	P value	0.0040	<0.0001	<0.0001	0.0795	0.0344	0.1791	0.3452	<0.0001	<0.0001	0.0005
Home	HCT	34.4	18.9	36.8	26.2	34.5	32.8	31.3	16.7	21.7	22.2
	Atenolol	22.4	50.8	17.4	37.5	21.8	27.1	29.2	55.0	59.4	36.8
	P value	0.0120	<0.0001	0.0019	0.2521	0.0650	0.4915	0.7801	<0.0001	<0.0001	0.0113
24-hour ambulatory	HCT	51.1	37.2	55.7	45.2	57.1	46.9	45.0	34.8	42.4	35.7
	Atenolol	45.3	71.1	37.8	62.5	50.6	39.0	55.6	73.8	71.9	64.8
	P value	0.2756	<0.0001	0.0105	0.1009	0.3891	0.3772	0.1937	<0.0001	<0.0001	<0.0001

Abbreviations: HCT, hydrochlorothiazide; PRA, plasma renin activity.

Table 5. Effect of race and age on PRA classification

PRA classification	Age < 50			Age ≥ 50		
	White subjects (*n* = 188)	Black subjects (*n* = 171)	*P* value	White subjects (*n* = 251)	Black subjects (*n* = 123)	*P* value
Suppressed PRA, No. (%)	41 (22%)	109 (64%)	<0.0001	100 (40%)	85 (69%)	<0.0001
Non-suppressed PRA, No. (%)	140 (74%)	56 (33%)	<0.0001	147 (59%)	34 (28%)	<0.0001

Abbreviation: PRA, plasma renin activity.

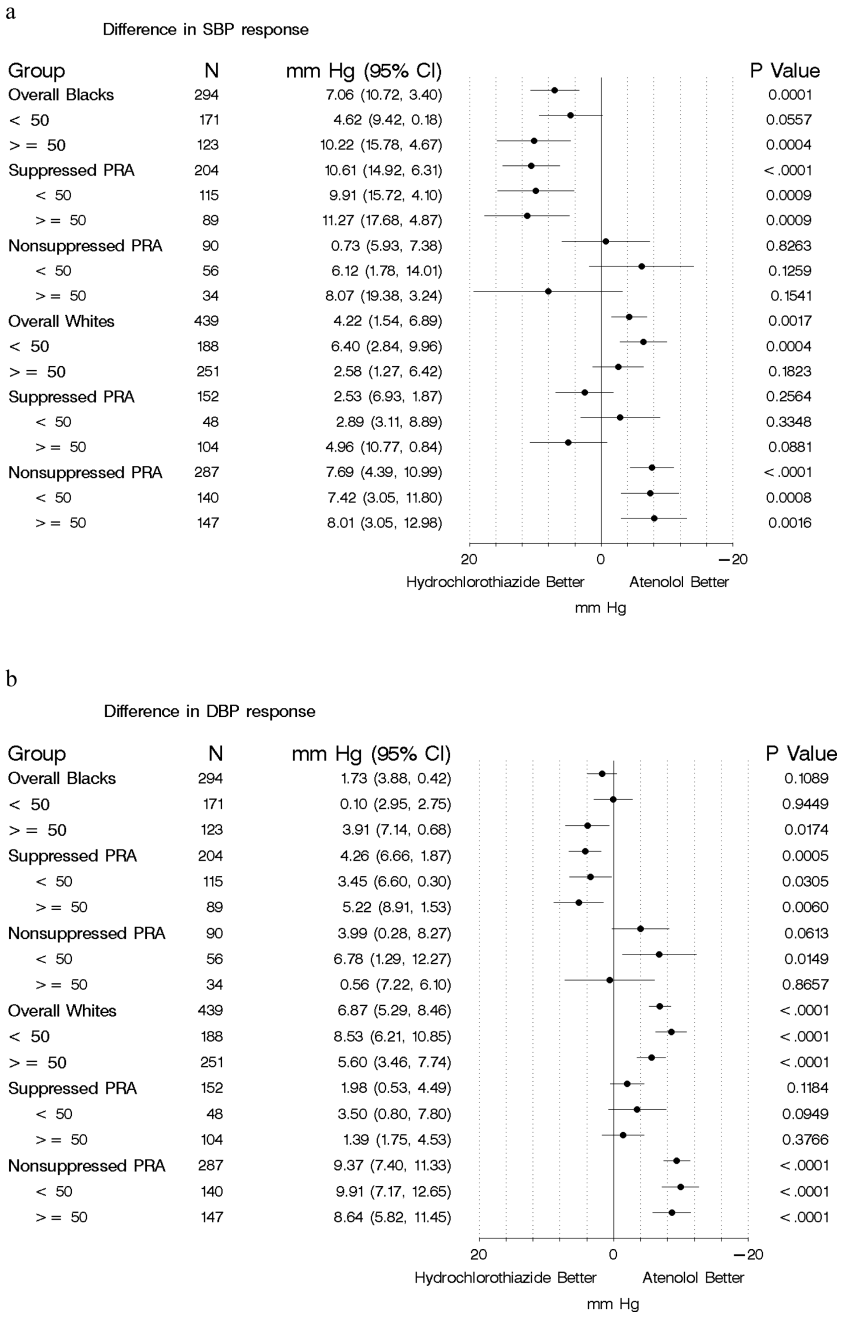

Figure 1 Differences in office (**a**) systolic (SBP) and (**b**) diastolic blood pressure (DBP) response (mean, 95% confidence interval (CI)) with hydrochlorothiazide (HCT) vs. atenolol for each racial subgroup overall and by age/plasma renin activity (PRA) strata.

or DBP ($P = 0.26$, and $P = 0.12$ respectively); this was also true in both age strata. In whites with non-suppressed PRA, compared to treatment with HCTZ, treatment with atenolol was associated with a greater decrease in both mean SBP response (by −7.7 mm Hg [95% CI = −4.4 to −11 mm Hg; $P < 0.0001$]) and DBP response (by −9.4 mm Hg [95% CI −7.4 to −11.3]; $P < 0.0001$) and this response difference was consistent across age strata.

The findings above were also observed for the home and 24-hour ambulatory BP responses, shown in Supplementary Figures 1 and 2.

DISCUSSION

In choosing an initial medication for treatment of uncomplicated HTN, three strategies have been suggested to help guide selection. These strategies are TD for all or drug selection based on age and race criteria or PRA. The results of the present analysis confirm our previous findings that drug selection based on PRA is associated with a higher BP control rate than either alternative strategy. This was true for the sample overall and for each racial subgroup. The present study not only confirms the previous study but also extends it to a different RAS blocker and to more robust measures of BP response that included home and ambulatory BP responses.

Beta-blockers are known to inhibit the RAAS. A study conducted by Laragh and colleagues found that beta-blocker therapy (propranolol) reduced plasma renin levels by blocking sympathetically (beta-1)-mediated renin release by the kidney in subjects with several types of HTN.[18] Their results demonstrated a strong correlation between reduction in PRA (by about 75%) and reductions in BP. Propranolol was also found to reduce aldosterone levels. They concluded that blocking the RAAS pharmacologically was a practical therapeutic strategy for HTN. Another study revealed that treating hypertensive subjects with a beta-blocker suppressed angiotensin II and PRA simultaneously.[19] Along with suppression of renin release, some evidence also exists suggesting that beta blockade could potentially inhibit intrarenal conversion of prorenin to renin.[19,20] Although beta-blockers lower BP through renin-dependent and renin-independent mechanisms (reduced heart rate and cardiac output), multiple studies have favored a greater effect in subjects with non-suppressed renin.[18,21]

As expected, the baseline home BP was lower than the baseline clinic BP. Thus, the absolute BP responses to treatment were less when measured by home than by office BP. Overall in black subjects, average systolic BP response was greater to the TD (HCTZ) than to the RAAS blocking drug (atenolol). This is consistent with previous studies that were conducted by Schwartz *et al.*[15] and others.[22] An adequate explanation for this is that the majority of hypertensive black subjects have suppressed values of PRA, which our study confirmed.

As previously reported in whites, average BP response to the RAAS-blocking drug was greater than to the TD. This can be partially explained by the higher prevalence of non-suppressed PRA in whites.[15] However, our data suggest that not all of the racial difference in response to atenolol vs. HCTZ can be explained by differences in PRA status. This is demonstrated by the observation that although the BP control rate was higher with atenolol than HCTZ overall in whites, and especially for the subgroup with non-suppressed PRA in both age strata, BP control rate was not higher with HCTZ than atenolol in whites with suppressed PRA.

Without considering PRA status, young whites (<50) responded better to atenolol than HCTZ for both systolic and diastolic ($P = 0.004$ and $P < 0.0001$, respectively). However, BP response was similar with HCTZ and atenolol among older whites (>50) except the DBP (Figure 1).

In older whites (>50), non-suppressed PRA predicted a greater BP response to atenolol than HCTZ (Table 6); whereas in younger whites response was greater with atenolol than HCTZ regardless of PRA status. This explains why the PRA strategy was superior to the TD for all strategy previously recommended by the Joint National Committee 7,[23]

Table 6. Comparing the delta change in systolic and diastolic BP between hydrochlorothiazide and atenolol in subgroups

Change in BP					
		Black subjects aged <50		White subjects aged ≥50	
		With non-suppressed renin (PRA ≥ 0.6)		With non-suppressed renin (PRA ≥ 0.6)	
		Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
Clinic	HCT	−8.4	−4.4	−10	−3.9
	Atenolol	−14.5	−11.2	−18	−12.5
	P value	0.13	0.015	0.0016	<0.0001
Home	HCT	−8.5	−4.9	−7.8	−4.2
	Atenolol	−6.2	−6.3	−13.4	−10.1
	P value	0.33	0.47	0.0004	<0.0001
24-hour ambulatory	HCT	−8.7	−6.5	−8.7	−3.8
	Atenolol	−10.5	−8.2	−17.2	−11.0
	P value	0.53	0.37	<0.0001	<0.0001

Abbreviations: BP, blood pressure; HCT, hydrochlorothiazide; PRA, plasma renin activity.

and the age and race strategy that directs selection of HCTZ for all older whites.

In contrast, in blacks, non-suppressed PRA predicted a greater BP response to atenolol than to HCTZ in young individuals (Table 6). The greater response in young blacks with non-suppressed PRA to atenolol than to HCTZ explains why the PRA strategy was superior to the other two strategies that directed treatment with HCTZ for all individuals.

Previous research conducted by Laragh and colleagues supported measurement of PRA in all hypertensive patients to direct initial antihypertensive drug selection.[13,14] However, this approach has been controversial and not adopted in most published guidelines. A study conducted by the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents (VACSG) that included a sample of 1,031 hypertensive black and white men randomized to six different monotherapies concluded that combining age (younger or older than 60 years) and race (black or white) was as effective as measuring PRA for initial drug selection and was preferable because it did not require the additional time and expense of laboratory measurements.[24]

The results of our study demonstrate that in white subjects ≥50 years of age, knowledge of PRA status provided additional information for drug selection, as atenolol was significantly more effective than HCTZ in this group when PRA was non-suppressed. However, atenolol was more effective than HCTZ in all whites <50 years of age regardless of PRA status. These results indicate that a RAS blocking agent (atenolol) is preferred in whites <50 years of age across PRA strata and in subjects older than 50 years with non-suppressed PRA.

In black subjects, knowledge of PRA status also provides additional information for drug selection as atenolol was significantly more effective in blacks <50 years of age when PRA was non-suppressed whereas in older blacks HCTZ was significantly more effective than atenolol regardless of PRA status. These results indicate that a TD is preferred in blacks ≥50 years of age across PRA strata and in blacks <50 years of age with suppressed PRA.

Based on these observations, a combination of PRA and age and race criteria may be the most effective strategy for selecting initial antihypertensive drug therapy. We propose an optimal strategy that combines age and race and PRA for drug selection.[15] This strategy directs a RAS blocker for all whites <50 years of age without measurement of PRA, whereas for whites ≥50 years of age drug selection should be based on PRA measurement. Drug selection in blacks <50 years of age would be guided by PRA measurement, whereas blacks ≥50 years of age would be given a diuretic without measurement of PRA.

The results of the present study should be viewed in light of its limitations. This was a retrospective analysis of data from a multicenter prospective randomized study. Additionally, our study population was limited to individuals who were aged <60 years, precluding the assessment of the predictive value of age on drug response in those who are above the age of 60. Assessment of BP control rates by selection strategy is limited to a relatively short period of observation. Long-term control with each drug was not assessed. Another limitation is that the practical application of renin profiling would be facilitated by a point-of-care renin test, which is currently not available.

CONCLUSION

These results suggest that initial antihypertensive drug selection based on PRA is associated with greater BP control than selection based on age and race criteria or a strategy that recommends a TD for all.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

ACKNOWLEDGMENT

This study had financial support from the Pharmacogenomics Research Network (PGRN U01 GM074492) and the National Center for Advancing Translational Sciences Clinical and Translational Science Award (NIH NCATS: UL1 TR000064, UL1TR000454, UL1 TR000135). PEAR efforts at the Mayo Clinic were also supported by funds from the Mayo Foundation.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011; 123:933–944.
2. Yoon SS, Gu Q, Nwankwo T, Wright JD, Hong Y, Burt V. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. *Hypertension* 2015; 65:54–61.
3. Bakris G, Sarafidis P, Agarwal R, Ruilope L. Review of blood pressure control rates and outcomes. *J Am Soc Hypertens* 2014; 8:127–141.
4. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. *MedGenMed* 2007; 9:58.
5. Dezii CM. A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. *Managed Care* 2000; 9(Suppl 9):2–6.
6. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
7. Bidiville J, Nussberger J, Waeber G, Porchet M, Waeber B, Brunner HR. Individual responses to converting enzyme inhibitors and calcium antagonists. *Hypertension* 1988; 11:166–173.
8. Turner ST, Schwartz GL, Chapman AB, Hall WD, Boerwinkle E. Antihypertensive pharmacogenetics: getting the right drug into the right patient. *J Hypertens* 2001; 19:1–11.
9. van Brummelen P, Man in 't Veld AJ, Schalekamp MA. Hemodynamic changes during long-term thiazide treatment of essential hypertension in responders and nonresponders. *Clin Pharmacol Ther* 1980; 27:328–336.
10. Guyton AC, Hall JE, Lohmeier TE, Jackson TE, Kastner PR. Blood pressure regulation: basic concepts. *Fed Proc* 1981; 40:2252–2256.

11. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. *J Hypertens* 2006; 24:983–991.
12. Kaplan NM. Renin profiles. The unfulfilled promises. *JAMA* 1977; 238:611–613.
13. Laragh JH, Sealey JE. Relevance of the plasma renin hormonal control system that regulates blood pressure and sodium balance for correctly treating hypertension and for evaluating ALLHAT. *Am J Hypertens* 2003;16:407–415.
14. Laragh JH, Sealey JE. The plasma renin test reveals the contribution of body sodium-volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. *Am J Hypertens* 2011; 24:1164–1180.
15. Schwartz GL, Bailey K, Chapman AB, Boerwinkle E, Turner ST. The role of plasma renin activity, age, and race in selecting effective initial drug therapy for hypertension. *Am J Hypertens* 2013; 26: 957–964.
16. Johnson JA, Boerwinkle E, Zineh I, Chapman AB, Bailey K, Cooper-DeHoff RM, Gums J, Curry RW, Gong Y, Beitelshees AL, Schwartz G, Turner ST. Pharmacogenomics of antihypertensive drugs: rationale and design of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study. *Am Heart J* 2009;157:442–449.
17. Sealey JE. Plasma renin activity and plasma prorenin assays. *Clin Chem* 1991; 37:1811–1819.
18. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. *Am J Hypertens* 2001; 14:296–304.
19. Blumenfeld JD, Sealey JE, Mann SJ, Bragat A, Marion R, Pecker MS, Sotelo J, August P, Pickering TG, Laragh JH. Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects. *Am J Hypertens* 1999; 12:451–459.
20. Atlas SA, Sealey JE, Laragh JH, Moon C. Plasma renin and "prorenin" in essential hypertension during sodium depletion, beta-blockade, and reduced arterial pressure. *Lancet* 1977; 2:785–789.
21. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006; 368:1449–1456.
22. Moser M, Lunn J. Responses to captopril and hydrochlorothiazide in black patients with hypertension. *Clinical Pharmacol Ther* 1982; 32:307–312.
23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
24. Preston RA, Materson BJ, Reda DJ, Williams DW, Hamburger RJ, Cushman WC, Anderson RJ. Age-race subgroup compared with renin profile as predictors of blood pressure response to antihypertensive therapy. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *JAMA* 1998; 280:1168–1172.