Age-Race Subgroup Compared With Renin Profile as Predictors of Blood Pressure Response to Antihypertensive Therapy

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Context.—Renin profiling and age-race subgroup may help select single-drug therapy for stage 1 and stage 2 hypertension.

Objective.—To compare the plasma renin profiling and age-race subgroup methods as predictors of response to single-drug therapy in men with stage 1 and 2 hypertension as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Design.—The Veterans Affairs Cooperative Study on Single-Drug Therapy of Hypertension, a randomized controlled trial.

Setting.—Fifteen Veterans Affairs hypertension centers.

Patients.—A total of 1105 ambulatory men with entry diastolic blood pressure (DBP) of 95 to 109 mm Hg, of whom 1031 had valid plasma and urine samples for renin profiling.

Interventions.—Randomization to 1 of 6 antihypertensive drugs: hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem (sustained release), or prazosin.

Main Outcome Measure.—Treatment response as assessed by percentage achieving goal DBP (<90 mm Hg) in response to a single drug that corresponded to patients’ renin profile vs a single drug that corresponded to patients’ age-race subgroup.

Results.—Clonidine and diltiazem had consistent response rates regardless of renin profile (76%, 67%, and 80% for low, medium, and high renin, respectively, for clonidine and 83%, 82%, and 83%, respectively, for diltiazem for patients with baseline DBP of 95-99 mm Hg). Hydrochlorothiazide and prazosin were best in low- and medium-renin profiles; captopril was best in medium- and high-renin profiles (low-, medium-, and high-renin response rates were 82%, 78%, and 14%, respectively, for hydrochlorothiazide; 88%, 67%, and 40%, respectively, for prazosin; and 51%, 83%, and 100%, respectively, for captopril for patients with baseline DBP of 95-99 mm Hg). Response rates for patients with baseline DBP of 95 to 99 mm Hg by age-race subgroup ranged from 70% for clonidine to 90% for prazosin for younger black men, from 50% for captopril to 97% for diltiazem for older black men, from 70% for hydrochlorothiazide to 92% for atenolol for younger white men, and from 84% for hydrochlorothiazide to 95% for diltiazem for older white men. Patients with a correct treatment for their renin profile but incorrect for age-race subgroup had a response rate of 58.7%; patients with an incorrect treatment for their renin profile but correct for age-race subgroup had a response rate of 63.1% (P=.30). After controlling for DBP and interactions with treatment group, age-race subgroup (P<.001) significantly predicted response to single-drug therapy, whereas renin profile was of borderline significance (P=.05).

Conclusions.—In these men with stage 1 and stage 2 hypertension, therapeutic responses were consistent with baseline renin profile, but age-race subgroup was a better predictor of response.
line agent, other antihypertensive medications are suggested for special conditions.

Some data suggest that the renin profile is useful for evaluating the pathophysiology of primary hypertension and for planning its treatment.5-10 The investigators of these studies suggest that the renin-profile model may be used to prospectively choose an initial antihypertensive drug, in addition to screening for secondary causes of hypertension and to estimate cardiovascular risk. These investigators suggest that biochemical stratification of patients by renin profile provides insight into the mechanisms contributing to hypertension and can be useful in predicting response to a particular antihypertensive drug. For example, diuretic therapy would be most effective in low-renin hypertension and least effective when renin levels are high.5,6,9,10 Conversely, angiotensin-converting enzyme inhibitors and β-adrenergic blockers, which potentially would be effective in patients with high renin levels, are expected to be less effective in low-renin hypertension. Therefore, plasma renin profiles have an important theoretical role in targeting specific antihypertensive therapies for the individual patient and for identifying drugs that may be ineffective. However, this model has not been tested prospectively in large numbers of patients comparing different classes of antihypertensive agents.

A second method for selection of an initial antihypertensive agent is by age-race subgroup.11,12 Recently, the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents published a trial of 1292 patients and determined that patients had different responses to different antihypertensive drugs based on their age-race subgroups. Specifically, younger black men responded best to diltiazem and atenolol, younger white men responded best to captopril and atenolol, older black men receiving diltiazem or hydrochlorothiazide, younger white patients receiving captopril or atenolol, and older white patients receiving atenolol or diltiazem.

We compared response rates (percentage of those achieving goal DBP <90 mm Hg at the end of titration) and respective changes in SBP and DBP on the various drugs according to renin profile and baseline DBP.5 This model indicates that a patient with a high-renin profile should respond best to either an angiotensin-converting enzyme inhibitor or a β-blocker. On the other hand, a patient with a low-renin profile should respond to a thiazide diuretic, an α₁-blocker, or a calcium antagonist.7 Patients with medium renin levels could receive any of the 6 drugs. We compared values of response rate and change in SBP and DBP for renin-profile–matched patients with the values obtained for patients receiving drugs that were found by our previous study to have the highest response rates based on age-race subgroup.11,12 In this model, we selected the best 2 drugs from each age-race subgroup and determined the combined response rates and respective changes in SBP and DBP. The subgroups selected were younger (<60 years) black patients receiving diltiazem or atenolol, older black patients receiving diltiazem or hydrochlorothiazide, younger white patients receiving captopril or atenolol, and older white patients receiving atenolol or diltiazem. We chose the best 2 drugs in each category because in any particular patient, there may be reasons for not prescribing a particular agent, or there may be adverse effects that result in use of the given drug being discontinued. Accordingly, we allowed for the possibility that the best drug in each category might not be suitable in every case.

**METHODS**

**Study Design**

The design of this study has been previously reported.11,12 At the time of randomization, patients with a DBP of 95 to 109 mm Hg after receiving a placebo for 2 weeks were assigned with equal probability in a double-blind manner to 1 of 7 treatment groups: placebo or 1 of 6 study drugs. Randomization was stratified by participating site. The drugs and their 24-hour doses (listed from initial to maximum dose) were hydrochlorothiazide (12.5, 25, and 50 mg daily), atenolol (25, 50, and 100 mg daily), clonidine (0.2, 0.4, and 0.6 mg in divided doses given twice daily), captopril (25, 50, and 100 mg in divided doses given twice daily), prazosin (4, 10, and 20 mg in divided doses given twice daily), and a sustained-release preparation of diltiazem (120, 240, and 360 mg in divided doses given twice daily). Prazosin was started at 1 mg given twice daily for 2 days to minimize the risk of hypotension with the first dose. All medications were started at the lowest dose, and the dose was increased every 2 weeks, as required, until a goal DBP of less than 90 mm Hg was reached without intolerance to the drug on 2 consecutive visits or until the maximal drug dose was reached. The blood pressure during treatment was taken as the mean of the blood pressures recorded during the last 2 visits during the titration phase. The group of patients randomized to placebo was not included in this analysis.

**Renin Profiling**

Renin profiling was performed during the prerandomization phase while the patient was taking single-blind placebo medication. The patients reported to the hypertension unit by 8 AM and a blood sample for plasma renin activity was collected in a vacuum tube (B-D Vacutainer, Becton Dickinson, Franklin Lakes, NJ) containing potassium-EDTA at room temperature. The sample was centrifuged at room temperature within 1 hour of collection for 10 to 12 minutes at 1000g to 1200g. The plasma was separated, transferred to a polystyrene test tube (taking care not to include erythrocytes), and quick-frozen in a dry ice–acetone or dry ice–alcohol mixture. It was then sent to a central laboratory (R.J.H.) on dry ice along with an aliquot of a 24-hour urine specimen that had been collected over the previous 24 hours. Plasma samples that thawed before arrival at the central laboratory were excluded from the analysis.

Plasma renin activity was determined by quantifying angiotensin I generated from endogenous substrate using the technique developed by Haber et al14 as modified for use in our laboratory.15 A radioimmunoassay kit (Clinical Assays, Gamma Coat 1251 Plasma Renin Activity Radioimmunoassay Kit, Travenol-Genentech Diagnostics, Cambridge, Mass) was used. Angiotensin I was generated at a pH of 5.5 using EDTA and phenylmethylsulfonylfluoride for inhibition of angiotensinconverting enzyme and angiotensinases. Sample dilution was minimized by using only 0.1 mL of buffer to adjust the pH of 1.0 mL of plasma. A standard generation time of 1.5 hours was used; samples having a plasma renin activity of 0.77 nanograms per milliliter were incubated for a total of 18 hours.14-17 The coefficients of variation for replicate determination of the same samples used to
standardize the method were 5.6% (n = 24, 4 separate analyses) and of samples within a single assay, 4.7% (n = 12).

A standard renin profiling curve was constructed by using normal volunteers who were given 3 test diets: less than 75 mmol/d (low), 75 to 150 mmol/d (medium), and more than 150 mmol of sodium/d (high) with a potassium content of 50 to 80 mmol/d. Patients from the current study were categorized as having low-, medium-, or high-renin essential hypertension if their values fell below, within, or above the 90% confidence limits for this plasma renin activity vs sodium excretion curve.25-29

### Statistical Methods

To determine whether the treatment groups were comparable at baseline, we compared mean age, SBP, DBP, heart rate, 24-hour urine sodium excretion, and body mass index (a measure of weight in kilograms divided by the square of height in meters) using 1-way analysis of variance (ANOVA).22 If the ANOVA P value was statistically significant, we used the Tukey test to determine which pairs of treatments were different.22 We compared race distributions across treatments using the χ² test. If this was statistically significant, we used the Grizzle-Starmer-Koch method to determine which pairs of treatments were different.22

To compare the renin profile and age-race subgroup methods, we performed a matched pairs analysis. In this analysis, each patient was classified according to whether he was matched or mismatched for each method. A 2 × 2 table was formed that defined 4 groups: (1) renin matched, age-race subgroup matched; (2) renin matched, age-race subgroup mismatched; (3) renin mismatched, age-race subgroup matched; and (4) renin mismatched, age-race subgroup mismatched. The statistical comparison essentially evaluated whether group 2 or 3 had a higher response rate, DBP change, or SBP change. For example, if group 2 had a higher response rate than group 3, then the renin-profile method would be considered more accurate than the age-race subgroup method.

We used logistic regression analysis to determine whether baseline DBP, age-race subgroup, and renin profile were significant predictors of response.23 This analysis included evaluation of interactions between age-race subgroup and drug and between renin profile and drug.

The SAS system (version 6; SAS Statistical Software, Cary, NC) was used for all statistical analysis.24 All statistical tests were 2-sided. The criterion for statistical significance was $P\leq 0.05$.

### Results

#### General Characteristics of the Patients

Baseline characteristics of the 1105 patients were well balanced across the 6 treatment groups, including 24-hour urinary sodium excretion.11,12 The mean (SD) age of the 470 younger patients (those <60 years) was 50 (8) years, and for the 635 older patients (those ≥60 years) it was 66 (4) years.

#### Renin Profile by Age and Race

Of the 1105 patients randomized to drug therapy, 1031 provided valid plasma-urine pairs for analysis. Of these, 653 (63.3%) were classified as having low-renin, 232 (22.5%) as having medium-renin, and 146 (14.2%) as having high-renin profiles. The renin profile by age-race subgroup is shown in Table 1.

#### Response Rates and Blood Pressure Changes

The logistic regression analysis determined the most important predictor of response to a single drug to be baseline DBP ($P<0.001$). Clonidine and diethylamino had high response rates regardless of renin profile (Table 2). Hydrochlorothiazide and prazosin performed best in patients with low-renin and medium-renin profiles. Captopril performed best in patients with medium-renin and high-renin profiles. As shown in Table 3, clonidine and diethylamino had high response rates regardless of age or race. Hydrochlorothiazide and prazosin produced poorer blood pressure responses in younger white patients, while captopril did worst among older black patients.

Using matched pairs analysis, we found no significant differences between the renin profile and age-race subgroup methods for choosing an initial antihypertensive agent with regard to response rate, change in SBP, or change in DBP (Table 4). For the renin-matched, age-race subgroup–mismatched patients, the response rate was 58.7% compared with 63.1% for the renin-mismatched, age-race subgroup–matched patients ($P = .30$). For DBP, the changes in these groups were −10.7 and −11.5 mm Hg, respectively ($P = .28$). The SBP changes were −12.9 mm Hg and −10.5 mm Hg, respectively ($P = .06$).

When age-race subgroup and renin profile were considered simultaneously in the logistic regression analysis, age-race subgroup was found to be a better predictor than renin profile (Table 5). The $P$ value for age-race subgroup and its interactions with treatment group added to a model that only included baseline DBP and treatment group was $P<.001$. The $P$ value for renin profile and its interactions with treatment group added to a model that included only baseline DBP and treatment group was .05.

In the presence of renin profile, adding age-race subgroup to the model produced an incremental improvement, whereas...
the converse was not true. When age-race subgroup and its interactions were added to a model that included baseline DBP, treatment group, renin profile, and its interactions, the \( P \) value for the age-race subgroup component of the model was <.001. When renin profile and its interactions were added to a model that included baseline DBP, treatment group, and age-race subgroup and its interactions, the \( P \) value for the renin-profile component of the model was .14.

**COMMENT**

The renin profiles in our study group (Table 1) are consistent with known renin-profile patterns. The black patients tended toward low-renin profiles while the white patients tended toward medium- and high-renin profiles. More than 70% of black patients had low-renin profiles, compared with less than 55% of whites. The results of response rate by blood pressure stage and by renin subgroup (Table 2) show that patients with stage 1 hypertension had the highest response rates to the individual drugs, but the response rates for the patients with stage 2 hypertension were not trivial. Diltiazem, clonidine, and atenolol had the best observed response rate in the patients with stage 2 hypertension, but this may have been at least in part due to relatively high doses permitted at the last titration step (diltiazem [sustained release], 360 mg; clonidine, 0.6 mg; and atenolol, 100 mg). Captopril had only a 14% observed response rate for stage 2 hypertension, but the maximum dose allowed was only 100 mg. Hydrochlorothiazide was capped at 50 mg, but this probably is a reasonable upper limit. Prazosin was used at its maximum recommended dose, but was less effective for patients with stage 2 hypertension.

For patients with stage 1 hypertension and a low-renin profile, prazosin, diltiazem, and hydrochlorothiazide had the highest response rates; clonidine and diltiazem were best for stage 2 hypertension. Patients with stage 1 hypertension and normal-renin profiles, diltiazem, captopril, and hydrochlorothiazide had the highest response rates; diltiazem, clonidine, and hydrochlorothiazide were best for stage 2 hypertension. Patients with stage 1 hypertension and high-renin profiles had the best response from captopril, atenolol, and diltiazem; for stage 2 hypertension, diltiazem, atenolol, and clonidine were best. Clonidine and diltiazem had high response rates for both stage 1 and stage 2 hypertension irrespective of the renin profile.

Our comparison of renin profiling and age-race subgroup for selection of an initial antihypertensive drug does not reveal a significant difference between the 2 methods (Table 4). The low response of the group with medium renin levels in the renin-profiling method may be due to the random assignment of the patients with medium renin levels to any of the 6 antihypertensive drugs. Actually, strict application of the renin-profiling method requires performing a captopril test by which additional patients with renin-dependent hypertension may be identified. Accordingly, we recalculated the overall response rate of the renin-profile patients substituting the higher figure 72.3% for the medium-renin response rate that was found for the patients with high-renin levels randomized to captopril or atenolol rather than the lower figure of 61.6% that was obtained by random assignment. The resulting figure is 68.6% for the renin-
profile method. Nevertheless, we could demonstrate no statistical difference between the 2 methods.

When both age-race subgroup and renin profile are considered simultaneously for selection of an antihypertensive drug, age-race subgroup is the more powerful predictor and renin profile has no additional predictive benefit after age-race subgroup is considered.

Our study addresses the choice of an initial antihypertensive agent with respect to its efficacy in long-term lowering of blood pressure. We have not addressed other potential applications of the renin-profiling method such as screening for secondary forms of hypertension or categorization of hypertensive patients in terms of overall cardiovascular risk. Although we did not perform a detailed cost analysis, the implications for cost savings in using the age-race method vs the renin-profiling method (which requires additional laboratory testing and a 24-hour urine collection) are clear.

It is important to note that our study subjects responded according to renin profile, consistent with prior clinical trials and published algorithms. However, classifying patients according to age-race subgroups is as good a predictor of antihypertensive response as renin profiling. We conclude that age-race subgroup is a useful predictor of antihypertensive response to drug therapy. This cost-free method for the selection of an initial single drug for treatment of stage 1 and stage 2 hypertension after consideration of morbidity and mortality trial results and other compelling indications is fully compatible with the recommendations of JNC VI.1

References