Determinants of Blood Pressure Response to Quinapril in Black and White Hypertensive Patients

The Quinapril Titration Interval Management Evaluation Trial


Abstract—Race has been considered an important factor in determining blood pressure response to treatment and selection of antihypertensive drug therapy. Data collected during a clinical trial that evaluated rapidity of medication up-titration with blood pressure response to monotherapy with the angiotensin-converting enzyme (ACE) inhibitor quinapril were used to characterize response in 533 black and 2046 white participants. Our objectives were to examine the influence of race and other factors on blood pressure response and to assess the degree to which nonrace factors account for apparent racial differences in response. Average systolic and diastolic blood pressure responses (baseline minus follow-up) to treatment were assessed with treatment groups combined. Crude systolic and diastolic blood pressure responses averaged 4.7 and 2.4 mm Hg less, respectively, in black compared with white participants; however, the response distributions largely overlapped. In multivariate linear regression models adjusted for study design variables and measured participant characteristics, the racial difference in systolic response was reduced by 51% to 2.3 mm Hg, and diastolic response by 21% to 1.9 mm Hg. In these models, participant characteristics, including age, gender, body size, and pretreatment blood pressure severity, significantly predicted either attenuated or enhanced blood pressure response to treatment. Our findings demonstrate that a large source of variability of blood pressure response to treatment is within, not between, racial groups, and that factors that vary at the level of the individual contribute to apparent racial differences in response to treatment. (Hypertension. 2004;43:1-6.)

Key Words: ACE inhibitors ■ antihypertensive therapy ■ blood pressure response ■ hypertension ■ race

Race has long been considered an important factor in determining blood pressure (BP) response to treatment, at least to single antihypertensive drugs. More specifically, blacks with hypertension have been reported to be less responsive to monotherapy with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and angiotensin receptor blockers than to diuretics and calcium antagonists. Many of these same studies have reported that white hypertensive patients respond better to these antihypertensive agents than do blacks. Authoritative treatment guidelines such as the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure have acknowledged this evidence of lesser BP response among blacks to certain drug classes and have not dismissed the notion that race be considered when selecting antihypertensive drug therapy.

There are concerns, however, with the interpretation of data from these studies. First, black and white hypertensives typically differ on baseline characteristics that may confound racial differences in BP response; observed response differences have almost never been adjusted for potential confounding factors other than baseline BP. Second, when racial BP response differences have been documented, the contribution of factors that vary at the level of the individual (eg, obesity, kidney function, gender) to observed racial differences have only infrequently been determined. Finally, much less attention has been given to the distribution of BP change in response to monotherapy within a racial group, in contrast to the focus on mean BP response differences between racial groups that only describe central tendencies of the respective BP distributions.

We used data collected during a clinical trial that evaluated rapidity of medication up-titration with BP response to monotherapy with the ACE inhibitor quinapril. Our objectives were to characterize BP response in black and white participants, to determine the influence of race group on BP response, to identify other factors that vary at the level of the individual and affect BP response, and to assess the degree to
which nonrace factors account for apparent racial differences in BP response. We examined mean values and distributions of systolic BP (SBP) and diastolic BP (DBP) responses within each racial group, assessed the degree of overlap of BP change distributions, and identified other factors that influenced responses. In addition, we investigated factors, including race, that were associated with SBP and DBP change in the upper and lower 25% of the overall BP response distributions. The Quinapril Titration Interval Management Evaluation (ATIME)\textsuperscript{15} study provided a unique opportunity to investigate these objectives given its relatively large sample size and use of ACE inhibitor monotherapy.

Methods

Participants and Overview of the Trial

The ATIME study was performed to determine whether slower-pace medication dose up-titration would result in greater likelihood of BP control and fewer adverse effects. Participants with JNC-VI stages 1 or 2 hypertension\textsuperscript{12} (SBP 140 to 169 or DBP 90 to 104) were randomly assigned to fast (every 2 weeks) or slow (every 6 weeks) blood pressure determination and, if necessary, up-titration of quinapril, an ACE inhibitor. All participants were initially prescribed 20 mg quinapril once daily with subsequent doubling of the dose to a maximum of 80 mg, if BP remained $\geq 140/90$ mm Hg. Follow-up evaluations occurred at weeks 2, 4, and 6 for those in the fast group, and weeks 6, 12, and 18 for those in the slow group. Data were available from 2935 eligible participants (1208 slow group; 1727 fast group) enrolled at 365 clinical care sites in the southeastern United States. Details of the ATIME study design and results of primary analyses have been previously reported.\textsuperscript{15}

Participants were characterized by age, gender, race/ethnicity (black, white, or other), education (high school or higher), and baseline SBP and DBP. Diabetes was defined if reported by participant, or if measured blood glucose $\geq 200$ mg/dL. Obesity status was determined from calculation of body mass index (BMI) ($\text{BMI} = \text{weight in kg/height in m}^2$); men and women with BMI $\geq 30.0$ were considered obese. Estimated glomerular filtration rate (eGFR) ($\text{eGFR} = \text{mL/min per 1.73 m}^2$) was calculated using a formula based on serum creatinine values;\textsuperscript{16} eGFR values $\leq 60$ mL/min per 1.73 m$^2$ indicated at least moderately reduced kidney function.

Study Objectives and Statistical Analyses

Statistical analyses (SAS version 8.0) of data collected as part of the ATIME trial were performed to evaluate BP response to ACE inhibitor monotherapy among black and white participants. Average SBP and DBP responses to treatment were assessed with treatment groups combined. Multiple response outcomes were evaluated: (1) mean values and distribution of SBP change from baseline (SBP response=baseline SBP−follow-up SBP); (2) mean values and distribution of DBP change from baseline (DBP response=baseline DBP−follow-up DBP); (3) likelihood of having SBP or DBP responses in the lower 25% of the response distributions; and (4) likelihood of having SBP or DBP responses in the upper 25% of the response distributions; outcomes were calculated for each follow-up visit.

Multivariate linear mixed-effect models for continuous outcomes and logistic models for dichotomous outcomes were developed to examine these outcomes across study visits by race group. Models were adjusted for the effects of time (study visit), treatment group (fast or slow up-titration), medication dose, and baseline BP, and considered the effects of participant demographic characteristics (age, gender, education), obesity status, kidney function (eGFR), and diabetes status on study outcomes. Multivariate models were also adjusted for within-subject correlation across repeated measures on individual participants, and for within-study site correlation of BP measures. Covariates were entered simultaneously into individual models. Additional models considered the interaction of race group with treatment group to examine whether differential advantage of slow versus fast medication up-titration existed for black or white participants.

Results

Black and white participants comprised 88% of the overall study population. Baseline characteristics of this subset population are presented in Table 1; 21% of participants identified as black. Black participants were primarily women (61%) and were younger, somewhat less educated, more likely to have diabetes or to be obese, but less likely to have reduced kidney function than white participants. Mean baseline SBP was significantly lower in black compared with white participants, whereas mean baseline DBP was significantly higher.

Figures 1 and 2 graphically display the distributions of SBP and DBP responses to monotherapy with quinapril for black and white participants. BP response values presented here were averaged over the duration of follow-up (1 to 3 visits); positive values represent greater BP lowering. The crude differences in mean SBP and DBP responses between black and white participants were 4.7 and 2.4 mm Hg, respectively, with lower mean values for blacks. The interquartile ranges (boundaries of the middle 50% of the BP response distributions) for white and black participants were similar—16.0 and 18.0 mm Hg for SBP response and 10.0 and 10.2 mm Hg for DBP response. There was substantial overlap of interquartile ranges of respective BP response distributions for black and white participants. In both race groups, interquartile ranges were 3- to 4-fold greater than crude differences in mean SBP and DBP responses between black and white participants.

Multivariate linear mixed models were developed to examine SBP and DBP responses across study visits, by race, with adjustment for potential confounding factors. In the

\begin{table}
\centering
\caption{Baseline Characteristics of Black and White ATIME Participants (N=2579)}
\begin{tabular}{lllll}
\hline
Characteristic & Black Participants (N=1246, 71%) & White Participants (N=1333, 29%) & P \\
\hline
Mean systolic BP, mm Hg & 139.4 (SD=9.6) & 153.2 (SD=11.0) & 0.004 \\
Mean diastolic BP, mm Hg & 84.6 (SD=6.0) & 94.9 (SD=6.4) & 0.011 \\
Mean age, years & 60.9 (SD=12.0) & 66.1 (SD=12.6) & <0.001 \\
Age 65 years and older, n (%) & 210 (21.6) & 266 (27.1) & <0.001 \\
Women, n (%) & 341 (27.5) & 393 (29.5) & 0.13 \\
Men, n (%) & 887 (72.5) & 937 (70.5) & 0.13 \\
Diabetes, n (%) & 159 (12.0) & 205 (15.3) & <0.001 \\
\geq High school education, n (%) & 326 (26.1) & 386 (28.9) & <0.001 \\
Fast treatment group & 330 (30.1) & 1193 (39.0) & 0.13 \\
Slow treatment group & 194 (38.5) & 853 (41.7) & 0.13 \\
Mean eGFR, 1.73 m\textsuperscript{2} & 91.3 (SD=21.6) & 75.9 (SD=19.2) & <0.001 \\
EGR $<60$, n (%) & 9 (1.8) & 215 (11.4) & <0.001 \\
Obese, n (%) & 295 (58.5) & 937 (48.3) & <0.001 \\
BP indicates blood pressure; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m\textsuperscript{2}); BMI, body mass index. \\
\hline
\end{tabular}
\end{table}
linear mixed model examining mean change in SBP from baseline during follow-up (Table 2), response was significantly attenuated (2.3 mm Hg lesser reduction) among black participants compared with white participants; however, this adjusted value was 51% less than the crude estimate of response difference by race. In this model, SBP response was also significantly attenuated with increasing age and among obese (BMI $\geq 30.0$) participants; gender, kidney function, and diabetes status were unrelated to SBP response. This model was adjusted for medication dose and baseline SBP; larger medication dose was associated with poorer response and greater baseline BP with greater response. Participants in the slow treatment group had a 1.1-mm Hg greater reduction in SBP over time than those in the fast group; however, there was no differential advantage of slow group participation for black or white participants.

In the linear mixed model examining mean change in DBP from baseline during follow-up visits (Table 2), black participants had a 1.9-mm Hg lesser reduction in DBP over time than white participants. This adjusted value was 21% less than the crude estimate of response difference by race. Increasing age was associated with greater DBP response and participants with diabetes had greater reduction in DBP than those without diabetes; obesity (BMI $\geq 30.0$) was associated with attenuated response. In this model, participants in the slow treatment group had a 1.0-mm Hg greater reduction in DBP than fast group members; however, there was no differential advantage of slow group participation for black or white participants.

Multivariate logistic regression models were developed to examine adjusted odds of SBP or DBP responses in the lower 25%, and in the upper 25% of the response distributions across study visits, by race. Response cutpoints were determined at each follow-up visit. Table 3 presents results of the analyses for SBP response distributions. Consistent with the previous analyses, black and older participants and participants with BMI $\geq 30.0$ were significantly more likely than others to have responded in the lower 25% of the overall SBP response distribution; those in the slow treatment group and male participants were less likely to respond in the lower 25%. Similarly, White and younger participants and those in the slow treatment group were more likely to respond in the upper 25% of the overall SBP change distribution.

Table 4 presents results of the analyses for DBP response distributions. Black, younger, and obese participants were more likely than others to have responded in the lower 25% of the DBP response distribution, whereas those in the slow treatment group, male participants, and participants with diabetes were less likely to respond. Similarly, white and older participants and those with diabetes were more likely to respond in the upper 25% of the DBP change distribution, whereas obese participants were less likely to respond.

**Discussion**

Our findings confirm the independent association of black race with attenuation of BP response to ACE inhibitor monotherapy, previously demonstrated in other studies. In addition, several other important findings were observed. First, the distributions of response values for SBP and DBP change were much greater within each race group than between the 2 groups. Second, the middle 50% of the BP response distributions for systolic and diastolic BP were similar in width for black and white participants and, for the most part, overlapped. It is clear from visual inspection of the response distributions, that race, per se, would be a poor predictor of an individual’s BP response to monotherapy with quinapril. This is true even though both crude and adjusted BP responses were significantly greater in white participants compared with black participants. The differences in mean BP response, stratified by race, represent a shift in the BP distributions rather than a frank separation of BP response distributions between the racial groups. Third, BP response differences between black and white participants were con-
found by other factors that varied at the level of the individual, including age, gender, body size, and pretreatment BP severity.

The results of these analyses highlight the potential pitfalls of comparing BP responses between race groups without adequate adjustment for a range of potential confounding variables. Results from unadjusted analyses can be misleading, if not in direction certainly in magnitude, because of gender, pretreatment BP severity, and body size. Further, in most hypertension trials, racial contrasts are post-hoc analyses that are not “protected” by the randomization procedure unless randomization was stratified by race. Among ATIME participants, blacks had a higher prevalence of several characteristics that predicted lesser BP response, including female sex, obesity, and lower mean baseline SBP.

### TABLE 2. Results From Multivariate Linear Mixed Effects Models Examining Factors Associated With Systolic and Diastolic Blood Pressure Response (Mean Change in BP from Baseline [Baseline BP minus Follow-up BP] Over Time Among Black and White Participants)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimate*</th>
<th>95% Confidence Interval</th>
<th>P</th>
<th>Estimate*</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.71</td>
<td>5.30, 8.12</td>
<td>&lt;0.001</td>
<td>5.51</td>
<td>4.65, 6.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slow treatment group</td>
<td>1.13</td>
<td>0.35, 1.91</td>
<td>0.005</td>
<td>0.99</td>
<td>0.51, 1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study visit (time)</td>
<td>4.13</td>
<td>3.79, 4.47</td>
<td>&lt;0.001</td>
<td>2.59</td>
<td>2.38, 2.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>-0.16</td>
<td>-0.20, -0.12</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.01, 0.05</td>
<td>0.009</td>
</tr>
<tr>
<td>Male</td>
<td>0.45</td>
<td>0.33, 1.23</td>
<td>0.26</td>
<td>0.06</td>
<td>-0.42, 0.54</td>
<td>0.82</td>
</tr>
<tr>
<td>Black</td>
<td>-2.34</td>
<td>-3.40, -1.28</td>
<td>&lt;0.001</td>
<td>-1.88</td>
<td>-2.53, -1.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school education</td>
<td>0.78</td>
<td>-0.23, 1.79</td>
<td>0.13</td>
<td>-0.44</td>
<td>-1.06, 0.18</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI ≥30.0</td>
<td>-0.84</td>
<td>-1.62, -0.06</td>
<td>0.034</td>
<td>-0.98</td>
<td>-1.46, -0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EGFR &lt;60</td>
<td>0.84</td>
<td>-0.58, 2.26</td>
<td>0.25</td>
<td>-0.14</td>
<td>-1.02, 0.74</td>
<td>0.76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.31</td>
<td>-1.46, 0.84</td>
<td>0.59</td>
<td>1.02</td>
<td>0.31, 1.73</td>
<td>0.005</td>
</tr>
<tr>
<td>Medication dose</td>
<td>-0.30</td>
<td>-0.32, -0.28</td>
<td>&lt;0.001</td>
<td>-0.17</td>
<td>-0.18, -0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline systolic or diastolic blood pressure</td>
<td>0.65</td>
<td>0.61, 0.70</td>
<td>&lt;0.001</td>
<td>0.61</td>
<td>0.57, 0.65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Estimate (β coefficient)—deviation from expected (mean intercept) blood pressure response in mm Hg for participants with this characteristic compared to those without, given inclusion of all other variables in this adjusted model.

### TABLE 3. Results From Multivariate Logistic Regression Models Examining Factors Associated With Likelihood of Having Systolic Blood Pressure Response in the Lower 25% or in the Upper 25% of the Overall Systolic Response Distribution at Each of the 3 Follow-up Visits Among Black and White Participants (Response Cutpoints Were Determined at Each Visit)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow treatment group</td>
<td>0.86</td>
<td>0.73–1.01</td>
<td>0.06</td>
<td>1.24</td>
<td>1.05–1.45</td>
<td>0.010</td>
</tr>
<tr>
<td>Study visit (time)</td>
<td>0.87</td>
<td>0.80–0.95</td>
<td>0.002</td>
<td>1.16</td>
<td>1.06–1.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.03</td>
<td>1.02–1.03</td>
<td>&lt;0.001</td>
<td>0.99</td>
<td>0.98–0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.79</td>
<td>0.67–0.93</td>
<td>0.005</td>
<td>0.90</td>
<td>0.76–1.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Black race</td>
<td>1.58</td>
<td>1.31–1.92</td>
<td>&lt;0.001</td>
<td>0.73</td>
<td>0.58–0.93</td>
<td>0.009</td>
</tr>
<tr>
<td>High school education</td>
<td>0.91</td>
<td>0.74–1.12</td>
<td>0.39</td>
<td>1.10</td>
<td>0.89–1.35</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI ≥30.0</td>
<td>1.24</td>
<td>1.05–1.46</td>
<td>0.009</td>
<td>0.94</td>
<td>0.80–1.11</td>
<td>0.49</td>
</tr>
<tr>
<td>EGFR &lt;60</td>
<td>0.93</td>
<td>0.68–1.26</td>
<td>0.63</td>
<td>1.22</td>
<td>0.95–1.57</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.96</td>
<td>0.76–1.22</td>
<td>0.73</td>
<td>1.16</td>
<td>0.92–1.48</td>
<td>0.22</td>
</tr>
<tr>
<td>Medication dose</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.001</td>
<td>0.94</td>
<td>0.93–0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>0.91</td>
<td>0.90–0.92</td>
<td>&lt;0.001</td>
<td>1.13</td>
<td>1.12–1.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Covariates were entered simultaneously into individual models. BP indicates blood pressure; BMI, body mass index; EGFR, estimated glomerular filtration rate (mL/min per 1.73 m²).
Also, up-titration of ACE inhibitor dose may also lessen race differences in BP response to therapy. The average dose of the ACE inhibitor quinapril in black and white ATIME participants was slightly less than one-half of the maximum allowed dose (data not shown). Thus, the traditional focus on BP responsiveness to monotherapy with any drug class, and racial differences in the same, has probably been overemphasized.

Our findings demonstrate that the distributions of BP response to ACE inhibitor monotherapy, examined for 2 race groups, largely overlap, and that a large source of variability of BP response to treatment is within, not between, race groups. In addition, we identified several factors that vary at the level of the individual and predict either attenuated or enhanced BP response. Black and white hypertensive patients may differ on individual characteristics that influence BP response and control rates, and thus contribute to observed race differences in BP response to monotherapy. These analyses suggest that racial contrasts of BP response to antihypertensive drug therapies should be adjusted for potential confounders; however, if they are not, the BP response differences are likely to be misleading. Our results question the wisdom of using black race, per se, as a major criterion on which to base decisions regarding ACE inhibitor monotherapy because of their presumed lack of effectiveness for lowering BP. Race differences in group BP responses to monotherapy with ACE inhibitors are an inaccurate means of predicting the magnitude of BP-lowering with an ACE inhibitor in individual patients of either race because of the near-complete overlap of the BP response distributions of blacks and whites, and because a significant portion of the race difference in BP response is attributable to factors that vary at the level of the individual.

**Perspectives**

We believe that the documentation of race differences in group BP responses to monotherapy with ACE inhibitors has
been an important and tantalizing observation, although not because it tells practitioners how to treat individual patients, but rather because of the potential clues that this discrepancy in BP response provides to scientists in formulating hypotheses and designing experiments to better understand the physiology of BP responses to antihypertensive agents. The driver(s) of the group difference in BP response are not likely to be unique to blacks because of the substantial overlap in the distributions of BP response. Though unproven, we have formulated a hypothesis to explain why drugs that expand venous capacitance (eg, ACE inhibitors) lower BP very effectively in persons with limited dietary sodium intake but lower BP much less effectively when sodium is not restricted—whereas agents that do not expand venous capacitance (eg, calcium antagonists) experience little diminution in their BP-lowering effect in settings of high sodium intake. Simply put, we hypothesize that obese persons, proven to have reduced venous capacitance, have centralized their blood volume and suppressed their circulating renin. When these patients are given drugs that expand their venous capacitance and decentralize their blood volume, plasma volume expansion occurs until a new intravascular volume steady-state is reached and the decrease in BP is limited, unless sodium intake is restricted or diuretics are prescribed. Though this speculation may ultimately prove to be incorrect, it has been formulated to scientifically probe a vexing observation that for too long has remained unexplained.

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