Associations Between Birth Weight and Antihypertensive Medication in Black and White Medicaid Recipients

Daniel T. Lackland, Brent M. Egan, Holly E. Syddall, David J.P. Barker

Abstract—The blood pressures of hypertensive patients living in the southeastern region of the United States are less responsive to several classes of antihypertensive medications. Birth weights are lower among blacks and those living in the Southeast, and evidence suggests that this developmental difference increases blood pressure. As an initial step in addressing the possibility that birth weight influences response to antihypertensive therapy, we examined the relationship between birth weight and class of antihypertensive medication among 3236 Medicaid beneficiaries in South Carolina with high blood pressure. Birth weight, obtained from birth certificates, was not related to use of either diuretics or beta blockers. However, among black women, there was an inverse association between birth weight and use of calcium channel antagonists (P=0.03), which persisted after adjustment for the number of antihypertensive medications.

Among white men, low and high birth weights were associated with greater use of angiotensin converting enzyme inhibitors than in men of normal birth weight (P=0.002 for quadratic trend [U-shaped]). This association remained after adjustment for comorbid conditions, including congestive heart failure and diabetes mellitus, which were associated with birth weight and for which angiotensin converting enzyme inhibitors are recommended. The findings indicate that birth weight is associated with use of calcium channel antagonists in black women and angiotensin converting enzyme inhibitors in white men. These observations suggest that further study of the relationship between birth weight and blood pressure responses to various antihypertensive medications may help elucidate pathophysiological factors contributing to geographic and racial disparities in therapeutic efficacy. (Hypertension. 2002;39:179-183.)

Key Words: hypertension, essential antihypertensive agents calcium channels angiotensin-converting enzyme inhibitors treatment response epidemiology

The geographic and racial disparity in hypertension and hypertension-related outcomes has long been recognized, with an excess burden in the southeastern region of the United States and among blacks.1–4 Geographic and racial disparities in response to various classes of antihypertensive medications have also been reported.5 The explanation for these disparities is unknown, although lifestyle factors may contribute.

Low weight at birth has been associated with higher blood pressure (BP) among children and adults in 80 studies.6 Low birth weight has also been linked to the development of the insulin-resistance syndrome and its complications, including hypertension, Type 2 diabetes mellitus, and cardiovascular disease.7 These observations led to the hypothesis that adaptations to undernutrition in utero result in permanent functional and structural changes in key organs that foster the insulin-resistance syndrome and in related complications later in life.8,9

The pathophysiological mechanisms by which low birth weight leads to high BP have not been defined. However, low birth weight is associated with functional and structural changes that modulate arterial blood pressure. These include fewer nephrons,10 changes in the renin-angiotensin system11 and hypothalamic-pituitary axis,12 and changes in vascular structure and function, including decreased elasticity and flow-mediated dilation.13,14

The BP response to various antihypertensive medications has been used to identify pathophysiological subsets. For example, angiotensin converting enzyme inhibitors (ACEI) have helped define a nonmodulator phenotype of salt-sensitive hypertension,15 and sympatholytics have been used to define neurogenic hypertension.16,17 Given this paradigm, we examined the relationship between birth weight and the use of various classes of antihypertensive medications in hypertensive Medicaid beneficiaries. Because race and gender differences in responsiveness to various classes of BP medications have been reported,5,18 analyses of relationships between birth weight and antihypertensive medications were stratified according to these variables.

Methods

Subjects

This study examined data on Medicaid beneficiaries in South Carolina. Name, date of birth, gender, and race data were obtained...
for all beneficiaries in the state with a diagnosis of hypertension (diagnosis on claim form), during the period 1993 to 1996. The database identified 16163 South Carolina residents, born in 1950 or later, who were diagnosed with hypertension and had a claim for hypertension during the study period. These data were matched to South Carolina birth certificates using a visual and computer process previously described. The second phase of the process was a manual search for the birth certificate. The Office of Vital Records successfully matched 7156 beneficiaries (44.3% of the total; 61.2% of males; 37.9% of females) born after 1949 to their birth records. The unsuccessful matches are explained in part by subjects who were born outside of South Carolina. The lower match rate for females reflects the difficulty in tracking women who changed their surnames at marriage. These limitations would only introduce bias and limit extrapolations if associations between birth weight and hypertension therapy were different in men and women who were born outside South Carolina or between women who were married or single. The birth weight of each baby born in South Carolina has been recorded on the birth certificate since January 1, 1950. As part of subsequent data checking, 71 duplicate Medicaid records, 313 birth records with missing data or an incredible birth weight, and 160 beneficiaries who were not of black or white racial origin were excluded. Age was calculated in completed years as of July 1, 1999, and 1157 subjects who were under 20 years of age were also excluded. The final database included 5455 hypertensive subjects, born between January 1, 1950, and July 1, 1979, of black or white race and of known birth weight, who were treated under Medicaid for hypertension at any time during the period 1993 to 1996.

Birth Weight
Birth weights were converted to grams for analysis and were grouped as follows: <2500 g, 2500 to 2999 g, 3000 to 3499 g, 3500 to 3999 g, and ≥4000 g.

Hypertension Treatment
Antihypertensive medications were identified from pharmacy claims. Any pharmacy claim for one of the following 4 classes of medications was included in the analysis: diuretics, β-adrenergic receptor blockers (BB), calcium channel antagonists (CCB), and ACEI.

Statistical Analysis
We used logistic regression to calculate odds ratios for prescription of drug therapy by birth weight. The odds ratios for prescription of diuretics and BB by birth weight were calculated using subjects who were not receiving any medication as a comparison group. The odds ratios for prescription of ACEI and CCB were calculated using subjects receiving other medications as a comparison group. Additionally, analyses controlled for the number of drug classes prescribed and the presence of birth weight related comorbidities including congestive heart failure, diabetes, stroke, and ischemic heart disease. All analyses were carried out separately for blacks and whites and for men and women. Odds ratios were adjusted for age and were calculated for each birth weight category with 3000 to 3499 g as the reference. Analyses were carried out using Stata software, version 6.0.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results
Among the 3236 hypertensive beneficiaries who were prescribed antihypertensive medications, 2572 were black (600 men and 1972 women) and 664 were white (386 men and 278 women). The mean age was approximately 35 years and did not differ for whites and blacks. Mean birth weight was lower in women than men, but similar in blacks and whites (white men, 3329 g; black men, 3245 g; white women, 3117 g; black women, 3146 g). The percentages of subjects who were below 2500 g (11.1%) or above 4000 g (8.2%) were similar in men and women and in blacks and whites.

During the study period (1993 to 1996), 2572 (59%) of the black subjects and 664 (59%) of the white subjects had a prescription for 1 or more of the 4 classes of antihypertensive medication. The frequency of filled prescriptions for each of the 4 classes of antihypertensive medication varied significantly. Seventy-five percent received a diuretic, 16% a BB, 42% an ACEI, and 19% a CCB. The percentages of filled prescriptions for each class of antihypertensive compound were similar among blacks and whites. The majority (~60%) of the hypertensive beneficiaries were treated with only 1 of the 4 classes of BP compounds, whereas ~30% received 2 of 4, and ~8%, 3 of 4. The number of medication classes prescribed was similar for blacks and whites, respectively: monotherapy, 61% versus 59%; 2 classes, 29% versus 32%; 3 classes, 8% versus 8%; 4 classes, 1% versus 2%.

Diuretics were the most frequently prescribed agent (“monotherapy”) of the 4 classes of antihypertensive compounds in hypertensive Medicaid recipients (Figure 1). Blacks were more likely to receive diuretic “monotherapy” than whites (65% versus 52%). In contrast, whites were slightly more likely than blacks to receive either an ACEI (28% versus 20%) or BB (9% versus 4%). CCB constituted the “monotherapeutic” agent in 9% to 10% of both whites and blacks. When 2 of the 4 antihypertensive drug classes were used, a diuretic was one of the agents in approximately 90% of patients (Figure 2).
The odds ratios for filling prescriptions for diuretics and BB were unrelated to birth weight. Among blacks, obtaining an ACEI was unrelated to birth weight (Table 1). Among whites, the odds ratios for receiving an ACEI were higher in those at both high and low birth weights. The significance of this U-shaped trend was restricted to men, though among women the highest odds ratios were among those with birth weight below 2500 g or above 4000 g. The difference in quadratic trends between men and women was not statistically significant. These findings persisted when adjusted for the number of classes of drugs prescribed and for the presence of diabetes mellitus and/or congestive heart failure.

Table 2 presents the odds ratios for obtaining CCB according to birth weight in the various race and gender groups. A significant inverse relationship was identified between birth weight and filling a prescription for a CCB among black women. The relationship of birth weight and CCB was not significant for the other 3 race-sex groups. The association of birth weight and the prescription of CCB remained significant

### Table 1. Odds Ratios (95% CI) for Prescription of ACE-Inhibitors According to Sex and Birth Weight Among Patients Treated for Hypertension

<table>
<thead>
<tr>
<th>Birth Weight, g</th>
<th>Prescribed ACE</th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>OR</td>
<td>95% CI</td>
<td>No</td>
<td>Yes</td>
<td>OR</td>
</tr>
<tr>
<td>Black patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>29</td>
<td>32</td>
<td>1.49 (0.83, 2.66)</td>
<td>142</td>
<td>89</td>
<td>0.93 (0.68, 1.26)</td>
<td></td>
</tr>
<tr>
<td>–3000</td>
<td>68</td>
<td>66</td>
<td>1.27 (0.82, 1.98)</td>
<td>303</td>
<td>207</td>
<td>1.00 (0.79, 1.27)</td>
<td></td>
</tr>
<tr>
<td>–3500</td>
<td>115</td>
<td>87</td>
<td>1.00 ...</td>
<td>419</td>
<td>283</td>
<td>1.00 ...</td>
<td></td>
</tr>
<tr>
<td>–4000</td>
<td>65</td>
<td>69</td>
<td>1.37 (0.88, 2.12)</td>
<td>231</td>
<td>135</td>
<td>0.88 (0.68, 1.14)</td>
<td></td>
</tr>
<tr>
<td>≥4000</td>
<td>38</td>
<td>31</td>
<td>1.04 (0.60, 1.81)</td>
<td>94</td>
<td>69</td>
<td>1.11 (0.79, 1.57)</td>
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</tr>
<tr>
<td>P for linear trend</td>
<td></td>
<td></td>
<td>0.51</td>
<td></td>
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<td>0.87</td>
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<tr>
<td>White patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>11</td>
<td>17</td>
<td>3.49 (1.46, 8.35)</td>
<td>18</td>
<td>17</td>
<td>1.36 (0.63, 2.95)</td>
<td></td>
</tr>
<tr>
<td>–3000</td>
<td>40</td>
<td>38</td>
<td>1.77 (0.99, 3.18)</td>
<td>45</td>
<td>29</td>
<td>0.93 (0.50, 1.72)</td>
<td></td>
</tr>
<tr>
<td>–3500</td>
<td>81</td>
<td>46</td>
<td>1.00 ...</td>
<td>59</td>
<td>41</td>
<td>1.00 ...</td>
<td></td>
</tr>
<tr>
<td>–4000</td>
<td>62</td>
<td>45</td>
<td>1.35 (0.79, 2.31)</td>
<td>31</td>
<td>20</td>
<td>0.93 (0.47, 1.85)</td>
<td></td>
</tr>
<tr>
<td>≥4000</td>
<td>22</td>
<td>24</td>
<td>2.06 (1.03, 4.14)</td>
<td>10</td>
<td>8</td>
<td>1.15 (0.42, 3.17)</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

### Table 2. Odds Ratios (95% CI) for Prescription of Calcium Channel Antagonists According to Sex and Birth Weight Among Patients Treated for Hypertension

<table>
<thead>
<tr>
<th>Birth Weight, g</th>
<th>Prescribed CCA</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>OR</td>
<td>95% CI</td>
<td>No</td>
<td>Yes</td>
<td>OR</td>
</tr>
<tr>
<td>Black patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>50</td>
<td>11</td>
<td>0.82 (0.39, 1.72)</td>
<td>186</td>
<td>45</td>
<td>1.16 (0.79, 1.70)</td>
<td></td>
</tr>
<tr>
<td>–3000</td>
<td>96</td>
<td>38</td>
<td>1.36 (0.82, 2.25)</td>
<td>422</td>
<td>88</td>
<td>1.02 (0.75, 1.38)</td>
<td></td>
</tr>
<tr>
<td>–3500</td>
<td>157</td>
<td>45</td>
<td>1.00 ...</td>
<td>580</td>
<td>122</td>
<td>1.00 ...</td>
<td></td>
</tr>
<tr>
<td>–4000</td>
<td>99</td>
<td>35</td>
<td>1.14 (0.68, 1.91)</td>
<td>319</td>
<td>47</td>
<td>0.66 (0.46, 0.95)</td>
<td></td>
</tr>
<tr>
<td>≥4000</td>
<td>52</td>
<td>17</td>
<td>1.04 (0.54, 1.98)</td>
<td>137</td>
<td>26</td>
<td>0.84 (0.53, 1.34)</td>
<td></td>
</tr>
<tr>
<td>P for linear trend</td>
<td></td>
<td></td>
<td>0.97</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>White patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>26</td>
<td>2</td>
<td>0.32 (0.07, 1.43)</td>
<td>32</td>
<td>3</td>
<td>0.41 (0.11, 1.49)</td>
<td></td>
</tr>
<tr>
<td>–3000</td>
<td>58</td>
<td>20</td>
<td>1.31 (0.67, 2.55)</td>
<td>58</td>
<td>16</td>
<td>1.09 (0.51, 2.31)</td>
<td></td>
</tr>
<tr>
<td>–3500</td>
<td>100</td>
<td>27</td>
<td>1.00 ...</td>
<td>81</td>
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<td>1.00 ...</td>
<td></td>
</tr>
<tr>
<td>–4000</td>
<td>80</td>
<td>27</td>
<td>1.28 (0.70, 2.37)</td>
<td>43</td>
<td>8</td>
<td>0.76 (0.31, 1.91)</td>
<td></td>
</tr>
<tr>
<td>≥4000</td>
<td>36</td>
<td>10</td>
<td>1.06 (0.46, 2.41)</td>
<td>13</td>
<td>5</td>
<td>1.78 (0.56, 5.68)</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
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<td></td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
</tbody>
</table>

CCA indicates calcium channel antagonist.
after adjustment for the number of other classes of therapy and the presence of comorbid conditions (not shown).

**Discussion**

The results of this observational study suggest that birth weight should be considered as a possible factor for future research into the geographic and racial disparities in response to different classes of antihypertensive medications. In this study of 5455 hypertensive Medicaid beneficiaries, birth weight was not related to the use of diuretics or BB in the entire group or in any of the race and gender subgroups. In contrast, among those receiving medication, black women who had lower birth weights were more likely to receive CCB. White men with low and high birth weights were more likely to receive ACEI. This is the first study to link birth weight to the use of antihypertensive medications. Birth weight is not routinely sought in the medical history of adults. It is unlikely that physicians were aware of the birth weight when prescriptions were written. Moreover, there are no guidelines for selecting antihypertensive therapy based on birth weight.

There are only a few plausible explanations to account for the observed relationships between birth weight and the class of BP medication prescription obtained by the patient. One possibility is that physicians change and/or add antihypertensive medications until the BP responds. As an example, the association between low birth weight and the use of CCB could reflect a greater severity of hypertension requiring more medications and/or BP which is more responsive to CCB. Black women have a higher prevalence of low birth weight as infants and obesity as adults. Low birth weight has been linked to a reduced number of nephrons, whereas adult obesity is associated with an increased renal filtration load. This allometric imbalance between the structural limitations for filtration and functional demands would tend to drive blood pressure higher to maintain sodium-volume homeostasis, i.e., pressure natriuresis. Of the various classes of antihypertensive medications, CCB appear to retain more antihypertensive efficacy on a high sodium (volume) diet. CCB are effective in reducing the glomerular hypertension and increased filtration fraction that occur on a high-salt diet in salt-sensitive individuals.

Given the preceding information, black women would tend to have more volume-dependent, resistant hypertension. They would then be more likely to receive a CCB. First, if their hypertension is more severe as postulated, their blood pressure control might simply require a greater number of medications. In this case, a CCB would be prescribed as one of several agents to treat hypertension. Another possibility is that CCB are more effective antihypertensive agents than the other 3 classes in low-birth-weight black women. The relationship between birth weight and CCB persisted after adjustment for the number of BP medications, which raises the possibility that CCB are more effective antihypertensives than the other medication classes in low-birth-weight black women.

Birth weight was associated with filling a prescription for ACEI in white men but not in women. One possible explanation for the absence of an association in women is that women in Medicaid are often pregnant or in their childbearing years. ACEI are contraindicated in pregnant women and relatively contraindicated in women who are likely to become pregnant. Prescription of ACEI among white men was associated with low and high birth weights. Because people with high birth weight tend to become overweight in later life, one possibility is that obese white men receive a second medication because their BP is more severe.

The association between ACEI and low birth weight in younger white men may be explained by amplification of diuretic resistance, which is explained by a more intense counter-regulatory activation of the renin-angiotensin system. Based on previous research, we speculate that low birth weight, especially in white men, exacerbates insulin resistance and magnifies the counter-regulatory response of their renin-angiotensin system to diuretic monotherapy. In this setting, ACEI would be highly effective in lowering BP.

An alternative or adjunctive explanation for the association in white men is that birth weight is linked to comorbid conditions such as diabetes mellitus, myocardial infarction, and congestive heart failure, for which an ACEI is recommended. The association between birth weight and ACEI use in white men persisted after adjustment for these comorbidities.

The associations between birth weight and use of CCB in black women and ACEI in white men persisted after adjustments for likely confounders, which raises the possibility that birth weight in these demographic groups influences the antihypertensive efficacy of these agents. We cannot prove this assumption in this study, but evidence indicates that physicians tend to change and/or add medications until BP responds.

The disproportionately high representation of blacks in our sample of Medicaid beneficiaries reflects known racial disparities in family income. In addition, young black women are more likely to be hypertensive than young white women. Racial differences in the prevalence of hypertension among young men are smaller. The prevalence of low birth weight, less than 2500 g, was higher in our sample (11%) than among the general population of South Carolina (9.5%). Although low birth weight is generally more common among blacks than whites in the United States, the prevalence of low birth weight was similar among blacks and whites in this sample of low income Medicaid recipients. The bias toward low income in our sample is unlikely to have produced the associations between birth weight and class of antihypertensive medications, because the comparisons in our analyses were internal to the sample. The bias may, however, affect quantification of the size of the associations in the general population.

This observational study has limitations. Treatment histories are incomplete, and BP measurements are not included. However, the associations between birth weight and BP medications support further study of the link between birth weight, treatment patterns, and BP responses. Although combination therapy emerges as a potential confounder, the majority of patients (60%) were receiving only 1 of the 4 classes of antihypertensive compounds. When patients were receiving 2 of the 4 classes, a diuretic was present 90% of the time. In this study, we did not observe any relationship between birth weight and diuretics. Thus, combination therapy does not emerge as a significant confounder in our study.
In summary, among blacks, particularly women, being treated for hypertension, CCB are more often prescribed to those who had low birth weight. Among white men being treated for hypertension, ACEI are more often prescribed to those who had either low or high birth weight. If these findings are related to differential antihypertensive efficacy as we postulate, they could provide the basis for more effective therapy in hypertensive patients by taking birth weight into consideration. The observations in this study may also provide clues to the mechanism(s) by which fetal adaptations to undernutrition in utero contribute to elevated BP later in life. Furthermore, these results suggest that birth weight should be considered in future studies that examine the racial and geographic disparities in the response to various classes of antihypertensive medications.

Acknowledgments

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References

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