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See Editorial Commentary, pp 1045–1046

Abstract—The prevalence of resistant hypertension is unknown. Much previous knowledge comes from referral populations or clinical trial participants. Using data from the National Health and Nutrition Examination Survey from 2003 through 2008, nonpregnant adults with hypertension were classified as resistant if their blood pressure was $\geq 140/90$ mm Hg and they reported using antihypertensive medications from 3 different drug classes or drugs from $\geq 4$ antihypertensive drug classes regardless of blood pressure. Among US adults with hypertension, 8.9% (SE: 0.6%) met criteria for resistant hypertension. This represented 12.8% (SE: 0.9%) of the antihypertensive drug–treated population. Of all drug-treated adults whose hypertension was uncontrolled, 72.4% (SE: 1.6%) were taking drugs from $<3$ classes. Compared with those with controlled hypertension using 1 to 3 medication classes, adults with resistant hypertension were more likely to be older, to be non-Hispanic black, and to have higher body mass index (all $P<0.001$). They were more likely to have albuminuria, reduced renal function, and self-reported medical histories of coronary heart disease, heart failure, stroke, and diabetes mellitus ($P<0.001$). Most (85.6% [SE: 2.4%]) individuals with resistant hypertension used a diuretic. Of this group, 64.4% (SE: 3.2%) used the relatively weak thiazide diuretic hydrochlorothiazide. Although not rare, resistant hypertension is currently found in only a modest proportion of the hypertensive population. Among those classified here as resistant, inadequate diuretic therapy may be a modifiable therapeutic target. Cardiovascular diseases, diabetes mellitus, obesity, and renal dysfunction were all common in this population. (Hypertension. 2011;57:1076-1080.)

Key Words: hypertension/epidemiology ▪ hypertension/drug treatment ▪ drug resistance ▪ antihypertensive agents/classification/therapeutic use ▪ diuretics ▪ United States/epidemiology

Resistant hypertension has been defined as blood pressure that remains above goal in spite of the concomitant use of antihypertensive medications from $\geq 3$ drug classes. Individuals with controlled blood pressure using $\geq 4$ drug classes are also considered to have resistant hypertension. Preferably, the regimen would include a diuretic, and all doses would be optimal.1–3 Although it is somewhat arbitrary and imprecise, this designation has been suggested to identify patients for whom special diagnostic investigations into reversible causes of hypertension may be warranted or those who may benefit from specific therapeutic considerations. The prevalence of resistant hypertension is unknown, but it is thought to be a common problem.1 Many of the evidence about the characteristics of individuals with resistant hypertension comes from studies conducted in referral populations that might not be generalizable to the overall population.

The National Health and Nutrition Examination Survey (NHANES) uses standardized assessments of blood pressure and prescription medications among a representative sample of the US population. It provides an opportunity to assess the prevalence of drug-resistant hypertension among US adults and to examine the characteristics of these individuals.

Methods

Data from the NHANES from 2003 through 2008 were used in these analyses. NHANES uses a multistage sampling design and appropriate weighting to provide a nationally representative sample of the noninstitutionalized US population. NHANES participants provided written informed consent, and the study was approved by the National Center for Health Statistics Research Ethics Review Board. NHANES data sets, study procedures, and questionnaires are publicly available from the National Center for Health Statistics.4 This study was limited to participants selected for the mobile examination sample of the NHANES who were nonpregnant and were $\geq 18$ years of age.

Blood pressures were measured by physicians using a standardized protocol. Participants were instructed to sit quietly for 5 minutes before the readings were taken. Three measurements were attempted.

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S.D.P. had full access to the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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If 3 readings were obtained, the first value was not used, and the mean of the subsequent systolic and diastolic readings was considered to be the average blood pressure, or if only 2 readings were obtained, the second reading alone was used. If only 1 reading was obtained, it was considered to be the average blood pressure.a Among the 15,968 nonpregnant adult participants, 13,154 had 3 blood pressure readings, 1,916 had 1 or 2 readings, and 989 had none. Participants with no recorded blood pressures were excluded. Participants were considered to have hypertension if the average systolic blood pressure was ≥140 mm Hg, the average diastolic blood pressure was ≥90 mm Hg, or they reported that they were currently taking a prescribed medication for hypertension or high blood pressure. Blood pressure was considered uncontrolled if the average systolic blood pressure was ≥140 mm Hg or the average diastolic blood pressure was ≥90 mm Hg.

In this study, participants were classified as having resistant hypertension if their blood pressure was ≥140/90 mm Hg (either systolic or diastolic) and they reported using antihypertensive medications from 3 different drug classes in the past 1 month or they reported using drugs from ≤4 antihypertensive drug classes in the past month regardless of blood pressure. Medication usage was assessed during home interviews, and interviewers reviewed prescription containers whenever available. Drug classes included angiotensin-convertase enzyme inhibitors, angiotensin receptor blockers, β-blockers, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, peripheral α-adrenergic receptor antagonists, central-acting and other antidiuretic drugs, direct vasodilators, and direct renin inhibitors. Prescription containers were directly observed for 89.8% of antihypertensive medications. Participants reported that they had been taking the medication for <30 days for 2.0% of antihypertensive medications.

Participants with hypertension receiving drug treatment who were not classified as resistant were classified in 2 other groups, uncontrolled (≥140/90 mm Hg) using ≤2 drug classes or controlled (<140/90 mm Hg) receiving ≤3 drug classes. Glomerular filtration rate was estimated from the serum creatinine using the Modification of Diet in Renal Disease equations. Participants self-reported comorbidities. Characteristics of participants with resistant hypertension were compared with participants in these other 2 groups with drug-treated hypertension.

All of the analyses used SAS 9.2 (SAS Institute, Inc., Cary, NC). Analyses were performed using appropriate NHANES sample weights that account for the probability of selection and nonresponse. Descriptive statistics and comparisons between groups used SAS survey procedures (SURVEYFREQ, SURVEYMEANS, and SURVEYREG) to account for the complex multistage sampling design. Comparisons between groups used the χ² test for categorical variables and linear regression for continuous variables.

Results

In 2003–2008, among noninstitutionalized nonpregnant US adults with hypertension, 8.9% (SE: 0.6%) met the criteria for resistant hypertension used here. This represented 12.8% (SE: 0.9) of all drug-treated hypertensive adults (Table 1). Among all of the drug-treated hypertensive adults whose blood pressure was uncontrolled, 72.4% (SE: 1.6%) were taking antihypertensive drugs from <3 drug classes.

Table 2 provides the characteristics of individuals with resistant hypertension, uncontrolled drug-treated hypertension using ≤2 medications, and drug-treated hypertension controlled using ≤3 medications. Adults with resistant hypertension differed in many ways from drug-treated hypertensive adults with blood pressure ≥140/90 mm Hg using 1 or 2 medications. Those with resistant hypertension were more likely to be non-Hispanic black and have higher mean body mass index, microalbuminuria and macroalbuminuria, an estimated glomerular filtration rate of <60 mL/min, and self-reported medical history of coronary heart disease, heart failure, stroke, and diabetes mellitus. Differences between those with resistant hypertension compared with drug-treated hypertensive individuals whose blood pressure was <140/90 mm Hg using 1 to 3 antihypertensive medication classes were similar. Those with resistant hypertension were also significantly older (Table 2).

The number and type of antihypertensive medications used by adults with resistant hypertension within the past month are provided in Tables 3 and 4, respectively. Use of diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were all common, and 9.1% (SE: 1.3%) used both an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker. Most (85.6%) individuals with resistant hypertension used a diuretic. Of the diuretic users, 64.4% (SE: 3.2%) used hydrochlorothiazide (55.1% of the total resistant hypertension population). Hydrochlorothiazide accounted for nearly all of the thiazide-like diuretic use (94.3% [SE: 1.4%]). Thiazide-like and loop diuretic use differed for resistant hypertensive participants with an estimated glomerular filtration rate <30 mL/min compared with others (Table 5). Although loop diuretic use and combination diuretic use were more common among persons with glomerular filtration rate <30 mL/min, 33.4% (SE: 11.2%) of this group did not use a loop diuretic.

Of those classified as resistant, 71.2% (SE: 2.8%) had blood pressure ≥140/90 mm Hg taking antihypertensive drugs from ≥3 drug classes, and the remainder had blood pressure <140/90 mm Hg using ≥4 drug classes. Approximately half, 49.5% (SE: 4.3%), of adults with resistant hypertension who used ≥4 antihypertensive medications had a blood pressure that was uncontrolled.

Discussion

This analysis indicates that 8.9% of all US adults with hypertension and 12.8% of antihypertensive drug-treated adults meet the operational definition of resistant hypertension used here. Most drug-treated adults with uncontrolled hypertension are receiving medications from only 1 or 2
pharmaceutical classes. At the population level, the underuse of adequate drug therapy for hypertension appears much more widespread than the lack of drug effectiveness.

The multidrug treatment regimens frequently used in the United States may often be less than optimal. Before considering someone to have resistant hypertension, treatment with 
\[\text{Resistant Hypertension, Uncontrolled, } \geq 3\text{ Drugs (N=539)} \]
\[\text{Uncontrolled Hypertension, } \leq 2\text{ Drugs (N=1136)} \]
\[\text{P*} \]
\[\text{Controlled Hypertension, } \leq 3\text{ Drugs (N=2035)} \]
\[\text{P*} \]

Table 2. Drug-Treated Hypertension Among Adults in the 2003–2008 National Health and Nutrition Examination Survey

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resistant Hypertension, Uncontrolled, (\geq 3) Drugs (N=539)</th>
<th>Uncontrolled Hypertension, (\leq 2) Drugs (N=1136)</th>
<th>(P^*)</th>
<th>Controlled Hypertension, (\leq 3) Drugs (N=2035)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in y, mean</td>
<td>66.4 (0.9)</td>
<td>64.7 (0.5)</td>
<td>0.1</td>
<td>59.5 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>53.8 (2.4)</td>
<td>59.2 (1.8)</td>
<td>0.07</td>
<td>53.8 (1.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td>0.02</td>
<td>3.5 (0.7)</td>
<td></td>
<td>6.0 (0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mexican American</td>
<td>1.9 (0.6)</td>
<td>4.4 (1.1)</td>
<td></td>
<td>3.7 (0.9)</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>72.6 (2.8)</td>
<td>75.9 (2.9)</td>
<td></td>
<td>77.8 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>18.5 (2.3)</td>
<td>13.7 (2.0)</td>
<td></td>
<td>12.6 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Other/multiracial</td>
<td>7.1 (1.7)</td>
<td>6.0 (0.9)</td>
<td></td>
<td>6.0 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index in kg/m², mean</td>
<td>32.4 (0.5)</td>
<td>29.7 (0.2)</td>
<td>&lt;0.001</td>
<td>31.0 (0.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Estimated GFR in mL/min, mean</td>
<td>69.1 (1.5)</td>
<td>78.9 (0.9)</td>
<td>&lt;0.001</td>
<td>80.2 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR &lt;60 mL/min, %</td>
<td>33.7 (2.6)</td>
<td>19.4 (1.6)</td>
<td>&lt;0.001</td>
<td>16.5 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium, mmol/L, %</td>
<td>4.03 (0.02)</td>
<td>4.00 (0.01)</td>
<td>0.4</td>
<td>4.00 (0.01)</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin:creatinine ratio, %</td>
<td>4.00 (0.02)</td>
<td>4.00 (0.01)</td>
<td>0.4</td>
<td>4.00 (0.01)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Numbers in parentheses represent SEs. GFR indicates glomerular filtration rate.**

*Data show the \(P\) value compared with the resistant hypertension group.

†Data are available for 97.9%.

‡Data are available for 94.2%.

§Data are available for 96.9%.

to drug resistance.1–3,7–9 Individuals with renal dysfunction, glomerular filtration rates <30 mL/min, may require loop diuretics. Although 86% of NHANES participants with resistant hypertension were using a diuretic, many may have inadequate diuretic treatment. Hydrochlorothiazide use was reported by 55% of adults classified as resistant, and it accounted for nearly all of the thiazide-like diuretic use in the resistant group. Although hydrochlorothiazide is part of most combination antihypertensive pills which include a diuretic marketed in the United States, there is evidence to suggest that it is not as effective as the diuretic chlorthalidone.10 Among adults with resistant hypertension and reduced renal function, many did not use a loop diuretic.

Several studies have shown that the use of aldosterone antagonists (spironolactone or eplerenone) may be a valuable strategy for individuals with difficult to control hypertension.11–13 During the time period studied (2003–2008), use of these agents among adults with resistant participants was very uncommon.

The characteristics of individuals with drug resistance observed in this cross-sectional study are concordant with previous observations, showing that increasing age, obesity, black race, and renal dysfunction are associated with drug resistance or lack of blood pressure control.14–18 This study also confirms a high prevalence of comorbid cardiovascular

Table 3. No. of Antihypertensive Medications Used in the Past Month Among Adults With Resistant Hypertension

<table>
<thead>
<tr>
<th>No. of Hypertensive Medication Drug Classes*</th>
<th>N</th>
<th>% (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>240</td>
<td>43.0 (2.7)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>43.2 (2.6)</td>
</tr>
<tr>
<td>≥5</td>
<td>79</td>
<td>13.8 (2.1)</td>
</tr>
</tbody>
</table>

*Drug classes considered were angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, \(\beta\)-blockers, dihydropyridine calcium channel blockers, nondihydropyridine calcium channel blockers, thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, peripheral \(\alpha\)-adrenergic receptor antagonists, central-acting and other anti-adrenergic drugs, direct vasodilators, and direct renin inhibitors. No individuals surveyed with resistant hypertension were taking a direct renin inhibitor.
Table 4. Type of Antihypertensive Medications Used in the Past Month Among Adults With Resistant Hypertension

<table>
<thead>
<tr>
<th>Antihypertensive Medication Class</th>
<th>Subclass</th>
<th>Number</th>
<th>Percentage (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td>317</td>
<td>57.0 (2.8)</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td>209</td>
<td>40.9 (2.8)</td>
</tr>
<tr>
<td>( \beta )-blocker</td>
<td></td>
<td>402</td>
<td>75.5 (2.1)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Dihydropyridine</td>
<td>272</td>
<td>50.7 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Nondihydropyridine</td>
<td>88</td>
<td>17.0 (2.5)</td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
<td>458</td>
<td>85.6 (2.4)</td>
</tr>
<tr>
<td>Thiazide like</td>
<td></td>
<td>300</td>
<td>58.5 (3.3)</td>
</tr>
<tr>
<td></td>
<td>HCTZ</td>
<td>279</td>
<td>55.1 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Loop</td>
<td>176</td>
<td>30.4 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Potassium sparing</td>
<td>57</td>
<td>12.5 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Aldosterone antagonist</td>
<td>20</td>
<td>3.0 (0.8)</td>
</tr>
<tr>
<td>( \alpha )-Adrenergic receptor antagonist</td>
<td></td>
<td>108</td>
<td>17.7 (1.7)</td>
</tr>
<tr>
<td>Central-acting and other</td>
<td></td>
<td>58</td>
<td>10.0 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Direct vasodilator</td>
<td>32</td>
<td>4.7 (0.9)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide.

disease and diabetes mellitus among adults with resistant hypertension.\(^{17}\) Unlike a referral population in which lower levels of serum potassium were found in resistant hypertension patients,\(^{19}\) in this population-based cohort, potassium levels were identical in the resistant and nonresistant drug-treated groups.

It is important to be aware of the limitations of these data when interpreting these results. The estimates provided here may overestimate the true prevalence of resistant hypertension in the current US adult population for several reasons. The medication use questionnaire used in NHANES does not distinguish whether medications were used consistently, only that they were used at all during the month before the examination. Some participants who were not fully adherent to their antihypertensive medication, discontinued a medica-
tion, or switched from one medication to another within the past month could be falsely classified as resistant. The NHANES did not record dose or frequency of medications; therefore, some individuals receiving drugs at low doses or with inadequate frequency (eg, once-daily short-acting loop diuretics) could have been falsely classified as resistant. Some individuals may have been falsely classified as resistant because of the white coat phenomenon if their examination blood pressure measurements were higher than what would have been observed using ambulatory blood pressure monitoring.\(^{20}\) However, the estimate of the cross-sectional prevalence of resistant hypertension provided here likely underestimates what the prevalence would be if all of the adults with uncontrolled hypertension were treated with adequate 3-drug regimens, because some individuals currently uncontrolled with \(<3\) drugs would remain uncontrolled even if 3 drugs were used. Lastly, the proportion with resistant hypertension would have been greater had a lower cut point for control been used for participants with diabetes mellitus or renal disease. The blood pressure target of \(<130/80\) mm Hg is recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for individuals with diabetes mellitus and renal disease, and lower targets may also be appropriate for individuals with ischemic vascular disease or others at high cardiovascular risk.\(^{2,21}\) Use of different target blood pressures was not used here for several reasons. There is no way to know the goal blood pressure selected by participants’ treating clinicians; different cut points would have greatly complicated the comparisons of characteristics between groups, and in light of recent findings in the Action to Control Cardiovascular Risk in Diabetes Study, the goal blood pressure that will be selected in future guidelines for individuals with diabetes mellitus is uncertain.\(^{22}\) Lastly, interpretation of diuretic use among individuals with resistant hypertension and glomerular filtration rates \(<30\) mL/min should be done cautiously, because few participants meeting these criteria were surveyed.

Perspectives

Resistant hypertension is not a rare phenomenon, but use of inadequate medical regimens for hypertension appears to be observed far more often than true resistance to a regimen that includes drugs from 3 different pharmaceutical classes. The group identified as resistant has many high-risk features, including a substantial burden of cardiovascular disease, stroke, diabetes mellitus, and underlying renal dysfunction. Special consideration may be needed to help mitigate these risks. More clinical research is needed to determine optimal therapeutic strategies for those with resistant hypertension.

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