Editorial Commentary

Resistant Hypertension
Bad and Getting Worse

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Resistant hypertension (RHTN) is most simply defined as high blood pressure (BP) requiring ≥4 antihypertensive medications, whether controlled or uncontrolled. The true prevalence of RHTN is unknown and is likely to remain so, because determining an accurate estimation of prevalence would require a large prospective study of a diverse hypertensive cohort in which subjects’ medications are force titrated if the BP remains above goal, adherence is closely monitored, and ambulatory BP monitoring is done to exclude white-coat RHTN. Given the cost and logistical challenges, such a study has not been done and is not likely to ever be done.

In the absence of a definitive study, clinical trials have been largely relied on to serve as surrogate opportunities to estimate the prevalence of RHTN. In that regard, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is probably the most relevant in that it included a large and diverse cohort, and, per protocol, subjects were to have continued escalation of their treatment regimen as long as the BP remained elevated. At the end of the 5-year treatment period, uncontrolled hypertension was common in ALLHAT, with 34% of subjects never having achieved BP control and with 27% of subjects receiving ≥3 antihypertensive medications. These data, as well as control rates from other clinical trials, have been interpreted to suggest a prevalence of RHTN of 20% to 30% of general hypertensive cohorts.

The problem, of course, is that ALLHAT and other clinical trials were not designed to determine the prevalence of RHTN. On one hand, enrollment criteria would have often resulted in underestimating the prevalence of RHTN by excluding subjects at highest risk of having RHTN, such as the patients with chronic kidney disease, the very elderly, the very obese, and, in the case of ALLHAT, patients with a known history of RHTN (ie, needing ≥2 medications to achieve a BP of <160/100 mm Hg). On the other hand, because the main purpose of these studies was to compare the efficacy and/or treatment benefit of different regimens, common and/or favorable drug combinations were often restricted from use, which likely served to diminish BP control. In ALLHAT, for example, subjects not randomized to receive chlorthalidone were precluded from receiving a diuretic as part of their treatment regimen.

The second approach to estimate the prevalence of RHTN is to rely on community-based observational studies of hypertension prevalence and control rates. In this regard, the NHANES is one of the most widely quoted, with data collected in 2007–2008 indicating an overall hypertension control rate of ≈50% and, among subjects receiving treatment, control rates of ≈70%. The 20% to 30% of patients with treated but uncontrolled hypertension reported in NHANES and other data sets have been interpreted to broadly reflect the underlying prevalence of RHTN. The problem with such an interpretation is that uncontrolled hypertension includes but is not the same as RHTN. The former would include patients with poorly controlled hypertension attributable to poor adherence and under treatment, which is separate from the latter, that is, true treatment resistance. Not accounting for such patients inflates the perceived prevalence of RHTN.

In the present edition of Hypertension, Persell4 applied the American Heart Association definition of RHTN of needing ≥4 medications to the 2005–2008 NHANES data to estimate the prevalence of RHTN to be ≈9% of all hypertensive subjects and ≈13% of treated hypertensive subjects. Of those classified as resistant, ≈70% were uncontrolled, with BP >140/90 mm Hg on ≥3 medications, and the remaining 30% were controlled with BP <140/90 mm Hg on ≥4 medications. Based on these figures and current estimates of there being 68-million hypertensive adult Americans, ≈6.1 million Americans have RHTN. Consistent with other reports, Persell4 found that, compared with patients with controlled hypertension, subjects with RHTN were more likely obese, older, black, and more likely to have diabetes mellitus and chronic kidney disease. Increased cardiovascular risk was reflected in greater rates of coronary heart disease, heart failure, and stroke.

The 9% rate likely represents the current best estimate of the prevalence of RHTN in the United States. In specifically relating lack of BP control to the number of antihypertensive medications being used, Persell4 has overcome a limitation of previous estimates that simply inferred treatment resistance from treated but still uncontrolled hypertension. What is still not fully accounted for is to what degree poor adherence is contributing to the apparent treatment resistance. The NHANES surveyors did report having observed prescription containers for ≈90% of the reported BP medications, sug-

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gesting at least that almost all of the prescribed medications were available to subjects at some point in time. It does not, however, confirm taking the medication on a reliable basis. Studies of small numbers of subjects that document BP control in subjects who had been previously uncontrolled with multidrug regimens when those same regimens are administered by clinical staff suggest that such poor adherence is an important cause of apparent treatment resistance. Likewise, to what extent white-coat effects are contributing to apparent treatment resistance in the clinic is not considered in the current analysis. Previous studies of patients with RHTN suggest that 20% to 40% of patients with elevated office BP levels may be controlled out of office when recorded by ambulatory monitoring.

Both of the above factors, that is, poor adherence and white-coat effects, if they could have been properly accounted for, would have reduced the observed prevalence of RHTN, suggesting that true RHTN is even less common than 9% of the general hypertensive population. However, countervailing those diminishing effects would have been the large proportion of patients who would have been accurately labeled as having RHTN if their medications had been properly titrated. That is, of the treated subjects whose BP remained uncontrolled, 72% were receiving only 1 or 2 antihypertensive medications. With titration to ≥3 medications, a proportion would have remained uncontrolled and, hence, added to the observed prevalence rate of RHTN. The end result of these competing effects is obviously unknown, but given the large number of uncontrolled hypertensive subjects, it seems reasonable to interpret the 9% prevalence rate as a minimum value. Even worse from a public health prospective, whatever the actual prevalence of RHTN, we can anticipate it increasing as populations worldwide are growing older and are increasingly affected by obesity, diabetes mellitus, and chronic kidney disease, all strong predictors of developing RHTN.

The findings of Persell\(^4\) also highlight the role that effective drug selection may play in reducing the prevalence of RHTN. In spite of the well-established superiority of chlorthalidone compared with hydrochlorothiazide in reducing BP, the majority of patients with RHTN (55%) were receiving hydrochlorothiazide as their diuretic.\(^7\) Also, in spite of consistent recommendations to use loop diuretics in patients with advanced chronic kidney disease, 33% of subjects with a glomerular filtration rate <30 mL/min lacked such treatment. Especially conspicuous was the pronounced lack of use of aldosterone antagonists. A substantial body of literature clearly demonstrates the broad benefit of spironolactone and eplerenone for treating RHTN, and, yet, only 3% of patients with RHTN were receiving these medications. With more appropriate diuretic selection, including more intensive use of aldosterone antagonists, the prevalence of RHTN would have, undoubtedly, been lower. These therapeutic deficiencies emphasize the importance of better educating clinicians on assembling effective multiple-drug combinations or convincing clinicians to more readily refer patients with RHTN to hypertension specialists.

Disclosures

None.

References
