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Resistant Hypertension: Incidence, Prevalence and Prognosis

Eduardo Pimenta, MD[1] and **David A. Calhoun, MD**[2]

[1]Endocrine Hypertension Rsrch Ctr & Clinical Ctr of Research Excellence in Cardiovascular Disease & Metabolic Disorders, University of Queensland School of Medicine, Princess Alexandra Hospital, Brisbane, QLD, Australia

[2]Vascular Biology & Hypertension Program, Division of Cardiovascular Diseases, University of Alabama at Birmingham, Birmingham, AL

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Since publication of the of the American Heart Association Scientific Statement on the Evaluation and Treatment of Resistant Hypertension in 2008, there has been growing clinical and research interest in the epidemiology, pathophysiology and therapeutic management of resistant hypertension.[1] Highlighted, however, by the authors of that AHA Scientific Statement were important deficiencies in our knowledge and understanding of resistant hypertension. Specifically commented on was the lack or even absence of data regarding the incidence, prevalence and prognosis of resistant hypertension.

Several recent publications have provided insight into the prevalence of resistant hypertension. In the current issue of *Circulation,* Daugherty et al provide important information on the incidence and prognosis.[2] Combined, these publications have made substantial progress in addressing deficiencies concerning the epidemiology of resistant hypertension.

Incidence

The analysis of Daugherty et al clearly represents the most rigorous if not the first determination of the incidence of resistant hypertension based on patients presenting with incident hypertension.[2] Utilizing patient data collected over a 4-year period in the Kaiser Permanente Colorado and Northern California health care systems, the authors identified over 200,000 patients who were started on antihypertensive therapy for newly diagnosed hypertension. During follow-up, approximately 21% were eventually prescribed 3 or more medications. Control or lack of blood pressure control was determined as close to 1 year as possible after being prescribed the 3rd antihypertensive medication. After excluding patients who were non-adherent, based on a <80% pharmacy refill rate for all prescribed

Address for Correspondence: Eduardo Pimenta, MD Hypertension Unit, Princess Alexandra Hospital Ipswich Road, 5thFloor Brisbane, QLD, 4102, Australia Phone: (617) 31765866 Fax: (617) 31765031 e.pimenta@uq.edu.au.

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antihypertensive medications, the authors found that approximately 1-year after starting treatment, 1 in 50 were resistant to treatment based on the AHA definition of having uncontrolled hypertension on 3 or more or controlled on 4 or more antihypertensive medications. This equals an incidence rate for resistant hypertension of 1.9%.

The current analysis undoubtedly represents the most accurate assessment to date of the incidence of resistant hypertension in the United States. The analysis is strengthened by having been done in a very large and ethnically diverse cohort. A major strength is also having excluded patients with pseudo-resistance because of non-adherence with prescribed antihypertensive medications. This determination, based on pharmacy refill rates, has been lacking in prior epidemiologic assessments of resistant hypertension.

The finding that 1 in 50 patients beginning antihypertensive treatment would need 4 or more medications within a median of just 1.5 years of follow-up is surprising. In the absence of chronic kidney disease, one would not have thought that even this small of proportion of patients would have needed so many antihypertensive mediations so soon after developing hypertension. With more extended follow-up, there is no doubt that the incidence would have been even higher, as medications were further titrated for the remaining uncontrolled patients, and, on an even longer time frame, as the cohort aged and gained weight, 2 of the most common risk factors for resistance to antihypertensive treatment. Overall, these current findings highlight the clinical reality that a growing proportion of patients will need a large number of medications (i.e., >3) to control their blood pressure.

Prevalence

Recently, the National Health and Nutrition Examination Survey (NHANES) dataset has been utilized to estimate the prevalence of resistant hypertension. Using data collected from 2003 through2008, Persell estimated that the prevalence of resistant hypertension was 8.9% of all US adults with hypertension, and perhaps more meaningfully, 12.8% of all US adults being treated for hypertension.[3] Looking at trends in blood pressure control as measured by NHANES, Egan et al found that the estimated prevalence of resistant hypertension has been increasing progressively over the last several decades.[4] Between 1988-1994 the estimated prevalence of resistant hypertension was 5.5% of all US hypertensive adults. Between 1999-2004, the rate was 8.5%, and most recently, between 2005-2008, the estimated prevalence was 11.8%. With an estimated 76 million adult Americans with hypertension, a prevalence rate of almost 12% would translate into an estimated 9 million Americans with resistant hypertension.[5]

Spanish investigators, based on an analysis of over 68,000 patients being followed by primary care physicians and specialists and who had been included in a registry of ambulatory blood pressure monitoring, found the prevalence of resistant hypertension to be 14.8% of treated subjects based on the AHA criteria.[6]White coat resistant hypertension, defined as an elevated clinic blood pressure (> 140/90 mm Hg), but controlled 24-hour ambulatory blood pressure (<130/80 mm Hg), was common in this cohort, comprising 37.5% of the patients diagnosed with resistant hypertension based solely on elevated clinic blood pressures.

Combined, these 3 studies indicate a prevalence of resistant hypertension among patients being treated for hypertension of 12-15%. These figures, however, have to be reconciled with results from clinical trials suggesting that the prevalence of resistant hypertension may, in fact, be considerably higher. For example, a recent analysis of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), a large, prospective, outcome study of 2 different antihypertensive treatment combinations, found that after a mean follow-up of approximately 5 years, 35% of the subjects who had been untreated prior to study entry and

50% of the previously treated subjects met diagnostic criteria consistent with having resistant hypertension (office blood pressure>140/90 mm Hg on 3 or more medications).[7] This extraordinarily high occurrence of resistant hypertension was not unique to ASCOT. In the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial(ALLHAT), after approximately 5 years of follow-up, 34% of participants remained uncontrolled on an average of 2 medications and 27% of participants were receiving 3 or more medications.[8]Overall, 49% of ALLHAT participants were controlled on 1 or 2 medications, meaning that approximately 50% of participants would have needed 3 or more blood pressure medications to achieve the goal blood pressure of <140/90 mm Hg. More recently, in the Avoiding Cardiovascular Events in Patients Living with Systolic Hypertension (ACCOMPLISH) study, 25-28% of subjects remained uncontrolled during the course of the study in spite of intensive treatment escalation.[9]

On the one hand, clinical trials, such as ASCOT, ALLHAT and ACCOMPLISH likely provide the best estimate of the prevalence of true treatment resistance as they were forced-titration studies, all medications were provided at no charge and medication adherence was closely monitored. These study features, designed to enhance blood pressure control, highlight that one of the biggest limitations of the observational studies, such as NHANES, is that a large proportion of participants remain undertreated, that is, uncontrolled on 1-2 antihypertensive medications. For example, in Persell's analysis of the NHANES data from 2003-2008, 28% of medication-treated hypertensive adults remained uncontrolled on ≤ 2 antihypertensive agents.[3] With appropriate intensification of treatment, an unknown percentage of these participants would continue to be uncontrolled on 3 medications and hence, properly designated as having resistant hypertension. The clinical trials, at least in design, would have minimized (although not eliminated) this clinical inertia and therefore, may more accurately reflect the degree of true treatment resistance.

On the other hand, clinical trials likely overinflate the apparent degree of treatment resistance as use of specific medication combinations may have been restricted per protocol and study enrollment was often limited to older subjects at high cardiovascular risk, which serves to enrich the study cohort with subjects more likely to be resistant to treatment. Fully reconciling the opposing effects of the different study designs is, of course, impossible, but with consideration of both the earlier clinical trial results and the more recent observational findings, the prevalence of resistant hypertension can be estimated with a higher-level confidence at between 15-30% of treated hypertensive patients.

The current analysis by Daugherty et al does not report the prevalence of resistant hypertension in relation to all treated hypertensive patients. Such an assessment would have strengthened the current estimates of prevalence, as it would have allowed for exclusion of patients non-adherent with their prescribed medications. Lack of this correction remains an important limitation of current determinations of prevalence.

Prognosis

Perhaps the most important and most intriguing finding of Daugherty et al is the considerably increased cardiovascular risk manifest in subjects with resistant hypertension. Important, because it is the first study to determine outcomes based on a longitudinal assessment of a large cohort of subjects with rigorously defined resistant hypertension. Multiple prior cross-sectional assessments of subjects with resistant hypertension compared to subjects without resistant hypertension have consistently indicated in the former an increased frequency of cardiovascular complications, including myocardial infarction, stroke, congestive heart failure and chronic kidney disease.[3,4,6]Although not done prospectively, the Daugherty el al analyzed longitudinal data collected over a 5-year period

to demonstrate a 50% increase in cardiovascular events (largely attributable to development of chronic kidney disease) in patients with resistant hypertension compared to patients whose blood pressure had been controlled on 3 medications.[2] Compared with all subjects being newly treated for hypertension, the risk of cardiovascular events in patients diagnosed with resistant hypertension was increased by more than 2-fold.

These findings are intriguing in that the difference in cardiovascular event rates occurred even though the duration of their hypertension should have been the same (only subjects with incident hypertension during the analysis period were included) and, presumably, the difference in blood pressure levels would have been minimized by application of system-wide treatment protocols. Differences in complication rates between patients with and without resistant hypertension have been attributed to presumed differences in accumulated blood pressure burden secondary to differences in duration and severity of hypertension. The current analysis, in minimizing those differences in blood pressure burden (but not eliminating them as blood pressure levels were higher in the resistant hypertensive patients when first starting antihypertensive treatment), suggests that a factor separate from blood pressure burden may be accelerating cardiovascular disease progression in patients with resistant hypertension.

It is tempting to speculate that one contributing factor to the greater frequency of cardiovascular complications observed in patients with resistant hypertension may be excess aldosterone. Multiple studies have shown hyperaldosteronism to be common in patients with resistant hypertension.[10,11] Additional studies have indicated that when combined with high dietary salt intake, aldosterone is an important mediator of cardiovascular disease severity, including resistance to antihypertensive treatment, chronic kidney disease and left ventricular hypertrophy.[12-15]If contributing to the higher risk of cardiovascular disease, preferential use of a mineralocorticoid receptor antagonist (MRA) for treatment of resistant hypertension may provide, beyond their well-recognized antihypertensive effect, specific benefit in terms of blunting the increased cardiovascular risk of having resistant hypertension. Daugherty et al were not in a position to assess this possibility, as the use of MRA's was extremely low in their cohort. Such an assessment, however, if possible in future analyses, would serve to guide optimal management of resistant hypertension while testing a potentially important pathophysiologic mechanism of heightened cardiovascular risk in patients with resistant hypertension.

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