Since the publication of the American Heart Association (AHA) 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. 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 on 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. Combined, these publications have made substantial progress in addressing deficiencies in the epidemiology of resistant hypertension.

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. Using patient data collected over a 4-year period in the Kaiser Permanente Colorado and Northern California healthcare systems, the authors identified 200 000 patients who were started on antihypertensive therapy for newly diagnosed hypertension. During follow-up, ≈21% were eventually prescribed ≥3 medications. Control or lack of blood pressure control was determined as close to 1 year as possible after the third antihypertensive medication was prescribed. After excluding patients who were nonadherent, on the basis of a <80% pharmacy refill rate for all prescribed antihypertensive medications, the authors found that ≈1-year after starting treatment, 1 in 50 were resistant to treatment on the basis of the AHA definition of having uncontrolled hypertension on ≥3 or controlled on ≥4 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 performed in a very large and ethnically diverse cohort. A major strength of the study is also that it excluded patients with pseudoresistance because of nonadherence with prescribed antihypertensive medications. This determination, based on pharmacy refill rates, has been lacking in prior epidemiological assessments of resistant hypertension.

The finding that 1 in 50 patients beginning antihypertensive treatment would need ≥4 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 proportion of patients would have needed so many antihypertensive medications so soon after developing hypertension. With more extended follow-up, there is no doubt that the incidence would have been even higher, as the 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 recent findings highlight the clinical reality that a growing proportion of patients will need a large number of medications (ie, >3) to control their blood pressure.

Recently, the National Health and Nutrition Examination Survey (NHANES) dataset has been used to estimate the prevalence of resistant hypertension. Using data collected from 2003 through 2008, 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. 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. Between 1988 and 1994, the estimated prevalence of resistant hypertension was 5.5% of all US hypertensive adults. Between 1999 and 2004, the rate was 8.5%, and most recently, between 2005 and 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.

Spanish investigators, on the basis of an analysis of 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 patients on the basis of AHA criteria. 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% to 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 5 years, 35% of the subjects who had been untreated before 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 medications). This extraordinarily high occurrence of resistant hypertension was not unique to ASCOT. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), after 5 years of follow-up, 34% of participants remained uncontrolled on an average of 2 medications and 27% were receiving ≥3 medications. Overall, 49% of ALLHAT participants were controlled on 1 or 2 medications, meaning that 50% of participants would have needed ≥3 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% to 28% of subjects were receiving ≥3 medications. This extraordinarily high occurrence of resistant hypertension was not unique to ASCOT. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), after 5 years of follow-up, 34% of participants remained uncontrolled on an average of 2 medications and 27% were receiving ≥3 medications. Overall, 49% of ALLHAT participants were controlled on 1 or 2 medications, meaning that 50% of participants would have needed ≥3 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% to 28% of subjects remained uncontrolled during the course of the study in spite of intensive treatment escalation.

On the one hand, clinical trials such as ASCOT, ALLHAT, and ACCOMPLISH likely provide the best estimate of the prevalence of true treatment resistance because 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 (ie, uncontrolled on 1–2 antihypertensive medications). For example, in Persell’s analysis of the NHANES data from 2003 to 2008, 28% of medication-treated hypertensive adults remained uncontrolled on 2 antihypertensive agents. 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 because 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 tends 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 of confidence at between 15% to 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 because it would have allowed for exclusion of patients who did not adhere to 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 on the basis of 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 with 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 Although the study by Daugherty et al was not done prospectively, it 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 with 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 2 fold.

These findings are intriguing in that the difference in cardiovascular event rates occurred even though the duration of the patients’ 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, given that 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. 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. If aldosterone contributes to the higher risk of cardiovascular disease, preferential use of a mineralocorticoid receptor antagonist for treatment of resistant hypertension may provide, beyond its 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 because the use of mineralocorticoid receptor antagonists was extremely minimal 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 pathophysiological mechanism of heightened cardiovascular risk in patients with resistant hypertension.

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References

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