The term “resistant hypertension” (RH) evokes a myriad of clinical descriptions, nearly all of which implicitly ascribe origins of the problem to characteristics inherent within the patient or maleficient qualities of the disease itself. The need for an operational definition to help identify and prioritize a higher-than-average-risk population that could benefit from special diagnostic and therapeutic considerations eventually resulted in the current definition of RH as blood pressure (BP) remaining above goal despite the use of ≥3 antihypertensive agents of different classes, including a diuretic, or BP that is controlled requiring ≥4 antihypertensive medications.¹ In clinical practice, however, RH is more often an umbrella term used to designate BP that is difficult to control in a patient taking (or having failed) several antihypertensives, the actual number often bearing little consequence to the frustrated clinician and patient alike. But is resistance only a story about the patient and his or her disease? Or, can it be more aptly described in many cases as resistant prescribing?

Whether adhering to a strict definition or a more broad practice designation, conspicuously absent when referring to RH is a quality metric (other than an arbitrarily defined absolute number of drugs) of the prescribing behavior that may have inadvertently contributed. In this issue of Hypertension, Hanselin et al² have added considerably to our knowledge of antihypertensive prescribing patterns in patients with RH. What they found largely substantiates earlier reports³,⁴ and implicates suboptimal drug selection as an important contributor to the epidemic of RH. Using anonymous claims data from >5 million patients with hypertension in the MarketScan Commercial Claims and Encounter database, Hanselin et al⁴ identified a cohort of 140 126 patients with RH, based on a definition of concurrent use of ≥4 antihypertensive agents. Although this may have resulted in a slightly lower prevalence of RH (2.7%) versus the 9.0% reported in an earlier study,³ it is a significantly large enough cohort to permit some very meaningful assessments of overall antihypertensive prescribing patterns in this important population.

Perhaps most revealing of their results is a low rate of prescribing “evidence-based and recommended therapies,” specifically the use of chlorthalidone (3.0%) and aldosterone antagonists (5.9%), as recommended in the American Heart Association guidelines for the treatment of RH.¹ In contrast, a fairly high prevalence (15.6%) was noted for regimens with less support for efficacy, such as dual use of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Importantly, the beginning of the analysis period (May 2008) roughly coincided with release of the American Heart Association guideline, making it particularly troublesome that, even after 15 months had elapsed, the chasm between guideline recommendations and actual treatments used in practice remains unacceptably wide.

Given that volume overload often contributes to RH, inclusion of a diuretic to the regimen greatly improves the chances of controlling BP. Recently reported data from the National Health and Nutrition Examination Surveys revealed that patients were less likely to have uncontrolled BP on 1 or 2 antihypertensives when one of the agents was a thiazide-type diuretic.⁴ However, for diuretic therapy to be effective, it must be optimized and tailored to the individual patient. Loop diuretics are preferred when chronic kidney disease is present, whereas evidence favors the more potent and longer-acting chlorthalidone over hydrochlorothiazide when selecting a thiazide-type diuretic for patients with normal renal function.⁵,⁶ Ample study also supports the additive BP-lowering effects of an aldosterone antagonist in patients with RH, regardless of the presence of primary aldosteronism.¹

Although a relatively high percentage of the cohort studied by Hanselin et al² received diuretics (93.2%), the use of loop diuretics in patients with a concurrent diagnosis of chronic kidney disease was quite low (26.4%), and when thiazide-type diuretics were used, the majority (94.6%) received the weakly potent hydrochlorothiazide (mean dose: 21.1 mg). Only 3.0% of patients received chlorthalidone, whereas aldosterone antagonists (primarily spironolactone) fared only slightly better (5.9%). This lack of diuretic optimization observed is not surprising given other reports¹ but remains an easily modifiable target.

Several important limitations should be considered in the study design. First, the RH cohort was identified based on having met a definition founded strictly on the number of antihypertensives, whereas the definition of RH rigorously applied includes that the agents should be from different classes. Second, without the actual BP, an essential criterion for defining RH, it is unknown whether BP in the majority of individuals was successfully controlled on their multidrug regimen. Selection of the population based solely on the number of medications in the absence of BP data or metrics evaluating the quality of prescribing makes it difficult to decipher whether it is really RH or perhaps an iatrogenic categorization attributed to overreliance on ineffective anti-
hypertensive regimens. In the case of the latter, one can only speculate whether patients classified as having RH in the cohort would respond to a regimen with fewer, more carefully selected agents. Finally, the observed cohort is an insured population, a relatively healthy group at a presumable advantage with regard to financial means and healthcare access, and most likely reasonably adherent to treatment; thus, the study may not accurately represent all of the elements of the population in which RH resides.

Despite these limitations typical of a claims-based pharmacoepidemiologic study, defining the cohort based on the number of medications used is a reasonable proxy, and the data are further strengthened by the size and geographic diversity of the cohort. Overall, they give us a reasonable picture of how patients in a real-world environment are currently treated. Although the main findings could easily disillusion clinicians about the quality of antihypertensive prescribing, there are silver linings not to be ignored. First, the overall prevalence of RH was lower than in other reports, suggesting aggressive pursuit of BP goals. Second, there was measurable use of chlorthalidone and aldosterone antagonists, albeit low, but indicating that at least some clinicians are rediscovering older, well-proven agents. In the case of chlorthalidone, rates were consistent with another recent report, where it was also suggested that these rates of use might be slowly increasing. Nearly three quarters of the cohort were receiving a combination of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a calcium channel blocker plus a diuretic, a highly effective combination regimen, and almost two thirds were using fixed-dose combinations products, a strategy that can reduce pill burden and improve adherence.

There is no question that RH is frequently encountered among primary care clinicians and hypertension specialists alike. As the population ages, becomes more obese, and experiences higher prevalences of related comorbidities, such as diabetes mellitus and chronic kidney disease, hypertension will remain difficult-to-treat for many. The burden of the disease makes it compelling that we better understand our current approaches to management so that we can focus on strategies for improvement. We are fortunate to practice during a time when the antihypertensive menu is full of multiple, fairly inexpensive, readily available agents. Hypertension that is not controlled with \( \geq 3 \) antihypertensives is clearly resistant to something. Before attributing it to host factors beyond our control, we need to first ensure that we have not contributed to its presence by failing to use effective combinations and evidence-based therapies. Such behavior would more appropriately make RH an issue of resistant prescribing.

Disclosures

None.

References

Resistant Hypertension or Resistant Prescribing?
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_Hypertension._ 2011;58:987-988; originally published online October 31, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.183459

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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