

Resistant Hypertension Medical Management and Alternative Therapies



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KEYWORDS

- Hypertension • Joint National Committee • Resistant hypertension • Secondary hypertension
- Device

KEY POINTS

- Resistant hypertension (HTN) is failure to achieve goal blood pressure (BP) in spite of using a minimum of 3 antihypertensive drugs of different classes, at maximal tolerated doses, one of which must be a diuretic.
- In patients with resistant HTN, causes of pseudoresistance (both patient- and provider-related factors), and secondary HTN should be ruled out.
- Treatment of resistant HTN focuses on lifestyle modification and pharmacologic management. The basic principle for intervention is to ensure that all possible mechanisms for BP elevation are blocked.
- In general, most patients with resistant HTN should be on a renin angiotensin system blocker along with a calcium antagonist and a diuretic. Further medications can be added on an individual basis.
- Device-based therapies for resistant HTN should be reserved for those in whom available pharmacologic agents failed to control BP.

INTRODUCTION

Hypertension (HTN) is a major public health problem that affects approximately 1 billion people worldwide.¹ In the United States, 1 in 3 adults (\approx 73 million) has high blood pressure (BP).² Several studies, including meta-analyses, have demonstrated a linear relationship between BP level and the risk for cardiovascular events, such as stroke, myocardial infarction, congestive heart failure, and chronic kidney disease (CKD), with the risk of cardiovascular mortality doubles with

every 20/10 mm Hg increase in systolic and diastolic BP.³ In the United States, the total cost of treating HTN in 2010 was estimated to be \$76 billion.² Persistent, suboptimal BP control is consequently the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease as well as the progression of CKD, and an estimated 7 million deaths and 64 million disability-adjusted life years annually.^{4,5} Analyses of the National Health and Nutrition Examination Survey (NHANES) have demonstrated that not

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only is HTN awareness poor, but approximately 50% of hypertensive patients are not adequately treated to their goal BP of less than 140/90 mm Hg, with worse control rates in participants greater than 60 years of age, CKD and diabetes mellitus (DM).⁶ Several, large HTN outcome trials also demonstrate a failure to achieve BP goals despite protocol-defined treatment regimens; 20% to 35% of participants were unable to achieve BP control despite receiving 3 antihypertensive medications or more.⁷⁻⁹ These patients, by definition, are referred to as having refractory or resistant HTN.

Evaluation and treatment of patients with resistant HTN should be focused on identifying and removal of contributing factors, correct diagnosis and management of secondary causes, and use of effective multidrug regimens. Management of these patients often necessitates consultation with an HTN specialist.

DEFINITION OF RESISTANT HYPERTENSION

The Seventh Joint National Committee Report on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined resistant HTN as failure to achieve goal BP less than 140/90 mm Hg or less than 130/80 mm Hg in patients with DM or CKD in patients with HTN who are on maximum doses of an appropriate antihypertensive drug regimen consisting of 3 or more agents of different classes, including a diuretic.¹⁰ The American Heart Association, however, defined resistant HTN as uncontrolled HTN despite at least 3 antihypertensive drugs or controlled HTN with at least 4 medications.¹¹ Although resistant HTN was not specifically addressed in the JNC-8 2014 Hypertension Guidelines, recommended goal BP was raised to less than 150/90 mm Hg in adults aged 60 years or older, and less than 140/90 mm Hg in patients less than 60 years old, including those with CKD, DM, or both.¹² Resistant HTN is not synonymous with uncontrolled HTN (**Box 1**). The latter includes all hypertensive patients who lack BP control under treatment, namely those receiving an inadequate treatment regimen, those with poor compliance, those who have elevated BP in the office but normal at home (white coat HTN) and those with undetected secondary HTN, as well as those with true treatment resistance.

PREVALENCE OF RESISTANT HYPERTENSION

Several clinical trials and epidemiologic data have estimated the prevalence of resistant HTN to be 20% to 30%,^{7-9,13-15} although the exact

Box 1 Definitions of various forms of hypertension

Resistant hypertension

Failure to achieve goal BP using a minimum of 3 antihypertensive drugs at maximal tolerated doses, 1 of which must be a diuretic.

Controlled resistant hypertension¹¹

Patients who meet the definition of resistant hypertension but whose BP is controlled on maximal tolerated doses of 4 or more antihypertensive medications.

Refractory hypertension

Patients who meet the definition of resistant hypertension but whose BP is not controlled on maximal tolerated doses of 4 or more antihypertensive medications.

Pseudoresistance

Lack of BP control with appropriate treatment in a patient who does not have resistant hypertension.

White-Coat hypertension

Patients who have clinic/office BP readings above goal on at least 3 separate visits with 2 measurements taken at each visit, and at least 2 BP readings at or below goal taken outside the clinic/office, and show no evidence of end-organ damage.

Masked hypertension

Patients who have normal clinic but high ambulatory BPs (opposite of white-coat hypertension).

Abbreviation: BP, blood pressure.

prevalence has been difficult to determine owing to the lack of large, prospective cohort studies of patients with true resistant HTN. Individuals with resistant HTN are more likely to be older than age 55, male, non-Hispanic black, have a high body mass index, with a history of DM, renal dysfunction, and cardiovascular disease, including coronary heart disease, heart failure, and stroke.⁶ A 2012 estimation by the American Heart Association based on NHANES 2005–2008 data showed that only 54% of hypertensive participants had a well-controlled BP on medications and that the prevalence of uncontrolled HTN despite being on 3 medications has almost doubled from 16% in 1998 through 2004 to 28% in 2005 through 2008.¹⁶ In patients with controlled as well as uncontrolled HTN, the number of medications taken has increased with time.⁶ NHANES data from 2005 through 2008 has shown that

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