

The Prevalence, Incidence, Prognosis, and Associated Conditions of Resistant Hypertension

Joshua Vega, MD,* and John D. Bisognano, MD, PhD†

Summary: Resistant hypertension is a relevant condition gaining special attention given its clinical and economic impact. Although the true prevalence is unknown, clinical trials and population-based studies have shown that it is a common clinical problem that likely will increase in incidence with an aging and more obese population. A complex interaction of various risk factors including lifestyle, associated conditions, and identifiable secondary causes can lead to uncontrolled hypertension. Important factors including improper blood pressure measuring technique, poor medication adherence, and the white coat phenomenon can lead to pseudoresistance, or a false impression of treatment resistance, which must be excluded. Patients with true resistant hypertension have a greater risk for developing adverse cardiovascular events compared with those with controlled blood pressure, leading to an unfavorable prognosis without adequate treatment. This article reviews the current understanding of the epidemiology of resistant hypertension.

Semin Nephrol 34:247-256 © 2014 Elsevier Inc. All rights reserved.

Keywords: Epidemiology, resistant hypertension, prevalence, incidence, associated conditions

Hypertension is a major contributor to the global burden of disease related to an estimated 7 million deaths and 64 million disability-adjusted life-years annually worldwide.¹ The National Health and Nutrition Examination Survey (NHANES) from 2005 to 2008 reported a prevalence of approximately 30% in adults older than age 25, or at least 65 million individuals with hypertension living in the United States, making it the most common chronic disorder.² Hypertension is a leading risk factor causing cardiovascular morbidity and mortality associated with serious adverse cardiovascular events including coronary artery disease, heart failure, stroke, and progression of chronic kidney disease (CKD).³ There are many lifestyle modifications and antihypertensive medications to treat hypertension and prevent cardiovascular events. Although hypertension is a common disorder, there remains a great number of individuals with uncontrolled hypertension who are untreated or treated inadequately despite multiple antihypertensive medications, leading to a higher risk for adverse cardiovascular effects and mortality, placing a strain on the health care delivery system.

This review discusses the current understanding of the epidemiology of resistant hypertension including the identification, prevalence, incidence, associated conditions, and prognosis of the disorder.

DEFINITION OF RESISTANT HYPERTENSION

The definition of resistant hypertension has been described by many investigators. A summary of key definitions can be found in [Table 1](#). Importantly, resistant hypertension and uncontrolled hypertension are not similar terms because the latter applies to all patients diagnosed with hypertension who have not achieved adequate blood pressure control despite treatment. As formally defined in the seventh report of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), resistant hypertension is the failure to achieve a goal blood pressure of less than 140/90 in average-risk hypertensive patients adherent to an appropriate combination of three or more antihypertensive medications of different classes at maximally tolerated doses including a diuretic.³ Evidence supports that patients with diabetes or CKD benefit from a lower goal blood pressure of less than 130/80.³ Of note, the lack of blood pressure control most often is secondary to isolated systolic hypertension, which is particularly prevalent in the elderly population.⁴ The JNC 7 formal definition helped set a standard reference for clinicians and researchers and was recognized in the 2008 American Heart Association (AHA) Position Statement on Resistant Hypertension for being useful in identifying patients at high risk of having reversible causes of hypertension as well as patients with persistently high levels of blood pressure who may benefit from special diagnostic and therapeutic measures.⁵

Controlled resistant hypertension refers to patients whose blood pressure is controlled with the use of four

*Department of Internal Medicine, University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, New York.

†Department of Internal Medicine, Division of Cardiology, University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, New York.

Financial disclosure and conflict of interest statements: none.

Address reprint requests to John D. Bisognano, MD, PhD, Department of Internal Medicine, Division of Cardiology, University of Rochester Medical Center, School of Medicine and Dentistry, 601 Elmwood Ave, Box 679-7, Rochester, NY 14642. E-mail: John_Bisognano@URMC.Rochester.edu

0270-9295/ - see front matter

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<http://dx.doi.org/10.1016/j.semnephrol.2014.04.002>

Table 1. Various Definitions of Resistant Hypertension

Resistant hypertension: failure to achieve goal blood pressure levels despite taking maximal doses of three or more antihypertensive medications of different classes, including a diuretic
Resistant hypertension and uncontrolled hypertension are not synonymous: the latter applies to all hypertensive patients who have not achieved adequate blood pressure control despite treatment
Controlled resistant hypertension: blood pressure that is controlled using maximal doses of four or more antihypertensive medications
Refractory hypertension: patients with resistant hypertension whose blood pressure remains uncontrolled despite maximal doses of four or more antihypertensive medications

or more maximal doses of antihypertensive medications.⁵ Conversely, patients who meet the definition of resistant hypertension and whose blood pressure remains uncontrolled despite four or more maximal doses of antihypertensive medications can be referred to as having *refractory hypertension*.⁶ Although imprecise, the definition of resistant hypertension when taken literally includes patients taking four or more medications. Regardless, it is important to provide special attention to individuals with difficult-to-control hypertension because they may benefit from diagnostic and therapeutic measures that may help prevent serious adverse cardiovascular effects.

PREVALENCE

The exact burden of resistant hypertension in either hypertensive patients or the general patient population has not been clearly determined, but is thought to be a common problem.⁵ Precisely estimating its prevalence is challenging because of the lack of a well-designed, large, prospective cohort study in an unselected hypertensive patient population with forced titration of at least three blood pressure medications, including a diuretic, to achieve a goal blood pressure.⁷ To date, the most representative estimates of the prevalence of resistant hypertension are from direct epidemiologic data in recently published population-based studies (Table 2).⁸ Before these reports, information from retrospective cohort studies in specialized hypertension

centers, post hoc analyses from major outcome trials, and electronic medical record and pharmacologic databases helped to estimate indirectly the prevalence of resistant hypertension.⁷

Indirect Estimates Using Non-Population-Based Studies

There are several reports of retrospective cohort studies estimating the prevalence of resistant hypertension among hypertensive patients referred to tertiary hypertension centers. The earliest of these reports is a study of 436 patients referred to the Yale Hypertension Center from 1986 to 1988 in which 21% of the cohort were indicated to have resistant hypertension owing to various causes, the most common being a suboptimal medication regimen.⁹ A lower prevalence was estimated in a cohort of 1,281 patients referred to Rush University Hypertension Center, of whom 11% met strict criteria for resistant hypertension.¹⁰ Etiologies of resistance were found in the majority of patients in this study, including drug-related causes and nonadherence to medication.¹⁰ Overall, 53% of patients achieved goal blood pressure through intense optimization of an appropriate medication regimen with an average of 4.1 antihypertensive drugs at the end of the follow-up evaluation.¹⁰ It is worth mentioning that some of the patients in the earlier-mentioned studies determined to have resistant hypertension did not all appropriately meet the definition of true resistance as defined in the

Table 2. Summary Points on the Prevalence of Resistant Hypertension

The exact prevalence of resistant hypertension remains unknown without a well-designed, large, prospective cohort study in an unselected hypertensive population using forced titration of medications
Information from retrospective cohort studies in tertiary clinics, post hoc analyses from major outcome trials, and electronic medical record databases have helped provide indirect estimates ranging from 10% to 40%
Population-based studies provide the most accurate estimates: the reported prevalence of a survey using NHANES 2003 to 2008 data showed 8.9% of all hypertensive adults and 12.8% of all treated hypertensive adults meeting criteria for resistant hypertension
Individuals with resistant hypertension are more likely to be male, older than age 55, non-Hispanic black, have a higher mean body mass index, albuminuria, renal dysfunction, and a reported history of diabetes mellitus, coronary heart disease, heart failure, and stroke
The incidence of resistant hypertension is expected to increase as the population ages, along with higher rates of obesity

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