# Apparent Treatment-Resistant Hypertension and Chronic Kidney Disease: Another Cardiovascular-Renal Syndrome?

Sreekanth Vemulapalli, Crystal C. Tyson, and Laura P. Svetkey

**To identify patients at increased risk of cardiovascular (CV) outcomes, apparent treatment-resistant hypertension (aTRH) is defined as having a blood pressure above goal despite the use of 3 or more antihypertensive therapies of different classes at maximally tolerated doses, ideally including a diuretic. Recent epidemiologic studies in selected populations estimated the prevalence of aTRH as 10% to 15% among patients with hypertension and that aTRH is associated with elevated risk of CV and renal outcomes. Additionally, aTRH and CKD are associated. Although the pathogenesis of aTRH is multifactorial, the kidney is believed to play a significant role. Increased volume expansion, aldosterone concentration, mineralocorticoid receptor activity, arterial stiffness, and sympathetic nervous system activity are central to the pathogenesis of aTRH and are targets of therapies. Although diuretics form the basis of therapy in aTRH, pathophysiologic and clinical data suggest an important role for aldosterone antagonism. Interventional techniques, such as renal denervation and carotid baroreceptor activation, modulate the sympathetic nervous system and are currently in phase III trials for the treatment of aTRH. These technologies are as yet unproven and have not been investigated in relationship to CV outcomes or in patients with CKD.**

**Key Words:** Resistant hypertension, Chronic kidney disease, Aldosterone, Diuretic, Cardiovascular outcomes

## Introduction

Hypertension is the number one attributable risk factor for cardiovascular (CV) disease and is responsible for over half of the estimated 17 million deaths per year resulting from CV disease worldwide.[1] Every 20/10 mm Hg increase in blood pressure (BP) correlates with a doubling of CV mortality.[2] Beyond mortality, hypertension is a significant risk factor for CV morbidity, including stroke, myocardial infarction, heart failure, and renal failure.[3] These events occur at higher rates in individuals with apparent treatment-resistant hypertension (aTRH)[4] and in individuals with chronic kidney disease (CKD). aTRH is particularly prevalent in patients with CKD.[5] This review will discuss the role of clinical and subclinical kidney disease in the epidemiology, pathogenesis, and treatment of aTRH.

### *Definition of Resistant Hypertension*

To identify a subset of patients at increased CV risk who may benefit from special therapeutic considerations, the American Heart Association (AHA) defined resistant hypertension in a 2008 scientific statement as BP that remains above goal despite the use of 3 optimally dosed antihypertensive agents of different classes.[6] By these terms, resistant hypertension includes patients at goal BP using 4 or more antihypertensive agents. Implicit in this definition is the exclusion of causes of pseudoresistant hypertension, including white-coat hypertension, medication nonadherence, and improper BP measurement technique. To effectively exclude causes of pseudoresistant hypertension, current guidelines recommend obtaining either home BPs or, if available, ambulatory BPs.[6,7] Furthermore, patient compliance with antihypertensive therapy should be assessed by medication reconciliation and questioning family members.[7]

### *Definition of aTRH*

aTRH has been coined to comprise patients meeting the AHA definition of resistant hypertension in whom causes for pseudoresistance have not been thoroughly investigated.[8] Given that the vast majority of studies on resistant hypertension in the literature do not completely address pseudoresistance, we will use the term aTRH for the rest of this review unless pseudoresistance has been specifically excluded.

### *Epidemiology of aTRH*

The prevalence of resistant hypertension is ill-defined. The accuracy of past estimates is complicated by a number of factors, including lack of a uniform definition for hypertension resistance, presence of referral bias in observed clinical cohorts, and the likely inclusion of individuals with pseudoresistant hypertension in observational studies. More recently, large prospective cohort studies have investigated the incidence and prevalence of aTRH. Daugherty and colleagues[9] examined the incidence of aTRH among patients in the combined Kaiser Northern California and Kaiser Colorado databases. Among 205,750 newly diagnosed hypertensive patients, 1.9% were found to have aTRH, defined as uncontrolled BP on 3 or more antihypertensive medications or controlled BP on 4 or more antihypertensive medications, plus at least 80% medication adherence at

*From Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, NC; Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC.*

*Financial Disclosures: S.V. reports grant funding from Boston Scientific and speaker's fees from Medtronic. C.C.T. reports speaker's fees and grant funding from Medtronic and grant funding from the National Institutes of Health (grant 1U01-HL-096720). L.P.S. reports grant funding from the National Institutes of Health (grant 1U01-HL-096720) and speaker's fees and grant funding from Medtronic.*

*Address correspondence to Sreekanth Vemulapalli, MD, Division of Cardiology, Duke University Medical Center, Box 3126, Durham, NC 27710. E-mail: sqvster@gmail.com*


*1548-5595/$36.00*
*http://dx.doi.org/10.1053/j.ackd.2014.08.006*

1.5 years of follow-up. Among those taking 3 medications or more for at least 1 month, the prevalence of aTRH was 16.2%.[9] Given that medication noncompliance is likely the most common cause of pseudoresistance, the study by Daugherty and colleagues represents the most careful estimate of aTRH to date.

Other large cohort studies have documented a similar but growing prevalence of aTRH. Using sequential National Health and Nutrition Examination Survey (NHANES) data, Egan and colleagues examined the prevalence of aTRH, defined as BP of 140/90 mm Hg or more while taking 3 or more antihypertensive medications, irrespective of dose, adherence, and BP measurement artifacts. From 1988 to 1994 to 2005 to 2008, the prevalence of aTRH among patients with hypertension grew from 5.5% to11.8%.[10] Similarly, in the International Reduction of Atherothrombosis for Continued Health (REACH) Registry of 67,888 patients with known atherosclerotic disease or atherosclerotic risk factors enrolled from 2003 to 2004, the prevalence of aTRH was 12.7% among hypertensive patients.[11] Thus, aTRH appears to affect about 12% of hypertensive adults, an estimated 8 million individuals in the United States.

### *CKD and aTRH*

Among patients with hypertension, CKD is a common comorbidity with a prevalence of 32% in those with diagnosed hypertension and 24% in those with undiagnosed hypertension.[12] Among those with aTRH, prospective cohort studies demonstrate remarkable consistency in the prevalence of CKD. In the REACH Registry, the prevalence of CKD at baseline, defined as estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 $m^2$, was 40.1%, whereas in 1999 to 2004 and 2005 to 2008, NHANES data showed a prevalence of 36.1% and 37.8%, respectively, among those with aTRH. Furthermore, Egan and colleagues reported an eGFR less than 60 mL/min/1.73 $m^2$ and albumin-to-creatinine ratio (ACR) greater than 300 mg/g to be associated with an increased odds ratio for aTRH among patients with hypertension.[10] Thus, among patients with aTRH, CKD is common and proteinuria is associated with increased risk for aTRH in patients with hypertension.

Conversely, those with CKD have increased risk of aTRH: an analysis from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study demonstrated an increasing prevalence and risk of aTRH among patients with lower eGFR and higher ACR (Table 1).[13] Among patients with CKD, an elevated ACR in the setting of normal eGFR was also associated with an increased prevalence of aTRH. Thus, aTRH and CKD are commonly comorbid. However, given that not all patients with aTRH have CKD and not all patients with CKD have aTRH, it is likely that mechanisms indirectly related to or independent of the kidney contribute to the pathophysiology of aTRH.

**CLINICAL SUMMARY**

- Apparent treatment resistant hypertension is common and increasing in prevalence.
- CKD and albuminuria are significantly associated with aTRH, and aTRH is associated with adverse renal and cardiovascular outcomes.
- Multiple biologic mechanisms contribute to aTRH, including volume expansion, mineralocorticoid receptor activity, arterial stiffness, and sympathetic nervous system activity.
- Carotid baroreceptor modulation and renal denervation are novel non-pharmacologic therapies under development for the treatment of resistant hypertension.

### *Proposed Pathophysiology of aTRH*

The pathophysiology of aTRH is multifactorial (Fig 1), and the degree to which culpable factors contribute to treatment resistance likely varies among individuals. The kidney is believed to play a significant role in the pathogenesis of aTRH. The interplay between volume expansion, aldosterone, mineralocorticoid receptor (MR) activity, the sympathetic nervous system (SNS), and arterial stiffness are highlighted subsequently.

#### Volume Expansion

The volume expansion that accompanies CKD contributes significantly to hypertension. Johnson and colleagues have suggested that primary subclinical renal microvascular disease leading to afferent arteriolopathy and tubulointerstitial disease may be responsible for the development of salt-sensitive hypertension.[14] Progressive tubulointerstitial disease will eventually result in microalbuminuria before the development of clinically apparent impairment of glomerular filtration. Concurrent microvascular damage is thought to result in renal vasoconstriction and subsequent local generation of angiotensin II. The resulting increased vascular resistance, reduced rate of ultrafiltration, and decreased sodium excretion cause sodium retention, volume expansion, and hypertension (Fig 2).[15] Additional inciting factors leading to subclinical microvascular injury include sympathetic overactivity, increased activity of the renin-angiotensin axis, decreased production of nitric oxide (NO), low potassium diet,[16,17] and presence of long-standing hypertension itself. Furthermore, these insults may be potentiated by known genetic factors affecting renal sodium handling and renin-angiotensin activity.[18,19]

#### Aldosterone and the Mineralocorticoid Receptor

Although the central roles of renin, angiotensin, and angiotensin II in the pathophysiology of hypertension have been well appreciated, the role of aldosterone has recently received increased attention. Up to 20% of patients consecutively referred to a hypertension clinic for aTRH were diagnosed with primary hyperaldosteronism based on suppressed renin activity and high 24-hour urinary aldosterone excretion.[20] Aldosterone is produced in the adrenal glands in response to local and systemic angiotensin II and serum potassium concentrations. It binds MRs found in the