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## Managing Resistant Hypertension - A Comprehensive Overview

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**Abstract** Resistant hypertension (RH) is defined as above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. RH also includes patients whose BP achieves target values on  $\geq 4$  antihypertensive medications. The diagnosis of RH requires assurance of antihypertensive medication adherence and exclusion of the “white-coat effect” (office BP above goal but out-of-office BP at or below target). The importance of RH is underscored by the associated risk of adverse outcomes compared with non-RH. This article is an updated American Heart Association scientific statement on the detection, evaluation, and management of RH. Once antihypertensive medication adherence is confirmed and out-of-office BP recordings exclude a white-coat effect, evaluation includes identification of contributing lifestyle issues, detection of drugs interfering with antihypertensive medication effectiveness, screening for secondary hypertension, and assessment of target organ damage. Management of RH includes maximization of lifestyle interventions, use of long-acting thiazide-like diuretics (chlorthalidone or indapamide), addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP. If BP remains uncontrolled, referral to a hypertension specialist is advised.

**Keywords** Resistant hypertension, BP, Management

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### Introduction

Hypertension is defined as persons 18 years of age and over with a systolic pressure reading of 140 mmHg or more or a diastolic reading of 90 mmHg or more, or those taking antihypertensive medications [1,2]. Between 90-95% of cases are essential hypertension in which there is no identifiable cause [3]. The remaining cases of hypertension are secondary to a distinguishable process and would likely resolve if the underlying condition was treated.

A considerable number of patients fail to reach target blood pressure ranges despite lifestyle advice and standard medical therapy. Resistant hypertension is defined as blood pressure that remains above 140/90 mmHg despite use of three antihypertensive medications of different classes at the best tolerated doses, one of which must be a diuretic.

### Key Points

Resistant hypertension (RH) affects about 10 to 15% of treated patients diagnosed with hypertension and is associated with an increased risk of adverse cardiovascular outcomes and hypertension-mediated organ damage (HMOD).



True RH must be confirmed by adequate in-office and out-of-office blood pressure (BP) measurements (home or ambulatory). Common causes of apparent RH include white-coat hypertension, nonadherence with prescribed antihypertensive therapy, inadequate antihypertensive combination therapy and the use of interfering concomitant medications.

Obesity, obstructive sleep apnoea and renal parenchymal disease are among the most common contributing features of RH; affected patients should be screened for secondary causes of hypertension (especially primary aldosteronism) regardless of their age.

Management of RH relies on lifestyle measures (maintaining a healthy weight through regular physical activity and a healthy diet, salt restriction, limiting alcohol intake and smoking cessation), pharmacotherapy and interventional approaches, where required.

Pharmacotherapy includes a combination of a renin-angiotensin-system blocker, a long-acting calcium channel blocker and a diuretic at maximally tolerated doses, ideally as a single pill combination.

Spironolactone is currently recommended as the preferred fourth-line therapy, with alpha blockers, beta blockers, centrally acting sympatholytic agents, or vasodilators as alternatives.

If BP control cannot be achieved with the above strategies, interventional approaches such as renal denervation and novel therapeutic agents (once available) should be considered.

### **Goal is Individualized, But Less than 130/80 for Most**

Blood pressure targets should be individualized based on patient characteristics, medication side effects, patient tolerance, and preferences.

In patients with cardiovascular disease or with a risk of an atherosclerotic cardiovascular disease event of 10% or higher in the next 10 years, the 2017 ACC-AHA guidelines say that a goal of less than 130/80 mm Hg “is recommended.”<sup>1</sup>

In patients at lower risk, the ACC-AHA guidelines say the same goal “may be reasonable.”<sup>1</sup>

In patients with chronic kidney disease, the 2021 Kidney Disease Improving Global Outcomes guidelines recommended keeping the systolic blood pressure lower than 120 mm Hg contingent on proper blood pressure measurement.<sup>7</sup> This recommendation is based largely on the cardiovascular benefits of this lower goal demonstrated in the Systolic Blood Pressure Intervention Trial,<sup>8</sup> in which patients at risk of cardiovascular disease but without diabetes were randomized to goal blood pressures of either less than 120 mm Hg or less than 140 mm Hg. In a chronic kidney disease subgroup analysis, the intensive group had a slightly higher rate of change in estimated glomerular filtration rate (-0.47 vs -0.32 mL/min/1.73 m<sup>2</sup> per year; P < .03) after 6 months. The decline in kidney function may be hemodynamically mediated as a result of more intensive blood pressure control. In patients with diabetes, the American Diabetes Association recommends a target blood pressure lower than 130/80 mm Hg.

Most people are not meeting these goals. According to an estimate from the US Centers for Disease Control and Prevention, of the 116 million Americans with hypertension, only 23.9 million (20.6%) have their blood pressure controlled using the 2017 ACC-AHA definitions. The control rate was 62.8% using the old threshold of less than 140/90 mm Hg.

### **What are the symptoms of resistant hypertension?**

However, symptoms may be felt when blood pressure first rises or during a hypertensive crisis, when levels are extremely high. These symptoms may include headaches, shortness of breath, chest pain and nosebleeds.

Dizziness is usually not a symptom of high blood pressure. In fact, dizziness can sometimes be a symptom of low blood pressure. Frequent or unexplained dizziness may be a warning sign of a serious condition and should be addressed by your physician.



**What causes resistant hypertension?****Underlying Medical Causes**

In about 25 percent (1 out of 4) of people with resistant hypertension, there's an identifiable, or secondary, cause. People whose blood pressure is raised by a medical condition are said to have secondary hypertension. Secondary hypertension will be very hard to control until those conditions are addressed. The more resistant the hypertension, the more likely there is to be a secondary cause.

Some common secondary causes of hypertension include:

**Structural Disorders**

Sleep apnea, a tendency to stop breathing for seconds during sleep

Renal (kidney) artery stenosis, a narrowing of the artery that sends blood to the kidneys

Coarctation of the aorta, a narrowing of part of the aorta (the artery that sends blood from the heart to the rest of the body)

Kidney failure

**Hormonal Disorders**

Primary aldosteronism, an adrenal gland disorder that raises blood pressure.

Pheochromocytoma, a tumor in the adrenal gland that produces too much epinephrine and/or other hormones that raise blood pressure

Hyperthyroidism (overactive thyroid) and hypothyroidism (underactive thyroid) can both raise blood pressure

Cushing's disease, often due to a tumor in the pituitary gland that causes overproduction of cortisol, the "stress hormone"

Other, more rare congenital neuroendocrine diseases

**How is resistant hypertension diagnosed?**

Full history and physical exam, which includes letting your doctor know about all medications and supplements, whether they are prescription, over-the-counter, herbal or recreational. It's important to mention if you skip doses of daily medicines.

True measurement of your blood pressure using correct technique and calibrated equipment.

Home blood pressure measurement during the day and 24-hour ambulatory blood pressure monitoring to record your blood pressure throughout a regular day. It may be used if your physician suspects your blood pressure readings in the office don't tell the whole story.

**How is resistant hypertension treated?**

Addressing any conditions that may have caused the hypertension.

Making lifestyle changes

Adjusting medications to find your optimal type and dosage

**Risk factors and pathophysiology**

Predictive risk factors for difficult-to-control hypertension include:<sup>7</sup>

higher baseline BP (especially systolic)

older age

obesity

African-American heritage

male sex

presence of left ventricular hypertrophy

CKD

diabetes.

**Management**

The general principles of treatment for RH are the same as those for milder forms of hypertension, including:

the modification of contributory lifestyle factors

the cessation of interfering substances/medications, where possible



the sequential addition of guideline-recommended antihypertensive agents with different modes of action, ideally in the form of single pill combinations to improve adherence using the full armamentarium of antihypertensive drugs, where required.

### Pharmacotherapy

The antihypertensive regimen for the management of RH is usually based on comorbidities, underlying secondary causes, previous medication intolerances and financial constraints.

A common and effective combination includes an ACE inhibitor or ARB, a long-acting calcium channel blocker and a thiazide or thiazide-like diuretic. This combination should be prescribed at maximally tolerated doses at an appropriate frequency, with reference to the half-life of the medications involved.

Maximised diuretic therapy is essential for the treatment of RH, as volume retention and sodium excess are common causes of RH, even though obvious signs of hypervolaemia (such as lower limb oedema) may be absent.<sup>30-32</sup> An important consideration for the management of ongoing residual hypertension is the switching of thiazide therapy to a more potent diuretic (e.g. indapamide or chlorthalidone) if the estimated glomerular filtration rate (eGFR) is 30 mL/min/1.73 m<sup>2</sup> or greater. Chlorthalidone is frequently used in the USA, but rarely prescribed in Australia, despite being a more potent diuretic with a longer half-life than hydrochlorothiazide

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