

Review Article

Identification and management of resistant hypertension

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ABSTRACT

Resistant hypertension is defined as blood pressure being higher than the patient's target blood pressure despite the use of three or more different types of antihypertensive drugs at the optimal dose, and one of them should be a diuretic. The evaluation of patients with resistant hypertension should first confirm that they have true resistant hypertension. By eliminating or correcting false resistance factors, such as white coat hypertension, poor blood pressure measurement technique, poor drug compliance, improper dosage or combination of antihypertensive drugs, and white coat effects and clinical inertia. Resistant hypertension therapy includes improved compliance with the use of drugs, secondary hypertension detection and treatment, use of lifestyle measures and treatment of obesity, and other comorbidities. switching to a long-acting diuretic type of thiazide like chlorthalidone could improve the BP from the patients taking hydrochlorothiazide. This review paper illustrates briefly the identification of the underlying causes of resistant hypertension and therapeutic strategies, which may contribute to the proper diagnosis and an improvement of the long term management of resistant hypertension.

Keywords: Resistant hypertension, Antihypertensive agents, Hypertension

INTRODUCTION

Hypertension is the main cause of cardiovascular disease and the main cause of morbidity and mortality worldwide, and patients with drug-resistant hypertension have a particularly high risk of cardiovascular complications.^{1,2} True resistant hypertension refers to a diagnosis of essential hypertension with exclusion of all other potential causes of uncontrolled blood pressure, including secondary hypertension, pseudo-resistance due to poor adherence to antihypertensive therapy or the white-coat effect.³ The independent and continuous relationship of hypertension with incident cardiovascular events along with its prevalence at 25–30 % of the adult population, render high blood pressure (BP) the most important modifiable cardiovascular risk factor and therefore a major issue of public health.⁴ Although awareness and treatment of hypertension have improved over the years, the rates of

control in the general hypertensive population remain unacceptably low, i.e., below 20–30% in many Western countries, with few exceptions in countries that implemented targeted public health programs aiming at improving hypertension care. Of note, an important proportion of the hypertensive population cannot achieve adequate BP control even when treated with three or more antihypertensive medications. These individuals currently fall within the diagnosis of resistant hypertension, an entity recently reported to have a prevalence between 6–12% of the hypertensive population and 8–28% among treated hypertensive patients.

The 2017 ACC/AHA Hypertension Guidelines recommend reducing the blood pressure of patients with ischemic heart disease, heart failure patients with reduced left ventricular ejection fraction, and heart failure patients with a preserved left ventricular ejection fraction, in

persons with lacunar stroke, in persons with peripheral arterial disease, in persons with diabetes mellitus to less than 130/80 mmHg.⁶ This Review will discuss the epidemiology, associated risks, diagnosis and management of resistant hypertension.

EPIDEMIOLOGY AND PREVALENCE OF RH

As the definition suggests, determining the true prevalence of resistant hypertension is extremely difficult. Patients who take two or fewer antihypertensive medications may have resistant hypertension, but they are not classified as such because they do not strictly meet the definition of requiring four or more drugs to control their blood pressure. Prevalent aTRH occurs in a higher percentage of the population-and clinic-based samples when an at-risk group is identified, for example, patients with treated hypertension and chronic kidney disease (CKD).^{7,8} The increased prevalence of aTRH among treated hypertensive adults in clinical trials (34%–39%) is probably due to the selection of patients with demographic and comorbidity characteristics that place them at high risk for the fatal and nonfatal CVD outcomes of interest.⁹ Furthermore, in population-and clinic-based studies, some RH cases may go unrecognized because patients are not prescribed ≥3 drugs at maximal doses despite uncontrolled BP. In contrast, clinical trials usually include forced titration schemes that unmask RH by reducing the prevalence of suboptimal treatment.¹⁰

DIAGNOSING RH

Identifying and correcting medication non-adherence

To prevent misdiagnosis due to pseudo-resistant hypertension (figure 1), patients with apparent resistant hypertension should undergo a thorough clinical review.¹¹ Non-adherence is the main cause of pseudo resistance. A quarter of patients who are initiated on new antihypertensive medications fail to fill their initial prescription, so drug adherence should always be evaluated in these patients. Non-adherence to medication is relatively common among hypertensive patients, with estimates ranging from 7% to 48%.^{12,13} About 12% and 66% of patients with apparent resistant hypertension are believed to have total or partial non-adherence. If patients do not take their medication, pharmacological therapy will be ineffective, and poor drug adherence is a major issue in those with resistant hypertension.¹⁴

In the diagnosis and treatment of patients with RH, it is important to assess and ensure optimal medication adherence. These patients are taking three antihypertensive medications by definition, and evidence on adherence to the prescribed regimen is critical for clinical reasoning and decision-making. However, for evaluating medication adherence, increasingly reliable and sophisticated indirect and direct methods are available.

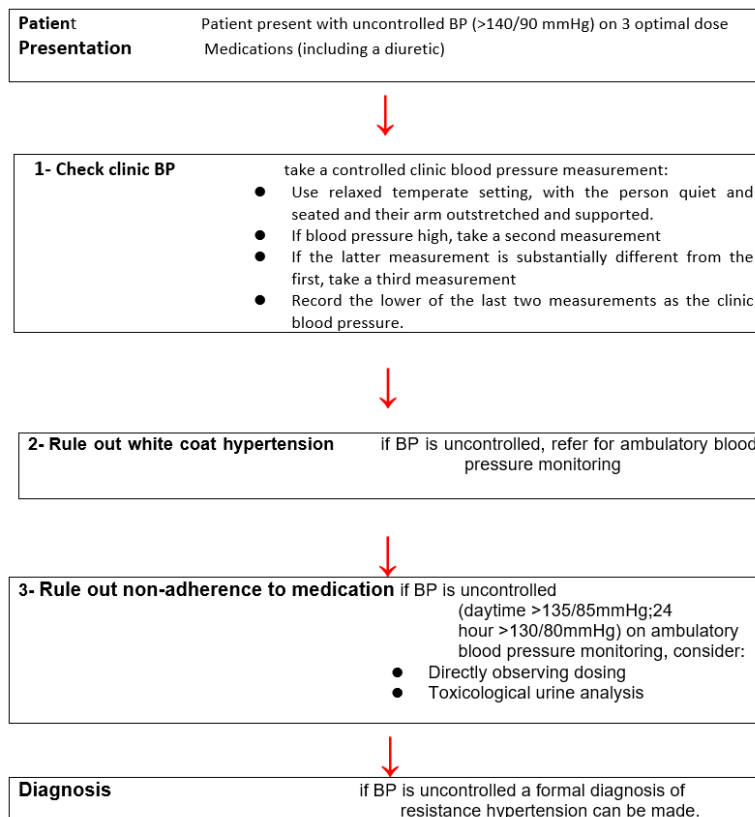


Figure 1: Stages of diagnosis of resistant hypertension. Clinic blood pressure measurement protocol taken from NICE guidelines for the management of hypertension, BP, blood pressure.¹¹

Indirect methods of evaluating therapeutic adherence, such as pill counts, patient interviews, self-reported use of medication, heart rate on β -blockers or activation of the renin-angiotensin-aldosterone system in response to treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers are all susceptible to bias or misclassification.¹⁴ The eight-item Morisky Medication Adherence Scale, which is based on patient interviews, can be used to evaluate adherence, with scores of 8, 6–7 and <6 indicating high, medium and low adherence, respectively.¹⁵ However, the Morisky questionnaire scores have been shown to be poorly linked with the amount of drugs in urine samples.¹⁶ Direct methods include witnessed drug intake, the Medication Event Monitoring System, and drug monitoring in body fluids. Witnessed drugs followed by impact monitoring on BP were effective in detecting potential non-compliance in trials with novel methods of treatment, although this technique has not been commonly used. Urine or blood measurements of drugs or mass spectroscopic metabolites depend on whether a drug is present or absent at a therapeutic level.¹⁷

Effective strategies for improving adherence to antihypertensive medications include (I) using agents that are dosed once daily over those that require multiple daily doses and using fixed-dose combination agents when available; (II) using low-cost and generic antihypertensives, particularly when cost of care is a barrier (patients with RH often have multiple chronic conditions requiring pharmacotherapy); and (III) consolidating refills, that is, minimizing the number of trips to the pharmacy to obtain all prescribed medications.^{18,19}

Poor BP measurement technique

Inaccurate measurement of BP can result in the appearance of treatment resistance. In a study comparing standard triage BP measurements by clinic staff with an automated device obtaining up to 6 BP measurements 1 minute apart while the patient was alone and seated in a quiet room, triage SBPs were a median of 17 mm Hg higher, and the difference was highest in the group of patients with initial SBPs >160 mmHg.²⁰

White-coat effect

White-coat HTN is defined as patients whose BP is elevated in the clinic but normal or controlled when monitored outside of the clinic.²¹ White-coat HTN is a complicating factor that falsely elevates BP and complicates the determination of HTN. Other signs include repetitive symptoms of overtreatment such as orthostatic hypotension and persistent fatigue as well as absence of target organ damage including left ventricular hypertrophy, retinopathy, and chronic kidney disease.²² According to the Jackson Heart Study (JHS), the prevalence of white-coat hypertension is 25.4% among non-antihypertensive participants and 34.6% among

antihypertensive participants. Moreover, white-coat HTN is more common with increasing age, in women, and in non-smokers.²³

The white-coat effect can be easily identified by 24-hour ABPM. However, ABPM is not readily available in all countries and, because of limitations in insurance reimbursement, is not even commonly used in the United States.²⁴ Oscillometric digital devices that can automatically record 3 to 6 BP measurements without a clinician in the examination room are now available for clinical use, a process called automated office BP. BP measurement by automated office BP attenuates the white-coat effect. Self-measured home BPs (with appropriate instruction in the BP measurement technique) correlate with average daytime BPs measured by 24-hour ABPM and can be used to identify the white-coat effect.²⁴ However, it is important to consider that individuals may alter their BP logs or under report high or low BP values.

Concomitant conditions

Obesity is associated with resistant hypertension. Obese patients have increased sympathetic activity, higher cardiac output, and a rise in peripheral vascular resistance due to reduced endothelium dependent vasodilation. Plasma aldosterone and endothelin are also increased, while excessive surrounding adipose tissue results in increased intrarenal pressures and changes in renal architecture.²⁵ As the body mass index increases, progressively higher doses of antihypertensive drugs are required to control blood pressure.²⁶ Weight loss has been found to reduce both systolic and diastolic blood pressure.^{27,28} Another common concomitant condition in hypertensive patients is diabetes. Insulin resistance increases sympathetic nervous activity, vascular smooth muscle cell proliferation, and sodium retention leading to elevated blood pressure resistant to treatment.²⁷ The common comorbidities of obesity, hypertension, and diabetes induce renal dysfunction, further hindering blood pressure treatment.

Drug-related RH

Several common medications can cause elevated blood pressure and hinder treatment (Table 1). However, the effects of these agents are found to be highly individualized, with the majority of individuals manifesting little or no effect and others demonstrating severe elevations in BP levels.

Table 1: Drugs and other substances with potential to induce or exacerbate elevated BP and hypertension.

Oral contraceptives	Alcohol
Sympathomimetic	Cocaine
Cyclosporine, tacrolimus	Amphetamines
Erythropoietin	Antidepressants
VEGF inhibitors	Glucocorticoids, mineralocorticoids

BP indicates blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; and VEGF, vascular endothelial growth factor.

Evaluation of RH

The evaluation of RH patients should focus on confirming true treatment resistance, identifying causes of resistance (including secondary causes of hypertension), and documenting complications of the hypertensive disease process (see the evaluation algorithm in Figure 2). To confirm RH, it is necessary to evaluate treatment adherence and use of ABPM (or home BP monitoring if ABPM is unavailable). True RH is usually caused by a combination of factors, such as an excessive salt intake, obesity, CKD, and OSA.²⁹

MANAGEMENT OF RH

Nonpharmacologic approaches to management

The potential causes of resistant hypertension must be examined before deciding if a treatment for resistant hypertension is appropriate. To rule out pseudo resistance, we must first assess drug adherence, BP procedure, and the risk of white-coat hypertension. In addition, evidence of contribution to the manifestation of resistance to high blood pressure such as heavy alcohol use, obesity and high salt intake is conflicting.³⁰ However, most clinical guidelines suggest encouraging patients Weight loss, a diet rich in fruits, vegetables, and low-fat dairy products with less saturated and total fat, smoking cessation, regular aerobic physical activity, avoidance of excessive alcohol intake, avoidance of excessive caffeine, and avoidance of drugs which can raise blood pressure, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, are all recommended.^{31,32}

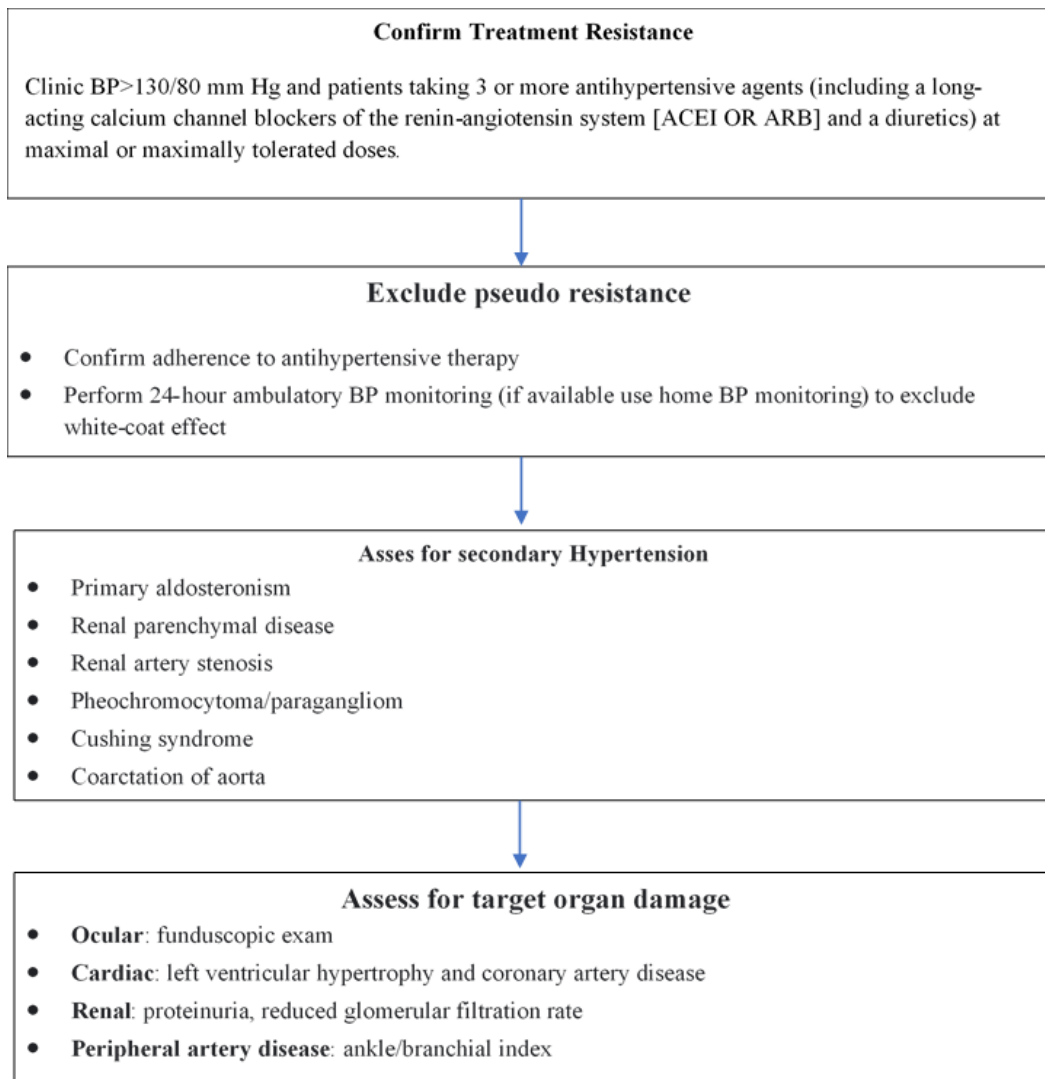


Figure 2: Algorithm depicting the evaluation of resistant hypertension. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and BP, blood pressure.

Table 2: Pharmacological treatment of resistant hypertension.

Combine first- line drugs with different modes of action such as thiazides or thiazidlike diuretics, selective β 1-blockers, long- acting dihydropyridine calcium- channel blockers, angiotensin- converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) according to the AB/CD rule. ³⁷
Maximize diuretic treatment.
Add a mineralocorticoid receptor antagonist (MRA) such as spironolactone.
Loop diuretics should be used only in patients with an estimated glomerular filtration rate of <30 ml/min/1.73 m ² ; MRAs should not be used in these patients because of the risk of severe hyperkalaemia.
Second- line agents include centrally acting antihypertensive drugs, α 1-blockers, non- dihydropyridine calcium- channel blockers, the vasodilator hydralazine and the direct renin inhibitor aliskiren.
Dual inhibition of the renin angiotensin system by combining ACE inhibitors, ARBs and/or aliskiren should be avoided.
Aliskiren should be used with restraint in patients with diabetes or chronic kidney disease owing to the high likelihood of adverse effects.

Pharmacological management

When high blood pressure is not controlled by three mechanistically complementary antihypertensive agents, such as with a long-acting CCB, an ACE inhibitor or ARBs, and a thiazide or thiazide-like diuretic, resistant hypertension is controlled with the addition of fourth-line therapy.

These three antihypertensive pharmacological classes must be given at maximally tolerated doses. Switching from hydrochlorothiazide to a thiazide-type diuretic with a longer half-life, such as chlorthalidone, can improve blood pressure control.^{31,33} The beneficial effects of thiazide diuretics are reduced when the glomerular filtration rate is reduced to less than 40 cc/min.^{31,34} Until the recent publication of the Prevention and Treatment of Hypertension With Algorithm Based Therapy-2 (PATHWAY-2).³⁵ The fourth-line agent was empirically selected, suggesting a lack of randomised controlled trials comparing various options. Although the causes of resistant hypertension are poorly understood, one hypothesis is that it is caused by inappropriate sodium retention in the kidneys.³⁶ For this reason, the National Institute for health and care Excellence (NICE) guidelines in the UK recommend spironolactone therapy (Table 2) as a fourth-line agent in patients with potassium of <4.5 mmol/L who are likely to respond to a mineralocorticoid receptor blocker.¹¹ For patients with potassium of >4.5 mmol/L it is recommended that the existing diuretic (thiazide or thiazide-like) is doubled. Switching to a loop diuretic such as furosemide or bumetanide may be helpful if control is not achieved.¹¹

CONCLUSION

Once a diagnosis of resistant hypertension is confirmed, optimization of drug treatment remains the cornerstone of its management. Therapy of resistant hypertension includes improving compliance with use of medication, detection, and treatment of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities. Switching the patient from hydrochlorothiazide to a longer acting thiazide type

diuretic such as chlorthalidone may improve blood pressure control. If a fourth antihypertensive drug is needed to control blood pressure in persons treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen.

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REFERENCES

1. GBD. Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390:1345-422.
2. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension*. 2011;57:1076-80.
3. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension- its identification and epidemiology. *Nat. Rev. Nephrol*. 2013; 9:51-8.
4. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M et al. 2013 ESH/ ESC practice guidelines for the management of arterial hypertension. Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology. *Blood Press*. 2014;23(1):3-16.
5. WC Cushman, CE Ford, JA Cutler. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT).” *Journal of Clinical Hypertension*. 2002;4(6):393-404.
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Coillins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ ACPM/AGS/APhA/ASH ASPC/NMA/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on

- Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;71:e127-248.
7. Tanner RM, Calhoun DA, Bell EK, Bowling CB, Gutierrez OM, Irvin MR et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. *Clin J Am Soc Nephrol.* 2013;8:1583-90.
 8. Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S et al. Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort Study. *Hypertension.* 2016;67:387-96.
 9. Muntner P, Davis BR, Cushman WC, Bangalore S, Calhoun DA, Pressel SL et al. For the ALLHAT Collaborative Research Group. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension.* 2014;64:1012-21.
 10. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. *Circulation.* 2012;125:1594-6.
 11. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence: Guidance. Hypertension: the clinical management of primary hypertension in adults: update of clinical Guidelines 18 and 34. London: Royal College of Physicians (UK) National Clinical Guideline Centre. 2011.
 12. Gwadry-Sridhar FH, Manias E, Lal L, Salas M, Hughes DA, Ratzki- Leewing A et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. *Value Health.* 2013;16:863-71.
 13. Daugherty SL, Powers JD, Magid DJ. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation.* 2012;125:1635-42.
 14. Burnier M, Wuerzner G, Struijker- Boudier H, Urquhart JJ. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension.* 2013;62:218-25.
 15. Morisky DE, Ang A, Krousel- Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens.* 2008;10:348-54.
 16. Jacobs L. Results of a randomized controlled pilot trial of intravascular renal denervation for management of treatment- resistant hypertension. *Blood Press.* 2017;26:321-31.
 17. Correa NB, de Faria AP, Ritter AM, Sabbatini AR, Almeida A, Brunelli V et al. A practical approach for measurement of antihypertensive medication adherence in patients with resistant hypertension. *J Am Soc Hypertens.* 2016;10:510-6.
 18. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med.* 2007;120:713-9.
 19. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296-310.
 20. Bhatt H, Siddiqui M, Judd E, Oparil S, Calhoun D. Prevalence of pseudoresistant hypertension due to inaccurate blood pressure measurement. *J Am Soc Hypertens.* 2016;10:493-9.
 21. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension.* 2018;72(5):e53-e90.
 22. CL Trewet, ME Ernst. Resistant hypertension: identifying causes and optimizing treatment regimens. *Southern Medical Journal.* 2008;101(2):166-73.
 23. Benjamin EJ, Muntner P, Alonso A. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation.* 2019;139(10):e56-28.
 24. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension.* 2008;52:10-29.
 25. Hall JE. The kidney, hypertension, and obesity. *Hypertension.* 2008;41(3):625-33.
 26. Kroon B. European Society of Hypertension 20th Meeting. Abstract 01, Oral Session 9D.
 27. Calhoun DA, Jones D, Textor S. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation.* 2008;117(25):e510-26.
 28. Calhoun DA. Resistant or difficult-to-treat hypertension. *Journal of Clinical Hypertension.* 2008;8(3):181-6.
 29. White WB, Turner JR, Sica DA, Bisognano JD, Calhoun DA, Townsend RR et al. Detection, evaluation and treatment of severe and resistant hypertension: proceedings from an American Society of Hypertension Interactive Forum held in Bethesda, MA, U.S.S., October 10th 2013. *J Am Soc Hypertens.* 2014;8:743-57.
 30. Shimbo D, Levitan EB, Booth JN. The contributions of unhealthy lifestyle factors to apparent resistant hypertension: findings from the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Hypertension.* 2013;31:370-6.
 31. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Coillins KJ, Himmelfarb DC, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH ASPC/NMA/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;71:e127-248.
 32. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA.* 2003;289:2560-72.
 33. Ernst ME, Carter BL, Geordt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, et al. Comparative

- antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension.* 2006;47:352-8.
34. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol.* 2008;52:1749-57.
 35. Williams B, MacDonald TM, Morant S. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *The Lancet.* 2015;386:2059-68.
 36. Khawaja Z, Wilcox CS. Role of the Kidneys in resistant hypertension. *Int J Hypertens.* 2011;2011:1-8.
 37. British Cardiac Society. JBS 2: joint British societies' guidelines on prevention of cardiovascular diseases in clinical practice. *Heart.* 2005;91:1-52.

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