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RESISTANT HYPERTENSION (L DRAGER, SECTION EDITOR)

Resistant Hypertension Management: Comparison of the 2017 American and 2018 European High Blood Pressure Guidelines

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Abstract

Purpose of Review To compare European and American guidelines for the diagnosis, evaluation, and management of resistant hypertension.

Recent Findings Resistant hypertension is defined as high blood pressure that remains above goal with the use of 3 or more antihypertensive agents, commonly a renin-angiotensin blocker (either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker), a long-acting calcium channel blocker, and thiazide or thiazide-like diuretic. Resistant hypertension is common, with a recent analysis indicating that it affects approximately 17–19% of adult Americans with hypertension. Pseudocauses of apparent resistant hypertension, including inaccurate blood pressure measurement, white coat effect, undertreatment, and poor medication adherence, must be excluded in order to confirm true resistant hypertension. Evaluation of resistant hypertension requires identifying and treating secondary causes of hypertension, including obstructive sleep apnea, primary aldosteronism, and renal artery stenosis. Treatment of resistant hypertension includes a combined use of lifestyle modification and prescription of effective multiple-drug combinations. Preferential use of a long-acting thiazide-like diuretic, either chlorthalidone or indapamide, and a mineralocorticoid receptor blocker, most commonly spironolactone, is recommended if needed to achieve blood pressure control.

Summary Aside for small exceptions, European and American guidelines agree in terms of recommendations for diagnosing, evaluating, and treating resistant hypertension.

Keywords Resistant hypertension · Pseudoresistance · White coat effect · Adherence · Aldosteronism · Spironolactone

Introduction

Hypertension is a complex disorder emanating from multiple genetic, environmental, and social determinants [1]. The leading risk factor for cardiovascular disease, stroke, disability and death, hypertension worldwide accounts for approximately 10 million deaths and over 200 million disability-adjusted life years annually [2]. Using the 2003 blood pressure classification system recommended in the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [3, 4], the current prevalence of hypertension (blood pressure ≥ 140/90 mmHg) in the USA among all adults (> 18 years of age) is 29% and among non-Hispanic black adults is as high as 40.6% [5]. Even more alarming, according to the 2017 American College of Cardiology/American Heart Association (2017 ACC/AHA) blood pressure reclassification criteria [6••], the prevalence of hypertension (blood pressure ≥ 130/80 mmHg) has been estimated as approximately 45.6% among American adults [3]. Although effective blood pressure management reduces cardiovascular risk, over half of US hypertensive adults taking antihypertensive drugs have uncontrolled hypertension [7]. Similar high prevalence of hypertension and low rates of blood pressure control have been reported for several European countries [8]. Among hypertensive patients with uncontrolled blood pressure, a subset has blood pressures resistant to antihypertensive drug therapy, a

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state termed "resistant hypertension." In this article, the current definition, estimated prevalence, and management of resistant hypertension will be compared and contrasted according to the recommendations of the 2017 ACC/AHA and the 2018 European hypertension guidelines, as well as the 2018 AHA scientific statement resistant hypertension: detection, evaluation, and management [6••, 9••, 10••]. This article does not examine the interventional (device-based) approaches to treatment in depth, given the fact that for both guidelines more evidence will be needed to make definitive recommendations [11].

Definitions of Resistant Hypertension

A uniform definition of resistant hypertension, applicable in both the USA and Europe, is the blood pressure of a hypertensive patient that remains elevated above goal despite the concomitant use of three antihypertensive drugs of different classes usually including a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system (angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)), and a diuretic [6••, 9••, 10••]. All antihypertensive medications should be administered at optimal or maximally tolerated doses and at the appropriate dosing frequency. According to some authorities, resistant hypertension also includes patients whose blood pressure achieves target values but requires 4 or more antihypertensive agents to achieve control [10••]. Although the definition of resistant hypertension is arbitrary with respect to the number of medications required, it is defined in this fashion to select patients at higher risk for morbid cardiovascular disease events and death. Importantly, patients meeting this definition of resistant hypertension are more likely to have drug-related adverse events, have a secondary cause of hypertension, and receive benefit from specifically designated therapeutic approaches (covered in this article) to control their blood pressure.

In spite of the above-mentioned common principles governing the definition of resistant hypertension, the numerical blood pressure thresholds separating resistant from nonresistant hypertension differ according to the 2017 ACC/AHA and the 2018 European guidelines, because the recommended blood pressure goals of antihypertensive therapy in each guideline are somewhat different [6••, 9••]. Both guidelines recommend lower blood pressure targets during combined lifestyle and drug therapy than had previously been recommended by JNC-7 [4, 12]. However, once antihypertensive drug therapy is initiated, the blood pressure targets recommended in the current guidelines are somewhat different. The American guideline recommends a blood pressure target of < 130/80 mmHg for virtually all patients. In older adults, the target is systolic blood pressure < 130 mmHg [6••]. The basis for this goal was an extensive Evidence Review Committee (ERC) systematic review and meta-analysis, together with recent meta-analyses not included in the ERC report and the results of the Systolic Blood Pressure Intervention Trial (SPRINT) [13–15]. In contrast, the European guideline recommends that the first objective is to reduce the blood pressure to < 140/90 mmHg. However, once that target is achieved in adults < age 65, a target of ≤ 130/80 mmHg, if tolerated, is recommended. For adults ≥ age 65, the stretch target, if tolerated, is 140/90 to 130/80 mmHg, but not lower [9••, 12]. In contrast to the American guideline, the European guideline prioritized safety boundaries which should not be crossed when lowering blood pressure in treated patients [16]. A further difference in the blood pressure target between the guidelines applies to patients with chronic kidney disease. Whereas the European guideline uniformly recommends a blood pressure target < 140/90 mmHg, the American guideline recommends a target of < 130/80 mmHg largely on the basis of the results of SPRINT [6••, 9••]. Since chronic kidney disease is common in patients with treatment resistant hypertension, these differences in blood pressure targets apply to a larger number of patients with resistant than with nonresistant hypertension.

There are additional commonalities in the definition of resistant hypertension between the guidelines. Both the European and American guidelines define resistant hypertension as excluding the "white coat effect," a condition in which office blood pressures are elevated, but out-of-office blood pressures are substantially lower and/or below the therapeutic target. Both guidelines also allow the term resistant hypertension to be employed only if medication nonadherence has been excluded. A minor difference is that the European guideline requires exclusion of secondary hypertension, whereas the American guideline includes workup for secondary hypertension as an important part of evaluation of patients with the diagnosis of resistant hypertension.

In summary, the definition of resistant hypertension is slightly more liberal in the 2018 European than in the 2017 American guideline, although the major principles of are similar in the two guidelines.

Prevalence of Resistant Hypertension

The 2018 AHA scientific statement on resistant hypertension updated the 2008 document [10••, 17]. The major difference in the definitions of resistant hypertension between these scientific statements is the blood pressure goal, < 140/90 mmHg for the 2008 statement and < 130/80 mmHg for the 2018 document [10••, 17]. To estimate the change in prevalence of apparent treatment resistant hypertension (aTRH) resulting from the change in blood pressure goal, Carey et al. performed an analysis of 2009–2014 National Health and Nutrition Examination Survey (NHANES) data comparing the two

goals [18]. The prevalence of aTRH was 17.7% and 19.7% according to the 2008 and 2018 scientific statement definitions, respectively. Thus, the prevalence of aTRH was only modestly higher (2%) using the definition in the 2018 versus 2008 resistant hypertension scientific statement. It is important to emphasize, however, that out-of-office blood pressure measurements and attempts to assure medication compliance were not performed in the NHANES study. Since the definition of resistant hypertension both in Europe and the USA excludes white coat hypertension and medication nonadherence, further studies are urgently needed to determine the prevalence of true resistant hypertension using the blood pressure goals recommended by the European and American guidelines [19]. These studies should examine data obtained under real-life conditions (such as the NHANES provide). Because patients in randomized clinical trials are under pressure and highly motivated, trials can overestimate good adherence to treatment.

Management of Resistant Hypertension

European and American recommendations for the evaluation and treatment of resistant hypertension are largely the same. In both cases, the evaluation emphasizes the importance of confirming true resistant hypertension by excluding pseudocauses of treatment resistance and screening for and identifying, if present, secondary causes of resistant hypertension [6••, 9••, 10••]. Patient-appropriate lifestyle modifications are likewise recommended by both the European and American documents when managing any patient with confirmed resistant hypertension. Lastly, the pharmacologic treatment approach with respect to building multiple-drug combinations, both in terms of which classes of agents to use and in what order, is similar in Europe and the USA. Differences between the respective treatment algorithms, which are minor, are highlighted below.

Evaluation of Resistant Hypertension

The evaluation of resistant hypertension is largely predicated on confirming true treatment resistance and screening for and identifying secondary causes of hypertension. Confirmation of true treatment resistance requires exclusion of pseudocauses of treatment resistance, including specifically inaccurate blood pressure measurement, a significant white coat effect, undertreatment, and poor medication adherence. A large body of literature clearly demonstrates that the routine office blood pressure technique is often inadequate, commonly resulting in inaccurate BP measurement, including patients with resistant hypertension [20]. The most common mistakes in the technique, including not having the patient sit comfortably for several minutes in a quiet area, use of too small of a blood pressure cuff, and placing the cuff over clothing, most often result in falsely high blood pressure readings and the consequential overdiagnosis of uncontrolled hypertension [20].

Both the European and American recommendations for confirming true resistant hypertension highlight these well-recognized shortcomings in measuring office blood pressure and strongly advise systematic training of office staff in the use of the proper blood pressure technique [6••, 9••, 10••]. It is worth noting that the 2019 AHA scientific statement on blood pressure measurement in humans recommends the consideration of automated office blood pressure measurement (AOBP) as perhaps the most accurate method of office blood pressure measurement [21]. This method of measurement can be either attended or unattended by the clinician and tends to exclude the white coat effect [22]. At some variance with the American position, the European position is that compared with classical BP measurement, epidemiological data on unattended AOBP remain limited, and evidence is lacking to prove that unattended AOBP is a more sensitive predictor of cardiovascular disease events. Nevertheless, measurement of out-of-office blood pressure, by ambulatory blood pressure monitoring or home blood pressure measurement, is recommended by both European and American organizations to identify significant white coat effects that can also cause the false appearance of poorly controlled hypertension. Indeed, the European organizations suggest that measuring *both* home and ambulatory blood pressure monitoring is desirable to detect situations in which one is high and the other normal or vice-versa, as this information may have an important relationship with the prediction of future cardiovascular disease events [23].

Secondary causes of hypertension are common in patients with resistant hypertension, including especially primary aldosteronism, obstructive sleep apnea (OSA), renal parenchymal disease, and renal artery stenosis [10••]. Rare secondary causes of hypertension include pheochromocytoma, Cushing's syndrome, and coarctation of the aorta. European and American recommendations similarly emphasize the importance of carefully screening for interfering substances that may be contributing to the elevation in BP, including commonly prescribed medications such as nonsteroidal antiinflammatory agents, sympathomimetic amines (decongestants, methylphenidate, amphetamine-based stimulants), oral contraceptives, glucocorticoids, and antidepressants. Less commonly used agents include cyclosporine, erythropoietin, and certain cancer therapies such as tyrosine kinase inhibitors. In addition, screening for use of certain recreational drugs that can have potent blood pressure raising effects, such as cocaine, amphetamines, and anabolic steroids, excessive licorice ingestion, and certain herbal remedies (ephedra and ma huang), is included in both sets of recommendations.

Lifestyle Recommendations

As with the treatment of hypertension in general, both the European and American recommendations for managing resistant hypertension advise broad lifestyle changes, when appropriate, including weight loss, regular exercise, reduction of dietary sodium intake, and moderation of alcohol ingestion [6••, 9••, 10••]. In a small difference between European and American recommendations, the latter specifically encourage at least 6 h of sleep per night to improve blood pressure control [10••]. This recommendation is based on a growing body of literature relating short sleep duration to both higher rates of incident and prevalent hypertension in general [24–27], as well as in a small number of studies that have specifically evaluated patients with resistant hypertension [28, 29].

As detailed in the AHA statement on resistant hypertension, while the efficacy and safety of lifestyle modifications are generally well established for treatment of hypertension in general, demonstration of specific antihypertensive benefit and tolerability in cohorts of patients with resistant hypertension is scant or absent [10••]. Benefit of meaningful dietary sodium restriction has been demonstrated in 2 small studies in patients with resistant hypertension and/or CKD [30, 31], while the antihypertensive benefit and safety of monitored exercise programs in patients with resistant hypertension have likewise been demonstrated in 2 small studies [32, 33]. While the challenges of having patients initiate and especially maintain meaningful lifestyle modifications are well recognized, the European and American recommendations agree in broadly encouraging such modifications, specifically not only to enhance blood pressure control but also to improve overall cardiovascular well-being in this high-risk hypertensive subgroup. Due to limitations of time and expertise in busy office practice, lifestyle counseling might optimally be performed by specifically educated and trained paramedical personnel.

Treatment of Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is especially common in patients with resistant hypertension with prevalence rates as high as 70–90%, particularly in men [34, 35]. Interestingly, symptoms of OSA in patients with resistant hypertension may be less pronounced compared with other cohorts such that the presence of OSA may be less suspected [34]. Studies have linked the high prevalence of OSA in patients with resistant hypertension to aldosterone excess and the associated increase in fluid retention, which is likewise common in this hypertensive phenotype [35, 36].

As with hypertensive OSA patients in general, the overall effects of treating OSA with continuous positive airway pressure (CPAP) in patients with resistant hypertension are modest. In perhaps the most rigorous assessment of the antihypertensive treatment effect of CPAP in patients with resistant hypertension, study participants with moderate-severe OSA were randomized to therapeutic CPAP or no CPAP [37]. After 8 weeks, CPAP reduced mean 24-h systolic and diastolic blood pressure by 3.1 and 3.2 mmHg, respectively, and nighttime systolic and diastolic blood pressure by 3.7 and 2.1 mmHg, respectively. There was however a strong relationship between adherence with CPAP and treatment effect. Among study participants using CPAP at least 4 h a night, the mean 24-h systolic and diastolic blood pressures were reduced by 4.4 and 4.1 mmHg, respectively, 7.1 and 4.1 mmHg at night. In participants using CPAP all night (i.e., 8 or more hours), the treatment benefit of CPAP on 24-h systolic blood pressure exceeded 10 mmHg. Accordingly, it is important to recognize that while the average benefit of CPAP is limited in terms of blood pressure reduction, this overall effect is diminished by a large proportion of patients who use CPAP sparingly or not at all. In several studies addressing the effects of CPAP on blood pressure in patients with OSA, the major issue has been the exclusion of those with symptomatic OSA. Indeed, CPAP compliance in asymptomatic patients with OSA has proven to be a challenge. In any event, if fully adherent, the antihypertensive benefit of CPAP on an individual patient basis can be substantial.

While highlighting OSA a common secondary cause of hypertension and encouraging screening for it as part of evaluating all patients with hypertension, the European recommendations do not specifically discuss the potential antihypertensive benefit of CPAP [9••]. In contrast, the AHA document on resistant hypertension recommends both careful screening and definitive testing for OSA if indicated and specific use of CPAP when OSA is diagnosed to assist with blood pressure control [10••].

Pharmacologic Treatment of Resistant Hypertension

The American algorithm for the management of resistant hypertension is shown in Fig. 1, and the European recommendations for drug treatment of resistant hypertension are depicted in Fig. 2. Both the European and American recommendations concur on the initial, standardized, 3-drug regimen for treating resistant hypertension, that is, the combination of a RAS blocker, either an ACE inhibitor or an ARB, a CCB, and a diuretic, at the highest tolerated doses [6••, 9••, 10••]. While neither set of recommendations specifies the initial choice of the diuretic, both documents specify that if the blood pressure remains uncontrolled on the standardized triple-drug regimen that includes a thiazide diuretic, a long-acting thiazide-like diuretic, i.e., chlorthalidone or indapamide, should be substituted for the thiazide diuretic for additional antihypertensive benefit.

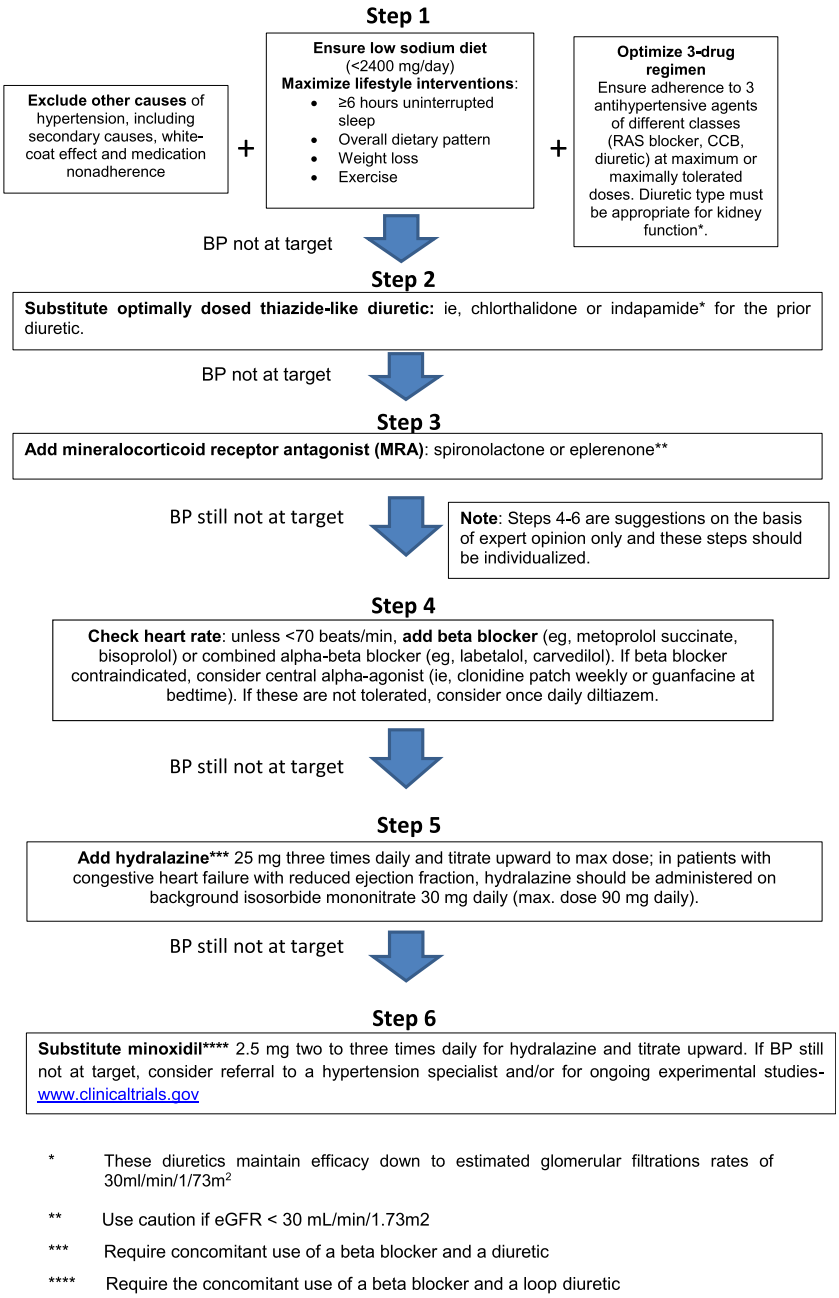
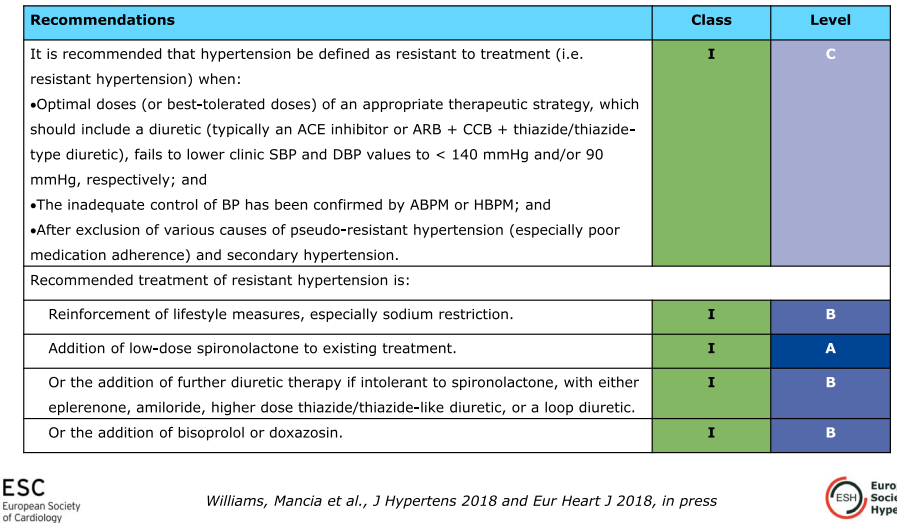


Fig. 1 American algorithm depicting the management of resistant hypertension. BP, blood pressure; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system. From *Hypertension*. 2018; 72:e53–e90 with permission

As discussed in both the European and American recommendations, the specific recommendation of the initial 3 antihypertensive agents being comprised of an ACE inhibitor or ARB, CCB, and a diuretic is not based on demonstration of definitive superiority compared with other 3-drug combinations, as no such comparisons exist. The recommendation is empiric, but based on established characteristics and benefits of the recommended classes of agents, including (1) the safety, tolerability, and antihypertensive efficacy of each of the individual classes of agents is well demonstrated; (2) the three classes of agents provide complementary mechanisms of action, thereby maximizing antihypertensive efficacy when used concomitantly; (3) each class of agent is availably generically reducing out-of-pocket costs to the patient; (4) each class of agent is available in long-acting compounds, allowing for effective once-a-day dosing; (5) the classes of agents are widely available in single 2- and even 3-drug combination pills, allowing for reduced pill burden and simplified dosing regimens, benefits known to improve adherence; (6) outcome benefit in a large number of randomized trials has been demonstrated for each class of agent individually, and in some cases, in combination with one of the other classes of agents when compared with placebo and/or active comparators; and (7) the triple combination of a RAS blocker, CCB, and



Recommendations	Class	Level
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when: •Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or ARB + CCB + thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to < 140 mmHg and/or 90 mmHg, respectively; and •The inadequate control of BP has been confirmed by ABPM or HBPM; and •After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	I	C
Recommended treatment of resistant hypertension is:		
Reinforcement of lifestyle measures, especially sodium restriction.	I	B
Addition of low-dose spironolactone to existing treatment.	I	A
Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher dose thiazide/thiazide-like diuretic, or a loop diuretic.	I	B
Or the addition of bisoprolol or doxazosin.	I	B

Fig. 2 European recommendations for treatment of resistant hypertension. From *European Heart Journal.* 2018; 39:3021–3104 with permission

thiazide diuretic has become the standardized baseline therapy for trials evaluating treatment of resistant hypertension, including trials of spironolactone and more recently, device-based therapies. These studies have been important in establishing the tolerability and ease of use of this 3-drug regimen, particularly when provided as a single triple-drug combination pill, and in establishing the 3-drug regimen as an effective platform upon which to add spironolactone as the 4th medication.

The European and American guidelines are likewise in agreement in use of a mineralocorticoid receptor antagonist (MRA), specifically, spironolactone, as the 4th agent for treating resistant hypertension [6••, 9••, 10••]. This shared recommendation is based on large bodies of literature identifying hyperaldosteronism as a common underlying cause of resistant hypertension and, separately, the preferential benefit of spironolactone in this group of patients. The antihypertensive benefit of spironolactone was rigorously confirmed by the PATHWAY-2 study (Prevention and Treatment of Hypertension with Algorithm Based Therapy), which was a randomized, 4-way crossover comparison of placebo, spironolactone, bisoprolol (a beta blocker), and doxazosin (an alpha blocker) in patients with confirmed resistant hypertension whose blood pressure was uncontrolled on a standardized 3-drug regimen of an ACE inhibitor or ARB, amlodipine, and indapamide [38]. In terms of BP reduction, after 12 weeks of treatment with each agent, spironolactone was significantly superior to placebo as well as the beta blocker and the alpha-blocker, clearly confirming its role as the most appropriate fourth medication for treating resistant hypertension after use of an ACE inhibitor or ARB, CCB, and a thiazide-like diuretic.

PATHWAY-2 further provided two important clinical findings for treating resistant hypertension [39]. Firstly, the benefit of spironolactone was effective across all levels of plasma renin activity, but was especially effective in patients with low renin levels, in whom the average reduction in home systolic BP exceeded 20 mmHg. This constitutes an extraordinary degree of blood pressure reduction with a single agent, especially when being added to treatment with 3 prior medications. It is also extraordinary in that the blood pressure reduction is predicted by a routine biochemical assessment. Secondly, PATHWAY-2 demonstrated amiloride to be comparable with spironolactone as the 4th agent for treating resistant hypertension. The assessment was done as an open-label extension of the main protocol and in a smaller number of subjects, so the finding is not as compelling as with spironolactone, but certainly provides support for use of amiloride if spironolactone is not tolerated. Both the European and American recommendations advise restricting use of spironolactone to patients with an estimated glomerular filtration rate of ≥ 45 mL/min/1.73 m^2 or a serum potassium level < 4.5 mEq/L. While the European recommendations include amiloride or eplerenone as alternatives if spironolactone is not tolerated, the American recommendations mention only eplerenone as a substitute for spironolactone (the PATHWAY-2 substudy was published after finalization of the AHA statement) [39].

Regarding the fourth drug in resistant hypertension, the ReHOT trial compared clonidine with spironolactone in 26 centers in Brazil [40]. This trial performed pill counting to confirm adherence in both the first phase (to select true resistant hypertension) and the second phase (comparing the BP effects of clonidine versus spironolactone). Both drugs achieved the primary blood pressure control endpoint in patients with true resistant hypertension, but spironolactone provided a greater reduction in secondary endpoints, such as 24-h and daytime ambulatory blood pressure, than clonidine. Overall, the drugs were both effective and well-tolerated. Considering the ease of administration and risk of blood pressure surge with clonidine withdrawal, spironolactone was recommended in preference to clonidine as the fourth antihypertensive drug.

After the first 4 medications for treating resistant hypertension, recommendations lack evidence-based outcomes and are largely based on expert opinion. The American scientific statement recommends use of a long-acting beta blocker (metoprolol succinate, bisoprolol) or a combined alpha-beta blocker, such as labetalol or carvedilol as the 5th agent [10••]. Of course, beta blockers should be used primarily if there is a specific indication such as coronary heart disease, especially postmyocardial infarction, congestive heart failure, or tachyarrhythmias. If the beta blocker is not tolerated or if used as the 6th agent, the American treatment algorithm then suggests use of a long-acting centrally acting agent such as the clonidine patch or guanfacine [10••]. Beyond that, the American algorithm advises that hydralazine should be considered for use as the 7th agent and subsequently minoxidil, as the last resort. The European algorithm only goes as far as to say "consider use of a beta blocker or alpha blocker if the blood pressure remains uncontrolled after use of 4 medications," but does indicate that direct vasodilators, such as hydralazine and minoxidil, are needed infrequently [9••]. Both European and American recommendations advise restricting use of long-acting loop diuretics to patients whose eGFR is < 30 mL/min/1.73 m^2.

Device-Based Therapy of Resistant Hypertension

Neither the American nor the European guidelines recommend device-based therapy (e.g., renal denervation or carotid baroreceptor activation therapy) for resistant hypertension [6••, 9••, 10••]. The American scientific statement concludes that device-based therapy was experimental at the time of writing [9••, 10••].

Conclusion

Resistant hypertension is a common clinical challenge. As reflected by both European and American guidelines, successful management of resistant hypertension requires confirmation of true treatment resistance, screening for and treating any contributing secondary causes of hypertension, and use of effective multiple-drug combinations. European and American guidelines recommend a standardized 3-drug regimen comprised of an ACE inhibitor or ARB, a long-acting CCB, and a diuretic. If the blood pressure remains uncontrolled on a thiazide diuretic, a long-acting thiazide, i.e., chlorthalidone or indapamide, should be used instead. Both sets of guidelines recommend preferential use spironolactone as the 4th antihypertensive when combining agents, and if not tolerated, either amiloride or eplerenone. Limitations of knowledge/evidence render clear-cut recommendations in resistant hypertension difficult. These include lack of clear-cut normal values for ambulatory and home blood pressure monitoring, lack of optimal methods for detection and reversal of medication nonadherence, lack of optimal blood pressure targets for resistant hypertension and their relationship to target organ damage, and the virtual absence of studies addressing the relationship of blood pressure reduction to prevention of cardiovascular disease events in resistant hypertension.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent All reported studies/experiments with human subjects or animals performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and control of hypertension: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(11):1278–93.
2. Collaborators GBDRF. 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(10100):1345–422.
3. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol. 2018;71(2):109–18.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206–52.
5. Fryar DC, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015–2016. NCHS data brief, no 289 Hyattsville, MD: National Center for Heatlh Statistics. 2017.
6.•• Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins 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. Hypertension. 2018;71(6):e13–e115 **The 2017 ACC/AHA clinical practice guideline for high blood pressure in adults provides and redefines resistant hypertension and provides a diagnostic and therapeutic algorighm for this disorder.**

7. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–e528.
8. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
9.•• Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104 **The 2018 ESC/ESH clinical practice guideline on high blood pressure in adults provides specific recommendations for the management of resistant hypertension.**
10.•• Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53–90 **The 2018 AHA scientific statement on resistant hypertension is a dedicated analysis of the disorder and provides algorithms for evaluation and management**.
11. Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K, et al. Updated ESH position paper on interventional therapy of resistant hypertension. EuroIntervention. 2013;9(Suppl R):R58–66.
12. Whelton PK, Williams B. The 2018 European Society of Cardiology/European Society of Hypertension and 2017 American College of Cardiology/American Heart Association blood pressure guidelines: more similar than different. Jama. 2018;320(17):1749–50.
13. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2(7):775–81.
14. Reboussin DM, Carey RM, Whelton PK. Evidence supporting the blood pressure treatment goal of less than 130/80 mm Hg. Hypertension. 2019;73(5):972–4.
15. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
16. Angeli F, Reboldi G, Trapasso M, Gentile G, Pinzagli MG, Aita A, et al. European and US guidelines for arterial hypertension: similarities and differences. Eur J Intern Med. 2019;63:3–8.
17. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High lood Pressure Research. Hypertension. 2008;51(6):1403–19.
18. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of apparent treatment-resistant hypertension in the United States. Hypertension. 2019;73(2):424–31.
19. Jones DW, Clark D 3rd, Wofford MR. Prevalence of apparent treatment-resistant hypertension. Hypertension. 2019;73(2):286–7.
20. Bhatt H, Siddiqui M, Judd E, Oparil S, Calhoun D. Prevalence of pseudoresistant hypertension due to inaccurate blood pressure measurement. J Am Soc Hyperten : JASH. 2016;10(6):493–9.
21. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension. 2019;73(5):e35–66.
22. Roerecke M, Kaczorowski J, Myers MG. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. JAMA Intern Med. 2019;179:351.
23. Mancia G, Bombelli M, Brambilla G, Facchetti R, Sega R, Toso E, et al. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. Hypertension. 2013;62(1):168–74.
24. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension. 2006;47(5):833–9.
25. Guo X, Zheng L, Wang J, Zhang X, Zhang X, Li J, et al. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. Sleep Med. 2013;14(4):324–32.
26. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med. 2017;32:246–56.
27. Lusardi P, Zoppi A, Preti P, Pesce RM, Piazza E, Fogari R. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. Am J Hypertens. 1999;12(1 Pt 1):63–8.
28. Friedman O, Bradley TD, Ruttanaumpawan P, Logan AG. Independent association of drug-resistant hypertension to reduced sleep duration and efficiency. Am J Hypertens. 2010;23(2):174–9.
29. Rogers A, Necola O, Sexias A, Luka A, Newsome V, Williams S, et al. Resistant hypertension and sleep duration among blacks with metabolic syndrome MetSO. J Sleep Disord Treat Care 2016;5(4).
30. McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol. 2013;24(12):2096–103.
31. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension. 2009;54(3):475–81.
32. Dimeo F, Pagonas N, Seibert F, Arndt R, Zidek W, Westhoff TH. Aerobic exercise reduces blood pressure in resistant hypertension. Hypertension. 2012;60(3):653–8.
33. Guimaraes GV, Cruz LG, Tavares AC, Dorea EL, Fernandes-Silva MM, Bocchi EA. Effects of short-term heated water-based exercise training on systemic blood pressure in patients with resistant hypertension: a pilot study. Blood Press Monit. 2013;18(6):342–5.
34. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19(12):2271–7.
35. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. Chest. 2007;131(2):453–9.
36. Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. Hypertension. 2010;56(6):1077–82.
37. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, Lloberes P, Diaz de Atauri MJ, Somoza M, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. Jama. 2013;310(22):2407–15.
38. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–68.
39. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. Lancet Diab Endocrinol. 2018;6(6):464–75.

40. Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JAS, Nogueira AR, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (resistant hypertension optimal treatment). Hypertension. 2018;71(4):681–90.