Grand Rounds

Resistant Hypertension
A Review of Diagnosis and Management

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Resistant hypertension—uncontrolled hypertension with 3 or more antihypertensive agents—is increasingly common in clinical practice. Clinicians should exclude pseudoresistant hypertension, which results from nonadherence to medications or from elevated blood pressure related to the white coat syndrome. In patients with truly resistant hypertension, thiazide diuretics, particularly chlorthalidone, should be considered as one of the initial agents. The other 2 agents should include calcium channel blockers and angiotensin-converting enzyme inhibitors for cardiovascular protection. An increasing body of evidence has suggested benefits of mineralocorticoid receptor antagonists, such as eplerenone and spironolactone, in improving blood pressure control in patients with resistant hypertension, regardless of circulating aldosterone levels. Thus, this class of drugs should be considered for patients whose blood pressure remains elevated after treatment with a 3-drug regimen to maximal or near maximal doses. Resistant hypertension may be associated with secondary causes of hypertension including obstructive sleep apnea or primary aldosteronism. Treating these disorders can significantly improve blood pressure beyond medical therapy alone. The role of device therapy for treating the typical patient with resistant hypertension remains unclear.

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Case Presentation

A 70-year-old man with a history of stage III chronic kidney disease and dyslipidemia was referred to the hypertension clinic for evaluation of resistant hypertension. He had been diagnosed with hypertension at age 39 years. His blood pressure was well controlled until 5 to 6 years ago. He was initially treated with telmisartan, hydrochlorothiazide, and atenolol. Despite titration to the maximal doses, his blood pressure remained elevated with his systolic pressure between 185 and 210 mm Hg and his diastolic pressure between 90 and 100 mm Hg. Aliskiren was then added to his medication regimen, but it did not control his blood pressure. Amlodipine was also prescribed, but he discontinued treatment because he developed lower extremity edema. He was then switched to a combination of valsartan, 160 mg daily; eplerenone, 50 mg twice daily; carvedilol, 25 mg twice daily; hydralazine, 100 mg 3 times a day; clonidine, 0.1 mg twice daily; and bumetanide, 1 mg daily, but his home blood pressure remained higher than 180/90 mm Hg. He did not use nonsteroidal antiinflammatory drugs or herbal supplements. He did not add salt to his meals but dined out regularly at Italian restaurants. He did not have a history of insomnia or loud snoring. A conventional renal angiogram in 2006 showed no evidence of renal artery stenosis. He reported adherence to all medications and stated he had not missed any medications prior to his clinic visit. On examination, with the patient seated, his blood pressure was 210/92 mm Hg and his heart rate was 58 beats/min. With the patient standing, his blood pressure was 202/91 mm Hg and his heart rate was 54 beats/min. His pulses were equal in all extremities, and he had no ascites or jugular venous distention. Mild nonpitting edema was present in his ankles bilaterally. His serum potassium was 3.5 mEq/L; estimated glomerular filtration rate was 48 mL/min per 1.73 m^2 (normal, >90 mL/min per 1.73 m^2).

The low normal serum potassium suggested possible primary aldosteronism. Therefore, his medications were adjusted before diagnostic tests were performed to test for primary aldosteronism. Medications that are known to alter circulating renin and aldosterone levels, including eplerenone, valsartan, and bumetanide, were discontinued and replaced by doxazosin. Hydralazine, carvedilol, and clonidine were continued at the same dose. After the patient no longer took eplerenone, valsartan, and bumetanide for 6 weeks, screening tests for aldosteronism were obtained. His serum aldosterone level was markedly elevated at 52 ng/dL (normal <16 ng/dL; to convert to pmol/L, multiply by 27.75) and his plasma renin activity was suppressed below the minimal detectable limit of 1 ng/mL per hour (normal, 2.9-10.8 ng/mL per hour). The patient underwent an intravenous saline suppression test, which showed a persistently elevated serum aldosterone of 26 ng/dL despite the salt load. A computed tomographic scan of his abdomen revealed adrenal nodules of 8 mm to 10 mm in diameter bilaterally without evidence of malignancy. However, subsequent adrenal vein sampling showed lateralization of aldosterone production to the right adrenal gland. He

underwent right adrenalectomy resulting in a marked improvement in blood pressure. After surgery, he required only 2 medications to keep his blood pressure lower than 140/90 mm Hg.

Definition and Prevalence of Resistant Hypertension

Resistant hypertension is defined by the seventh Joint National Committee (JNC 7) as the inability to achieve a blood pressure lower than 140/90 mm Hg despite optimal doses of 3 or more antihypertensive drugs, including 1 diuretic.[1] The 2008 American Heart Association (AHA) position statement defines resistant hypertension as uncontrolled hypertension despite treatment with at least 3 antihypertensive drugs or controlled hypertension with at least 4 drugs.[2] Although the prevalence of hypertension in the United States remains unchanged in the past decade, the prevalence of uncontrolled hypertension despite prescription with at least 3 drugs has almost doubled from 16% of patients treated for hypertension from 1998-2004 to 28% between 2005-2008.[3] It is estimated in the 2005-2008 National Health and Nutrition Examination Survey that 13% of all patients with hypertension (treated or untreated) meet the JNC 7 definition of resistant hypertension, whereas 21% of all patients with hypertension meet the AHA definition of resistant hypertension.[3,4] Resistant hypertension is associated with increased cardiovascular disease[5,6] and with emotional stress.[7]

The pathogenesis of resistant hypertension is unknown but appears to be multifactorial. Epidemiological studies demonstrate that older age, obesity, impaired renal function, and diabetes mellitus are all associated with resistant hypertension.[8-11] Patients with resistant hypertension typically have elevated systemic vascular resistance and expanded plasma volume in the presence of normal cardiac output.[12,13] Mechanisms underlying this abnormal hemodynamic pattern are unknown, but minor elevation in the circulating aldosterone levels and suppression of plasma renin activity have been identified in the majority of patients with resistant hypertension.[13-15] In this review, factors associated with uncontrolled hypertension and the efficacy of pharmacological and nonpharmacological interventions for treating resistant hypertension are described.

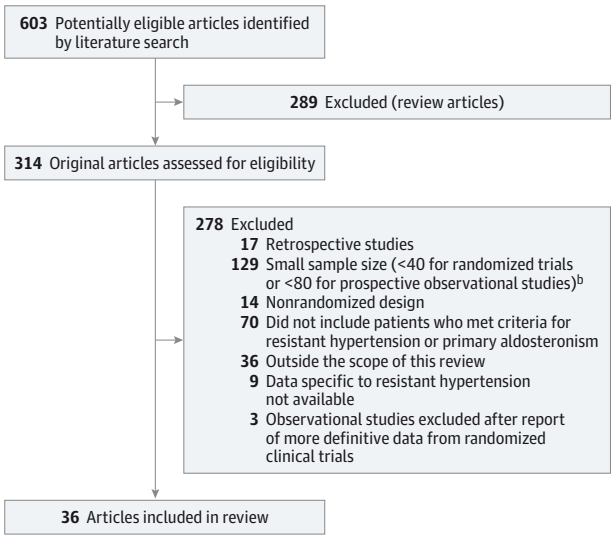
A comprehensive search was performed to identify relevant literature on resistant hypertension in MEDLINE, PubMed, OVID, and the Cochrane Library between January 1, 1985, and March 31, 2014. Six hundred three potentially eligible trials were identified, from which 36 studies met the inclusion criteria (as outlined in **Figure 1**) and are included in this review.

Diagnosing Resistant Hypertension: Evaluating Patients for the White Coat Syndrome and Pseudohypertension

Before diagnosing resistant hypertension, clinicians must exclude medication nonadherence and the white coat syndrome. Isolated elevation of office blood pressure despite normal home blood pressure or 24-hour ambulatory blood pressure is common during treatment with antihypertensive medications and may lead clinicians to incorrectly diagnose patients as having resistant hypertension. A recent study estimated that the prevalence of white coat syndrome (defined as office blood pressure of ≥140/90 mm Hg or higher but normal 24-hour ambulatory blood pressure of ≤130/80 mm Hg) to be as high as 30% among patients with elevated office blood pressure despite treatment with at least 3 drugs.[16] In multiple population studies, individuals with a white coat effect had fewer cardiovascular events than those with resistant hypertension and similar rates of cardiovascular events compared with patients with well-controlled hypertension.[10,17] However, the prognosis of hypertensive patients with white coat syndrome is worse than that of the general normotensive population.[18] Continued home blood pressure or repeated ambulatory blood pressure monitoring is advisable for patients with white coat syndrome because between 20% and 25% of these patients may develop true resistant hypertension (uncontrolled office and 24-hour blood pressure while taking ≥ 3 or more drugs) within 3 to 6 months of follow-up.[19]

Nonadherence to antihypertensive medications is another cause of pseudoresistant hypertension. Adherence can be monitored with patient self-report, pill counts, or prescription refill rates. Self-report tends to overestimate adherence to antihypertensive medications by as much as 80% compared with electronic monitoring of pillboxes (which record the date and time of bottle openings).[20] Similarly, pill counts are accurate in determining adherence in only 50% to 70% of patients compared with electronic pillboxes.[21,22] Prevalence of medication nonadherence among patients with presumed resistant hypertension was 8% to 40% in the studies using

Figure 1. Diagram of Study Selection[a]



[a] Only randomized clinical trials with a minimum sample size of 40 for a 2-group parallel design or prospective observational studies with a minimum sample size of 80 in patients with resistant hypertension were included. Priority was given to randomized clinical trials over observational studies. Review articles, retrospective studies, nonrandomized clinical trials, and studies that failed to include patients who met the definition of resistant hypertension were excluded.

[b] The sample size of 40 will have adequate statistical power to detect a clinically meaningful difference of more than 9/10 mm Hg[66,67] between the treated and control group with a standard deviation of 10 and 80% to 86% power at a 2-sided .05 significance level for the 2-group parallel design. This level of blood pressure difference between the treated and control groups has been used to calculate the sample size in previous clinical trials of resistant hypertension.[66,67] For a prospective observational study, the sample size of 80 patients and a standard deviation of 10 mm Hg for systolic blood pressure allows detection of a relationship between systolic blood pressure and the dependent variables at a 2-sided .05 significance level with power of 80% assuming that the correlation coefficient between the 2 variables is at least 0.3 or more. Because the correlation coefficient of between 0.2 and 0.4 is generally considered to be weak,[71] this sample size would allow detection of at least modest predictors of blood pressure elevation.

Table 1. Secondary Forms of Hypertension Associated With Resistant Hypertension

Conditions	Prevalence in Resistant Hypertension, %	Diagnostic Tests	Treatment	Level of Evidence[a]
Obstructive sleep apnea[34]	60-70	Polysomnography	Continuous positive airway pressure[41,42]	High
Primary aldosteronism [35-38]	7-20	Serum aldosterone, plasma renin activity	Spironolactone, eplerenone, or surgical resection of tumor in unilateral aldosterone-producing adenoma [37-40]	High
Renal artery stenosis [34,43]	2-24	Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography	Renal revascularization in selected patients[44,45]	High
Renal parenchymal disease [34]	1-2	Serum creatinine	Correction of underlying causes if possible[2]	High
Drug-induced or heavy alcohol use[9,34]	2-4	History taking	Discontinuation of offending agents[2]	Moderate
Thyroid disorders[34]	<1	Thyrotropin, free thyroxine	According to underlying disorders[2]	Moderate

[a] High level of evidence is defined as evidence derived from well-designed, well-executed randomized clinical trials that adequately address populations to which the results are applied and directly assess effects on health outcomes or evidence from well-conducted meta-analyses of such studies. Moderate level of evidence is defined as evidence derived from randomized clinical trials with minor limitations affecting confidence in, or applicability of the results or evidence from well-designed observational studies in well-conducted meta-analyses of such studies. Low level of evidence is defined as evidence derived from randomized clinical trials with major limitations, or nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of the results, case reports, or case series.

questionnaires or pharmacy refill data.[8,23] The prevalence of medication nonadherence was 50% to 60% when the more sensitive technique of therapeutic drug monitoring in the serum samples was used.[24] Thus, physicians caring for patients with resistant hypertension should be highly vigilant regarding medication nonadherence.

In the United States, assays to assess serum levels of most antihypertensive drugs are available in clinical practice, and costs of these assays are covered by most health insurance plans.[25] In contrast, electronic pillboxes are limited to research settings and not available for clinical use. Thus, therapeutic drug monitoring is a viable option for adherence assessment when patients forget to bring their pill bottles to the clinic or pharmacy when data are not readily available. Once medication nonadherence is established, every effort should be made to identify barriers to medication adherence. These barriers may include adverse effects to antihypertensive drugs, excessively complex drug regimens, financial limitations, or patient cognitive dysfunction.[25,26] A plan for improved adherence should be developed in partnership with each patient according to his/her specific situation.

Lifestyle Interventions for Patients With Resistant Hypertension

All patients with resistant hypertension should be counseled about lifestyle modification to lower blood pressure. Sodium intake is a major factor contributing to resistant hypertension. Meta-analyses of clinical trials indicated that sodium restriction to approximately 1.7 g/d was associated with a reduction in office blood pressure by 5/3 mm Hg in patients with mild uncomplicated hypertension.[27] The antihypertensive effects of sodium restriction are even more pronounced in patients with resistant hypertension. In 1 study, 24-hour ambulatory blood pressure was reduced by 23/9 mm Hg when sodium intake was decreased to 1.1 g/d in patients with uncontrolled blood pressure on a 3-drug regimen that included a diuretic.[28] However, the average sodium consumption in the United States is far above the level recommended (8.5 g of salt per day). Approximately 75% of the sodium consumed in the United States is obtained from processed foods or restaurant cuisine. Approximately 25% of consumed sodium is added at meals.[29] Advising patients to read nutritional labels carefully is essential to restrict sodium intake and optimize blood pressure control.

Physical inactivity has been identified in more than 40% of patients.[9] Guidelines suggest that patients with hypertension should engage in at least 30 minutes per day of aerobic physical activity most days of the week.[2,30] A recent randomized trial involving patients with resistant hypertension showed that a training program, consisting of walking on a treadmill 3 times weekly for 8 to 12 weeks, significantly reduced ambulatory blood pressure by 6/3 mm Hg compared with a sedentary control group.[31] Thus, aerobic exercise should be encouraged in most patients with resistant hypertension.

Is Secondary Hypertension Common Among Patients With Resistant Hypertension?

Secondary hypertension is detected in 5% to 10% of all patients with hypertension.[1,30,32] However, several secondary forms of hypertension are more prevalent in resistant hypertension than in uncomplicated hypertension (**Table 1**). Obstructive sleep apnea is observed in 30% to 40% of patients with hypertension[33] and in 60% to 70% of patients with resistant hypertension.[34] Primary aldosteronism is present in 5% to 10% of all patients with hypertension and in 7% to 20% of patients with resistant hypertension.[35-37]

Primary Aldosteronism

Screening tests for primary aldosteronism include measuring plasma renin activity and serum aldosterone levels. These tests can be performed while patients are taking most antihypertensive drugs, but mineralocorticoid receptor antagonists and direct renin inhibitors should be stopped before these measures. However, a confirmatory assessment with an intravenous saline suppression test, to identify the presence of insuppressible aldosterone production after sodium loading, should be performed 2 to 3 weeks after discontinuing diuretics, angiotensin-converting enzyme inhibitors, and angioten-

sin II receptor blockers and 4 to 6 weeks after discontinuing mineralocorticoid receptor antagonists. Serum potassium should be maintained closest to 4.0 mEq/L as much as possible because hypokalemia may impair adrenal aldosterone release, which may lead to a false-negative test.[38] During the evaluation, patients should be switched to antihypertensive agents with minimal effects on the renin angiotensin aldosterone system, including calcium channel blockers, hydralazine, or α-blockers.[38] These changes require close follow-up to avoid excessive increases in blood pressure associated with withdrawal of antihypertensive agents. Patients who are found to have suppressed renin levels in the presence of elevated serum aldosterone levels (≥15 ng/dL) should undergo an intravenous saline suppression test (intravenous infusion of saline of 2 L over 4 hours) or other confirmatory tests recommended by the Endocrine Society.[38] Patients with insuppressible aldosterone levels of 10 ng/dL or more after the intravenous saline suppression test should undergo adrenal vein sampling. In these patients, computed tomography or magnetic resonance imaging of adrenal glands alone are not reliable in distinguishing individuals with idiopathic (bilateral) hyperplasia from those with a unilateral aldosterone-producing adenoma.[38] Patients with bilateral aldosterone overproduction should be treated with spironolactone or eplerenone.[39] Patients with a unilateral tumor should undergo surgical removal of the adenoma, which has been shown to cure hypertension in 50% to 60% of patients.[40]

Obstructive Sleep Apnea

In contrast to primary aldosteronism, clinical trials have shown that treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) resulted in modest blood pressure reductions in patients with resistant hypertension approximating 3 to 5 mm Hg.[41,42] However, greater blood pressure reductions of 7 to 10 mm Hg were reported in patients with resistant hypertension who regularly adhered to the CPAP treatment.[41] Hormonal testing to exclude other endocrine forms of hypertension such as pheochromocytoma, Cushing syndrome, or thyrotoxicosis should be performed when indicated based on clinical presentation. Certain substances or drugs, including oral contraceptives, are associated with resistant hypertension (Table 1).[34] Thus, a thorough history of prescription and nonprescription drug use, which may interfere with the efficacy of antihypertensive medications or directly increase blood pressure, should be obtained.

Renal Artery Stenosis

Renal artery stenosis is another common cause of secondary hypertension, identified in 2% to 24% of patients with resistant hypertension.[34,43] Although multiple renal stent systems have been approved for clinical use by the US Food and Drug Administration, the benefit of renal revascularization remains a controversial resistant hypertension treatment. The largest study, involving 947 patients with renal artery stenosis and resistant hypertension, showed that renal artery stenting led to only a 2-mm Hg reduction in systolic blood pressure.[44] Furthermore, there was no improvement in cardiovascular or renal outcomes compared with optimal medical therapy alone. However, these studies included patients with atherosclerotic renal artery stenosis. Revascularization remains a treatment option for hypertension related to fibromuscular dysplasia.[45] In addition, a recent large observational study suggested revascularization was beneficial when compared with medical therapy in reducing blood pressure in patients with resistant hypertension with atherosclerotic renal artery stenosis experiencing a rapid decline in renal function.[46] However, prospective randomized studies are needed to confirm these findings.

Initial Therapy for Resistant Hypertension

Pharmacological treatment for patients with uncontrolled blood pressure despite a triple-drug regimen should begin with optimization of diuretic use.[47] A prospective observational study involving 3550 patients with resistant hypertension demonstrated that diuretic use is associated with improved blood pressure control after a year's follow-up.[8] Chlorthalidone, a thiazidelike diuretic, is at least twice as potent as hydrochlorothiazide, a thiazide-type diuretic, in lowering blood pressure.[48] Chlorthalidone was more effective than lisinopril in reducing the risk of heart failure and stroke in black patients[49] and, therefore, should be considered as an initial therapy for patients with resistant hypertension. In the British 2011 National Institute for Health and Clinical Excellence (NICE) consensus statement, indapamide, another thiazidelike diuretic, is recommended over hydrochlorothiazide due to greater antihypertensive efficacy based on a meta-analysis.[32] In contrast, chlorthalidone is the only diuretic recommended by the 2008 AHA position statement,[2] whereas the 2014 report from the JNC 8[50] did not specify that 1 thiazide diuretic was preferred for lowering blood pressure. However, this 2014 report did not specifically address treatment of resistant hypertension.

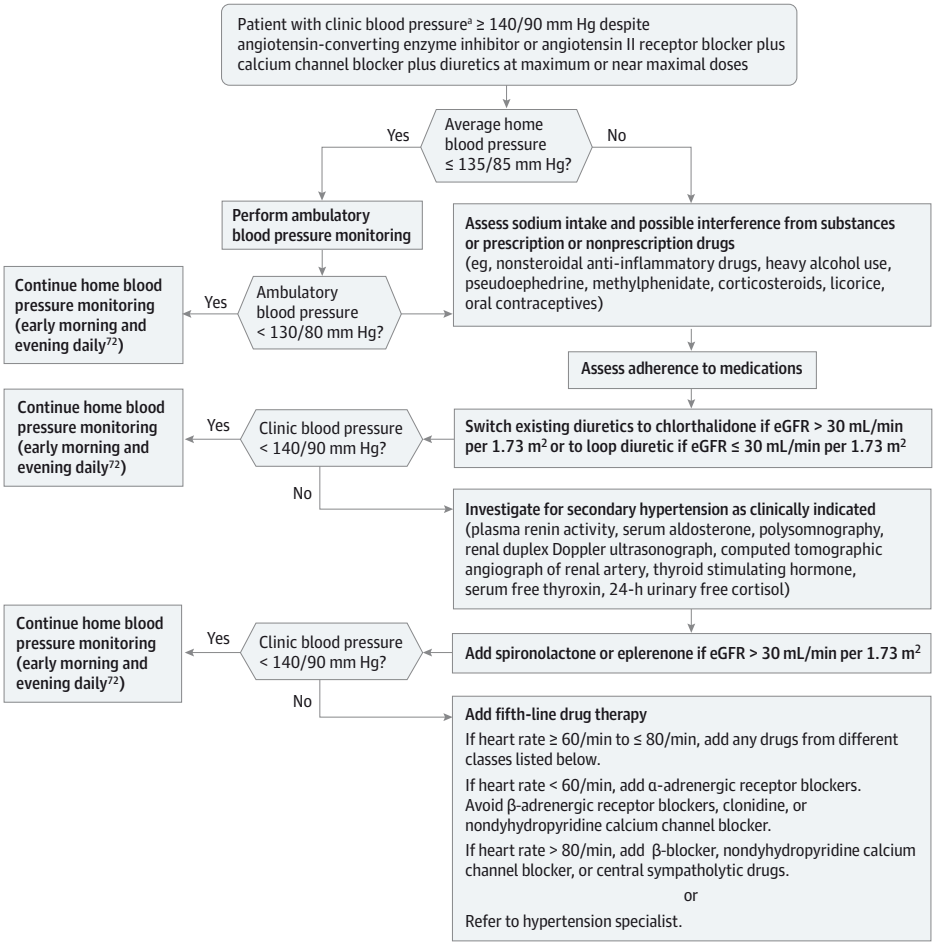
Angiotensin Converting-Enzyme Inhibitors and Calcium Channel Blockers

After optimizing diuretic therapy, the combination of both angiotensin-converting enzyme inhibitors and calcium channel blockers should be prescribed for resistant hypertension. This combination regimen is superior to the combination of both angiotensin-converting enzyme inhibitors and thiazide diuretics in reducing cardiovascular events in hypertensive patients with high cardiovascular risk.[51] A recent randomized clinical trial demonstrated that the combination of angiotensin II receptor blockers and calcium channel blockers controlled blood pressure in more than 60% of patients whose previous medication regimens of a 3-drug regimen that included a diuretic had failed to achieve their goal blood pressure.[52] Thus, this combination is a reasonable alternative regimen for initial treatment of resistant hypertension.

Mineralocorticoid Receptor Antagonists and α-Blockers

The optimal fourth-line drug therapy for resistant hypertension has not been extensively investigated. In a recent randomized, double-blinded trial (Addition of Spironolactone in Patients With Resistant Arterial Hypertension, ASPIRANT), spironolactone at a dose of 25 mg/d reduced 24-hour ambulatory systolic blood pressure by 10 mm Hg compared with placebo in 117 patients with resistant hypertension treated with 3 drugs including a diuretic.[53] A similar reduction in 24-hour ambulatory blood pressure was observed in another randomized trial involving patients with resistant hypertension and diabetes mellitus when spironolactone was added to a triple-drug regimen containing either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[54] In an observational study, the addition of spironolactone was associated with rapid regression of left

Figure 2. Proposed Algorithm for Management of Resistant Hypertension



eGFR indicates estimated glomerular filtration.

[a] Blood pressure should be measured after patients are resting quietly for 3 to 5 minutes with the upper arm supported at heart level, using appropriate sized arm cuffs. Three readings should be obtained in each sitting, separated by at least 1 minute. The average of the 3 readings should be used as the blood pressure reading. Home blood pressure measurements should be obtained in the early morning and the evening.[72] The list of validated home blood pressure monitors can be found at http://www.dableducational.org.

ventricular hypertrophy in the resistant hypertension population with or without primary aldosteronism.[55] Eplerenone, a more selective mineralocorticoid receptor antagonist without the antiandrogenic adverse effects of spironolactone, was associated with a 10-mm Hg reduction in 24-hour ambulatory systolic blood pressure when used as a fourth-line agent at the dose of 50 mg twice daily.[56] The antihypertensive associations of both spironolactone and eplerenone were observed even in the presence of normal serum aldosterone levels.[53,56] α-Blockers are an alternative to spironolactone, particularly in the patients undergoing screening for primary aldosteronism since plasma renin activity and serum aldosterone levels are not affected by α-adrenergic receptor blockers.[38] An observational analysis from a clinical trial involving 10 069 patients treated with amlodipine plus perindopril vs atenolol plus bendroflumethiazide showed that adding doxazosin to either treatment combination was associated with a lower blood pressure by 12/7 mm Hg without an increase in heart failure.[57]

In contrast to mineralocorticoid receptor antagonists, adding angiotensin II receptor blockers to maximal doses of angiotensin-converting enzyme inhibitors resulted in small blood pressure reductions in patients with resistant hypertension.[58,59] In a recent clinical trial involving patients with vascular disease or high-risk diabetes mellitus, the combination of the telmisartan and ramipril was associated with an increased risk of syncope and renal dysfunction without an increase in benefit compared with either drug administered alone.[60] Consequently, this treatment regimen should be avoided. Similarly, the direct renin inhibitor aliskiren has not been found to be more effective than placebo in lowering blood pressure in patients not reaching their target blood pressure goal with a combination of angiotensin II receptor blockers and thiazide diuretics.[61] Furthermore, a recent clinical trial involving patients with diabetes mellitus showed an increased risk of hyperkalemia, renal dysfunction, and nonfatal stroke when aliskiren was used in combination with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[62] β-Blockers should be used as the fifth-line drug therapy in the absence of compelling indications such as congestive heart failure or prior myocardial infarction. The cardiovascular protection offered by the combination of β-blockers and thiazide diuretics has been shown to be inferior to combinations of calcium channel blocker plus angiotensin-converting enzyme inhibitor[63] and angiotensin II receptor blocker plus thiazide diuretic, respectively,[64] in large clinical trials. A suggested algorithm for selecting antihypertensive agents is shown in **Figure 2**. However, this algorithm has not been validated in a clinical setting. A list of antihypertensive drugs and their adverse effects is shown in **Table 2** and **Table 3**.

Table 2. First-Line 3-Drug Treatment With Diuretic Therapy for Resistant Hypertension

Drug	Dosing Range, mg/d	Dosing per Day	Adverse Effects	Special Indication	Level of Evidence[a]
Diuretics					
Thiazide diuretics[32,47-49]			Hyponatremia, hypokalemia, volume depletion, renal dysfunction, glucose intolerance, diabetes mellitus, hyperuricemia, gout[48,49]	Initial therapy for blacks and elderly patients with isolated systolic hypertension[30,49,50]	High
Chlorthalidone	12.5-25	1			
Indapamide	1.25-5	1			
HCTZ	12.5-50	1			
Metolazone	2.5-10	1			
Loop diuretics[30,32,47]			Hypokalemia, volume depletion, renal dysfunction[1,30,47]	Congestive heart failure, advanced chronic kidney disease[1,2,30]	Moderate
Furosemide	20-160	2			
Torsemide	2.5-80	1-2			
Bumetanide	0.5-2.0	2			
Ethacrynic acid	25-100	2			
Potassium-sparing diuretics[30,32,47]			Hyperkalemia, volume depletion, renal dysfunction[30,47]	None	Moderate
Amiloride	5-20	1			
Triamterene	25-100	1			
Calcium channel blockers[32,47,63]				All calcium channel blockers: Raynaud phenomenon, angina pectoris, vasospastic angina[1]	Moderate
Dihydropyridines			Dihydropyridine calcium channel blocker: lower-extremity edema, gingival hyperplasia[47,63]	Dihydropyridine calcium channel blockers: Initial therapy for blacks and elderly patients with isolated systolic hypertension [30,32,49,50]	High
Amlodipine	2.5-10	1			
Felodipine	2.5-20	1-2			
Isradipine CR	2.5-20	2			
Nicardipine SR	30-120	2			
Nifedipine XL	30-120	1			
Nisoldipine	10-40	1-2			
Nondihydropyridines			Nondihydropyridine calcium channel blocker: lower-extremity edema, gingival hyperplasia, heart block, bradycardia, congestive heart failure[47]	Nondihydropyridine calcium channel blockers: supraventricular tachycardia [1,2,30]	Moderate
Diltiazem CD	120-540	1			
Verapamil HS	120-480	1			
Angiotensin-converting enzyme inhibitors[b,32,47,60,64]			Cough, hyperkalemia, angioedema[32,47,60,64]	Congestive heart failure, and chronic kidney diseases[1,30,32,50]	High
Benazepril	10-80	1-2			
Captopril	25-150	2			
Enalapril	2.5-40	2			
Fosinopril	10-80	1-2			
Lisinopril	5-80	1-2			
Moexipril	7.5-30	1			
Perindopril	4-16	1			
Quinapril	5-80	1-2			
Ramipril	2.5-20	1			
Trandolapril	1-8	1			
Angiotensin-receptor blockers[32,47,60,64]			Hyperkalemia[32,47,60,64]	Congestive heart failure and chronic kidney diseases[1,30,32,50]	High
Azilsartan	40-80	1			
Candesartan	8-32	1			
Eprosartan	400-800	1-2			
Irbesartan	150-300	1-2			
Losartan	25-100	2			
Olmesartan	5-40	1			
Telmisartan	20-80	1			
Valsartan	80-320	1-2			

Abbreviation: HCTZ, hydrochlorothiazide.

[a] See Table 1 footnotes for a definition of the levels of evidence.

[b] Should not be used in combination with angiotensin II receptor blockers.

Table 3. Fourth- and Fifth-Line Drug Therapy for Resistant Hypertension

Drug	Dose Range, mg/d	Dosing per Day	Adverse Effects	Special Indication	Level of Evidence[a]
Fourth-line drug therapy					
Mineralocorticoid receptor antagonists [30,32,39,53-56]			Hyperkalemia, volume depletion, renal dysfunction[30,32,47]	Congestive heart failure, post-myocardial infarction with left ventricular dysfunction,[b,1,2,30] and primary aldosteronism[39]	High
Spironolactone	12.5-400	1-2			
Eplerenone	25-100	1-2			
Fifth-line drug therapy					
Direct renin inhibitors[61,62]			Hyperkalemia, diarrhea[61,62]	None	High
Aliskiren	75-300	1			
β-Blockers[1,32,47]			Bradycardia, heart block, bronchospasm, fatigue, depression[32,47]	Myocardial infarction, congestive heart failure[b,1,2,30]	High
Acebutolol	200-800	2			
Atenolol	25-100	1			
Betaxolol	5-20	1			
Bisoprolol	2.5-20	1			
Metoprolol tartrate	50-450	2			
Metoprolol succinate	50-200	1-2			
Nadolol	20-320	1			
Nebivolol	5-20	1			
Pindolol	10-60	2			
Propranolol	40-180	2			
Propranolol LA	60-180	1-2			
Timolol	20-60	2			
Labetalol	200-2400	2			
Carvedilol	6.25-50	2			
α-Blockers[1,32,47,57]			Nasal congestion, dizziness, orthostatic hypotension[32,47]	Pheochromocytoma[b,1,2,30]	Moderate
Doxazosin	1-16	1			
Prazosin	1-40	2-3			
Terazosin	1-20	1			
Phenoxybenzamine	20-120	2			
Central sympatholytics[1,32,47]			Drowsiness, orthostatic hypotension, depression[32,47]	None	Moderate
Clonidine	0.2-1.2	2-3			
Clonidine patch	0.1-0.6	Weekly			
Guanfacine	1-3	1			
Methyldopa	250-1000	2			
Direct vasodilators[1,32,47]			Reflex tachycardia, lower extremity edema, drug-induced lupus (hydralazine)[32,47]	None	Moderate
Hydralazine	10-200	2			
Minoxidil	2.5-100	1			

[a] See Table 1 footnotes for a definition of the levels of evidence.

[b] Should be considered as the first-line drug therapy in the presence of special indication.

Device Therapy for Resistant Hypertension

Devices to treat resistant hypertension mainly target the sympathetic nervous system, which is known to contribute to the pathogenesis of essential hypertension and many forms of secondary hypertension.[65] However, these devices are not uniformly successful in treating resistant hypertension. Chronic electrical stimulation of the carotid sinus nerves with a surgically implantable device, which was designed to trigger baroreflex-mediated inhibition of sympathetic nerve activity, has been shown to reduce blood pressure in 54% of patients with resistant hypertension in a randomized, double-blind, parallel-designed clinical trial (n = 181).[66] However, improved blood pressure control was also observed in 46% of control group patients (n = 81) in whom the devices were deactivated for unknown reasons (P = .97).[66]

Catheter-based renal sympathetic denervation is another potential therapeutic strategy for resistant hypertension. This technique uses radiofrequency energy to ablate renal nerves alongside renal arteries in the adventitial layers.[67] Although the initial unblinded trial using this technology showed promising results,[67] a subsequent randomized sham-controlled trial (SIMPLICITY-HTN3)[68] showed no difference in the office blood pressure or 24-hour ambulatory blood pressure in a denervation group compared with a sham-procedure group treated with medical therapy alone. It re-

mains unclear whether renal denervation may benefit a subset of patients with resistant hypertension.

Conclusions

Treating resistant hypertension, particularly in patients who are already prescribed 5 or more drugs, is challenging. Selection of additional blood pressure–lowering agents should be based not only on the antihypertensive efficacy but also on the incremental cost, the drugs' adverse effects, and their potential cardiovascular benefits. Because half of patients with uncontrolled hypertension while taking 3 or more antihypertensive drugs are prescribed medications at suboptimal doses[69] and less than 5% are treated with mineralocorticoid receptor antagonists in the United States,[70] optimization of antihypertensive regimen should be performed prior to extensive investigation for secondary hypertension.

ARTICLE INFORMATION

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Correction: This article was correctedon June 20, 2014, for an incorrect dosing range in Table 2.

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