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RESISTANT HYPERTENSION (L DRAGER, SECTION EDITOR)

Approaches for the Management of Resistant Hypertension in 2020

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Abstract

Purpose of Review Resistant hypertension is diagnosed if the blood pressure (BP) is not controlled despite optimum doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate BP control needs 4 or more antihypertensive drugs from different classes.

Recent Findings Pseudohypertension and white coat hypertension must be excluded. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office BP measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension. Secondary hypertension must be excluded and treated. 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 BP control. The beneficial effects of thiazide diuretics are reduced when the glomerular filtration rate is reduced to less than 40 mL/min/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 h. 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. Further research is needed on investigational drugs and device therapy for treating resistant hypertension.

Summary Clinical trials are indicated for the treatment of resistant hypertension by sacubitril/valsartan and also by firibastat.

Keywords Resistant hypertension · Antihypertensive drugs · Diuretics · Mineralocorticoid receptor antagonists · Lifestyle measures · Device therapy for hypertension

Introduction

The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines reported that stage 1 hypertension is a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg [1••]. Stage 2 hypertension is a systolic blood pressure of 140 mmHg and higher or a diastolic blood pressure of 90 mmHg and higher [1••]. These hypertension guidelines recommend lifestyle measures plus blood pressure-lowering drugs for secondary prevention of recurrent cardiovascular disease events in persons with clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average systolic blood pressure of 130 mmHg and higher or an average diastolic blood pressure of 80 mmHg and higher [1••, 2, 3]. The prevalence of resistant hypertension has increased with these new guidelines. These guidelines recommend lifestyle measures plus blood pressure-lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease ≥ 10% [4] and an average systolic blood pressure of 130 mmHg and higher or an average diastolic blood pressure of 80 mmHg and higher [1••, 5]. These guidelines recommend lifestyle measures plus blood pressure-lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease of < 10% [4] and an average systolic blood pressure of 140 mmHg and higher or an average diastolic blood pressure of 90 mmHg and higher [1••,

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5, 6]. These guidelines recommend treatment with antihypertensive drug therapy with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in persons with a blood pressure of 140/90 mmHg and higher or with a blood pressure more than 20/10 mmHg above their blood pressure target [1••, 6]. White coat hypertension must be excluded before using antihypertensive drugs in persons with hypertension at low risk for atherosclerotic cardiovascular disease [1••].

Secondary hypertension should be suspected if there is new onset or uncontrolled hypertension in adults [1••, 7]. Screen for secondary hypertension if there is drug-resistant/induced hypertension, abrupt onset of hypertension, onset of hypertension in a person younger than 30 years or later after 50 years, exacerbation of previously controlled hypertension, disproportionate target organ damage for the degree of hypertension, accelerated/malignant hypertension, onset of diastolic hypertension in older persons, or unprovoked or excessive hypokalemia [1••, 7]. Common causes of secondary hypertension include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug- or alcohol-induced hypertension [1••]. Uncommon causes of secondary hypertension include pheochromocytoma/paraganglioma, Cushing's syndrome, hypothyroidism, hyperthyroidism, aortic coarctation, primary hyperparathyroidism, congenital adrenal hyperplasia, mineralocorticoid excess syndromes, and acromegaly [1••].

The 2017 ACC/AHA hypertension guidelines recommend that the blood pressure should be lowered to less than 130/80 mmHg in persons with ischemic heart disease [1••, 3, 8–13], in persons with heart failure with a decreased left ventricular ejection fraction [1••, 14], in persons with heart failure with a preserved left ventricular ejection fraction [1••, 14], in persons with chronic kidney disease [1••, 15], in persons after renal transplantation [1••], in persons with lacunar stroke [1••, 16, 17], in persons with peripheral arterial disease [1••, 2], in persons with diabetes mellitus [1••, 18–21], in noninstitutionalized ambulatory community-dwelling persons older than 65 years of age [1••, 8, 9], and for secondary stroke prevention [1••, 22].

Lifestyle Measures

Lifestyle modification should be used in the treatment of hypertension [1••, 23••]. Weight reduction, consuming a diet rich in fruits, vegetables, and low-fat dairy products with less saturated fat and total fat, sodium reduction to not exceed 1.5 g daily, smoking cessation, regular aerobic physical activity, avoidance of excessive alcohol intake, avoidance of excessive caffeine, and avoidance of drugs which can increase blood pressure, including nonsteroidal anti-inflammatory drugs, glucocorticoids, and sympathomimetics, are recommended [1••, 6, 23••, 24].

Drug Treatment of Primary Hypertension

The 2017 ACC/AHA hypertension guidelines recommend for white and other non-black persons younger than 60 years of age with primary hypertension, the first antihypertensive drug should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, the second drug a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker should be administered [1••]. For white and other non-black persons aged 60 years of age and older with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is required, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be administered [1••]. For African-Americans with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be administered [1••].

Drug Treatment of Hypertension Associated with Comorbidities

Patients with stable ischemic heart disease and hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and if a third antihypertensive drug is needed, a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic or a calcium channel blocker should be administered [1••, 25••, 26–33]. If a fourth antihypertensive drug is needed to adequately control hypertension, a mineralocorticoid receptor antagonist should be added [1••]. In patients with stable ischemic heart disease who have angina pectoris despite beta blocker therapy and persistent uncontrolled hypertension, a dihydropyridine calcium channel blocker should be added [1••, 25••, 26, 34]. Beta blockers which should be administered in treating ischemic heart disease with hypertension include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol [1••]. Atenolol should not be given [1••, 28]. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are contraindicated if there is left

ventricular systolic dysfunction [1••]. If there is left ventricular systolic dysfunction, the beta blockers that should be administered are carvedilol, metoprolol succinate, or bisoprolol [1••, 25••, 26, 35].

If hypertension persists after treatment with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with an acute coronary syndrome, a long-acting dihydropyridine calcium channel blocker should be added to the therapeutic regimen [26]. Aldosterone antagonists should be administered to patients treated with beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction and either heart failure or diabetes mellitus if their serum potassium is less than 5.0 meq/L and if their serum creatinine is ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women [1••, 25••, 26, 36].

Patients with hypertension who have heart failure with a decreased left ventricular ejection fraction should be treated with a beta blocker (carvedilol, metoprolol succinate, or bisoprolol) plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or preferably an angiotensin receptor-neprilysin inhibitor plus a diuretic and if indicated with a mineralocorticoid receptor antagonist [1••, 14, 25••, 26, 28, 36]. Nondihydropyridine calcium channel blockers are contraindicated in patients with heart failure and a decreased left ventricular ejection fraction [1••, 14, 25••, 26, 37, 38].

Patients with hypertension and heart failure with a preserved left ventricular ejection fraction should have their volume overload treated with diuretics, their other comorbidities treated, and their hypertension treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin blocker plus a mineralocorticoid receptor antagonist [1••, 14, 39, 40].

Patients with hypertension and chronic kidney disease stage 3 or higher or stage 1 or 2 chronic kidney disease with albuminuria ≥ 300 mg per day should be treated with an angiotensin-converting enzyme inhibitor to slow progression of chronic kidney disease [1••, 41]. If an angiotensin-converting enzyme inhibitor is not tolerated, these patients should be treated with an angiotensin receptor blocker [1••]. Patients with stage 1 or 2 chronic kidney disease who do not have albuminuria may be treated with usual first-line antihypertensive drugs [1••]. If 3 antihypertensive drugs are necessary, these patients should be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker. After kidney transplantation, treat hypertension with a calcium channel blocker to improve glomerular filtration rate and kidney survival [1••].

Patients with hypertension and a prior stroke or transient ischemic attack should receive treatment with a thiazide diuretic or angiotensin-converting enzyme or angiotensin receptor blocker [1••, 42]. If a third antihypertensive drug is needed, these patients should be treated with a thiazide diuretic plus an angiotensin-converting enzyme or angiotensin receptor blocker plus a calcium channel blocker.

Patients with hypertension and peripheral arterial disease should be treated with an angiotensin-converting enzyme or angiotensin receptor blocker or a calcium channel blocker or thiazide diuretic or beta blocker [1••, 43]. There is no evidence that any one class of antihypertensive drugs is superior to treat hypertension in patients with peripheral arterial disease [1••, 43].

Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are effective antihypertensive drugs in patients with hypertension and diabetes mellitus and may be used as initial therapy [1••, 44]. Angiotensin-converting enzymes or angiotensin receptor blockers should be used for treating diabetics with hypertension and persistent albuminuria [1••, 45]. Chlorthalidone was better than lisinopril, amlodipine, and doxazosin in reducing cardiovascular disease and renal outcomes in nondiabetics with hypertension and the metabolic syndrome [1••, 46].

Beta blockers are the preferred antihypertensive drugs in patients with hypertension and thoracic aortic aneurysm [1••, 47]. Beta blockers also improve survival in adults with type A and with type B acute and chronic thoracic aortic dissection [1••]. If thoracic aorta dissection develops, beta blockers are the initial drug of choice for reducing blood pressure, ventricular rate, dP/dt, and stress on the aorta [47, 48]. Systolic blood pressure should be lowered to 100 to 120 mmHg and the ventricular rate decreased to less than 60 beats/min by intravenous propranolol, metoprolol, labetalol, or esmolol [47, 48, 49••].

Pregnant women with hypertension should not receive treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, or atenolol because these drugs are fetotoxic [1••]. Pregnant women with hypertension should be treated with methyldopa, nifedipine, and/or labetalol [1••].

Treatment-Resistant Hypertension

Resistant hypertension is diagnosed if the blood pressure is not controlled despite optimum doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate blood pressure control needs 4 or more antihypertensive drugs from different classes [1••, 49••, 50, 51]. The National Institute for Health ad Clinical Excellence guideline suggests that the 3 drugs should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a calcium channel blocker plus a thiazide-type diuretic [51]. Pseudohypertension and white coat hypertension must be excluded.

Pseudohypertension in the elderly is a falsely high systolic blood pressure which results from markedly sclerotic arteries which do not collapse under the blood pressure cuff [1••, 25••]. Pseudohypertension can be confirmed by measuring intra-arterial pressure [1••, 25••]. White coat hypertension is diagnosed in persons with persistently elevated office blood pressure but normal home blood pressure or normal 24-h ambulatory blood pressure [1••, 25••]. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office blood pressure measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension [1••, 25••, 52].

Factors contributing to resistant hypertension include obesity, a high-sodium, low-fiber diet, excess alcohol intake, physical inactivity, obstructive sleep apnea, use of cocaine, amphetamines, nonsteroidal anti-inflammatory drugs, oral contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills), erythropoietin, licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy [1••, 25••, 51, 53].

Persons with resistant hypertension also need to be screened for secondary causes of hypertension with treatment of these secondary causes [1••, 25••]. Lifestyle measures as previously discussed must be instituted [1••, 6, 23••].

Among 205,750 patients with incident hypertension, 1.9%, mean age 60.6 years, developed resistant hypertension within a median of 1.5 years from initial treatment [54]. Over 3.8 years median follow-up, cardiovascular events were 47% (33 to 62%) higher in those with resistant hypertension [54]. In 53,380 patients with hypertension and atherothrombotic disease in the International Reduction of Atherothrombosis for Continued Health (REACH) registry, the prevalence of resistant hypertension was 12.7% with 4.6% receiving 4 antihypertensive drugs and 1.9% receiving 5 or more antihypertensive drugs [55]. Those with resistant hypertension had at 4 years follow-up a higher incidence of cardiovascular death or myocardial infarction, or stroke and a higher incidence of hospitalization for congestive heart failure [55]. Of 614 patients with hypertension followed in a university cardiology or general medicine clinic, 40 patients (7%) were receiving 4 antihypertensive drugs, and 9 patients (1%) were receiving 5 antihypertensive drugs [52]. Of 14,684 patients with hypertension in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) randomized to chlorthalidone, amlodipine, or lisinopril, 9.6%, 11.4%, and 19.7%, respectively, had treatment-resistant hypertension [56]. The 2018 AHA Scientific Statement on resistant hypertension [57••] stated that the prevalence of treatment-resistant hypertension among 4158 US persons with hypertension taking antihypertensive drugs in the 2009 to 2014 National Health and Nutrition Examination Survey was 17.7% using the criteria for diagnosis stated in their 2008 statement [49••] and 19.7% using the criteria for diagnosis recommended by the 2017 ACC/AHA hypertension guidelines [1••]. Using the 2018 definition [1••, 57••], 3.2% of US adults taking chlorthalidone or indapamide and 9.0% taking spironolactone or eplerenone had resistant hypertension.

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 [1••, 23••]. 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 [1••, 50].

Patient nonadherence to both lifestyle measures and antihypertensive drug therapy is a major factor for treatment-resistant hypertension [58–63]. Methods for assessment of patient nonadherence to antihypertensive drug therapy include clinical impression, questioning of the patient, self-reports, pill counts, refill records, electronic bottle cap monitoring, and measuring concentrations of prescribed antihypertensive drugs in blood and urine [58–63]. The prevalence of nonadherence to antihypertensive drug therapy in patients with treatment-resistant hypertension in a pooled analysis of 24 studies was 31.2% [64••].

The prevalence of nonadherence to antihypertensive drug therapy in patients with treatment-resistant hypertension varies from 20.3 to 41.1% depending on the assessment method used [65, 66••]. In a study of 76 patients with treatment-resistant hypertension prescribed at least 4 antihypertensive drugs who had urine screening for nonadherence, 40 patients (53%) were found to be non-adherent to taking their antihypertensive drugs [63]. Of these 40 patients, 30% had complete adherence and 70% had incomplete adherence to their antihypertensive drugs [63]. An analysis of 62 trials showed that interventions that may improve adherence to self-administered antihypertensive drugs include policy interventions to reduce drug copayments or improve prescription drug coverage, system interventions to offer case management, and patient-level educational interventions with behavioral support [60].

Drug Treatment of Resistant Hypertension

Drug treatment of resistant hypertension should maximize diuretic therapy [1••, 25••]. Excess sodium and fluid retention is an important cause of resistant hypertension [49••, 66••, 67]. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve blood pressure control [1••, 68]. The beneficial effects of thiazide diuretics are reduced when the glomerular filtration rate is reduced to less than 40 cc/min [1••, 25••, 49••, 66••, 69]. These patients should be treated with a loop diuretic such as furosemide every 12 h [1••, 25••, 66••].

Increased activation of the renin-angiotensin-aldosterone system also plays an important role in the development of treatment-resistant hypertension [66••, 67, 70••]. Low-dose eplerenone has also been found to reduce aortic stiffness in patents with resistant hypertension [71]. The available data support the use of mineralocorticoid receptor antagonist such as spironolactone or eplerenone as the fourth antihypertensive drug to prescribe in patients with treatment-resistant hypertension [1••, 25••, 51, 66••, 67, 70••, 71, 72••, 73–77]. In the PATHWAY-2 trial, spironolactone was superior to placebo, bisoprolol, and doxazosin in the treatment of drug-resistant hypertension [74].

The patient should receive appropriate antihypertensive drugs for their comorbidities as discussed earlier in this review. For example, patients with coronary heart disease or heart failure should be treated with beta blockers. If additional antihypertensive drug therapy is indicated, centrally active alpha agonists such as clonidine or methyldopa or direct vasodilators such as hydralazine and minoxidil are further options [1••, 25••, 51, 77].

A pooled analysis of 14,094 patients treated for hypertension in the Systolic Blood Pressure Intervention Trial and the Action to Control Cardiovascular Risk in Diabetes trial showed that 2710 patients (19.2%) had resistant hypertension [78••]. The optimal systolic blood pressure goal for reducing the outcome of myocardial infarction, stroke, cardiovascular death, and heart failure and the same outcomes plus all-cause mortality in patients with and without resistant hypertension was less than 120 mmHg [78••].

Investigational Drugs for Resistant Hypertension

Investigational drugs for treatment of resistant hypertension include aldosterone synthase inhibitors, activators of the angiotensin-converting enzyme 2/angiotensin (1-7)/MAS receptor axis, centrally acting aminopeptidase inhibitors, vasopeptidase inhibitors, dual-acting angiotensin receptor-neprilysin inhibitors, dual-acting endothelin-converting enzyme-neprilysin inhibitors, natriuretic peptide receptor agonists, soluble epoxide hydrolase inhibitors, vasoactive intestinal peptide receptor agonists, intestinal Na^+/H^+ exchanger 3 inhibitors, and dopamine beta-hydroxylase inhibitors and are discussed elsewhere [70••, 79–81]. None of these investigational drugs has been approved in the USA for treatment of resistant hypertension.

Sacubitril/valsartan was demonstrated in a double-blind, randomized controlled trial to be superior to olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in 454 patients, mean age 67.7 years, with systolic hypertension and stiff arteries [82]. A meta-analysis of 11 randomized controlled trials in 6028 participants found that sacubitril/valsartan was more effective than angiotensin receptor antagonists for the management of patients with hypertension [81]. Sacubitril/valsartan merits investigation of treatment of resistant hypertension [82–84].

A phase 2, open-label, multicenter, dose-titrating study in 256 overweight or obese hypertensive patients (56% black or Hispanic) showed that firibastat, a first-in-class brain aminopeptidase A inhibitor, was effective in lowering blood pressure [85]. Firibastat should be investigated for the treatment of resistant hypertension.

Device Therapy for Drug-Resistant Hypertension

Device therapy under investigation for drug-resistant hypertension includes radiofrequency sympathetic denervation of the renal arteries, baroreflex activation therapy, carotid body ablation, a central arteriovenous anastomosis, carotid artery ablation, and neurovascular decompression [70••, 79, 86–93]. None of these devices has been approved for treatment of resistant hypertension in the USA. The novel device of greatest interest under investigation is sympathetic denervation of the renal arteries [86–91]. A sham-controlled trial of renal artery denervation in 535 patients with resistant hypertension showed no significant reduction in systolic blood pressure 6 months after renal artery denervation compared with the sham procedure [86]. This trial also did not show a benefit of renal artery denervation on reduction in ambulatory blood pressure in either the 24-h or day and night periods 6 months after the procedure compared with the sham procedure [87]. However, an analysis of 6 trials with 977 patients suggested a benefit in reducing blood pressure by this procedure [91]. The 2017 ACC/AHA hypertension guidelines do not recommend any device therapy for treatment of resistant hypertension [1••]. These guidelines state that 2 randomized controlled trials of renal sympathetic nerve ablation have been negative [1••, 86, 87, 94••].

Conclusion

Despite advances in this important area, resistant hypertension still presents significant challenges for appropriate diagnosis and management. White coat hypertension and pseudohypertension must be excluded before diagnosing resistant hypertension. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office blood pressure measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension. Secondary hypertension must be excluded and treated. Primary hypertension and hypertension associated with different comorbidities must be treated as recommended by the 2017 ACC/AHA hypertension guidelines. Factors contributing to resistant hypertension include obesity, a high-sodium, low-fiber diet, excess alcohol intake, physical inactivity, obstructive sleep apnea, use of cocaine, amphetamines,

nonsteroidal anti-inflammatory drugs, oral contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills), erythropoietin, licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy. Patient nonadherence to both lifestyle measures and antihypertensive drug therapy are major factors for treatment-resistant hypertension. 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. The beneficial effects of thiazide diuretics are reduced when the glomerular filtration rate is reduced to less than 40 mL/min/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 h. 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. Further research is needed on investigational drugs and device therapy for treating resistant hypertension. Clinical trials are indicated for the treatment of resistant hypertension by sacubitril/valsartan and also by firibastat.

Compliance with Ethical Standards

Conflict of Interest Dr. Aronow has no conflicts of interest to disclose. This author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or drugs or devices discussed in this manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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