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LEADING ARTICLE

Treatment of Resistant Hypertension in 2020

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Abstract

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 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. Primary hypertension and hypertension associated with different comorbidities must be treated as recommended by the 2017 American College of Cardiology/American Heart Association 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, non-steroidal 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 non-adherence to both lifestyle measures and antihypertensive drug therapy are major factors for treatment-resistant hypertension. Treatment 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/minute/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 hours 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

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

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Introduction

The 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) hypertension guidelines state that Stage 1 hypertension is a systolic blood pressure (SBP) of 130–139 mm Hg or a diastolic blood pressure (DBP) of 80–89 mm Hg [1]. Stage 2 hypertension is a SBP of≥140 mm Hg or a DBP of≥ 90 mm Hg. [1]. These hypertension guidelines recommend lifestyle measures plus BP lowering drugs for secondary prevention of recurrent cardiovascular disease events in patients who have clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average SBP of≥ 130 mm Hg or an average DBP of≥80 mm Hg. [1–3]. These guidelines recommend treatment with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease≥10 % [4] and an average SBP of≥ 130 mm Hg or an average DBP of≥80 mm Hg. [1,5]. These guidelines recommend treatment with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease of< 10 % [4] and an average SBP of≥140 mm Hg or an average DBP of≥ 90 mm Hg. [1, 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 patients with a BP of≥140/90 mm Hg or with a BP higher than 20/10 mm Hg above their BP target [1, 6]. White coat hypertension must be excluded before using antihypertensive drugs in treatment of patients with hypertension at low risk for atherosclerotic cardiovascular disease [1].

Suspect secondary hypertension 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 patient younger than 30 years or older than 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 patients, 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 BP should be reduced to< 130/80 mm Hg in patients with ischemic heart disease [1, 3, 8–13], in patients with heart failure with a reduced left ventricular ejection fraction (HFrEF) [1, 14], in patients with heart failure with a preserved left ventricular ejection fraction (HFpEF)[1, 14], in patients with chronic kidney disease[1, 15], in patients after renal transplantation [1], in patients with lacunar stroke [1, 16, 17], in patients with peripheral arterial disease[1, 2], in patients with diabetes mellitus[1, 18–21], in noninstitutionalized ambulatory community-dwelling patients older than 65 years of age [1, 8, 9], and for secondary stroke prevention [1, 22].

Treatment with lifestyle measures

Lifestyle modification should be used to treat 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 grams daily, smoking cessation, regular aerobic physical activity, avoidance of

excessive alcohol intake, avoidance of excessive caffeine, and avoidance of drugs which can increase BP, including nonsteroidal antiinflammatory drugs, glucocorticoids, and sympathomimetics, are recommended [1, 6, 23].

Antihypertensive drug treatment of primary hypertension

The 2017 ACC/AHA hypertension guidelines recommend for the treatment of white and other non-black patients younger than 60 years of age with primary hypertension that 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 necessary, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker should be given [1]. For white and other non-black patients 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 needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given [1]. For blacks 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 given [1].

Antihypertensive drug treatment 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 necessary, a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic or a calcium channel blocker should be given [1, 24–32]. If a fourth antihypertensive drug is indicated 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, 24, 25, 33]. Beta blockers which should be used 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, 27]. 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 given are carvedilol, metoprolol succinate, or bisoprolol [1, 24, 25, 34].

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 treatment regimen [25]. Aldosterone antagonists should be given 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, 24, 25, 35].

Patients with hypertension who have HFrEF 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-neprolysin inhibitor plus a diuretic and if needed with a mineralocorticoid receptor antagonist [1, 14, 24, 25, 27, 35]. Nondihydropyridine calcium channel blockers are contraindicated in the treatment of patients with HFrEF [1, 14, 24, 25, 36, 37]. Patients with hypertension and HFpEF 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, 38, 39].

Patientswith 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, 40]. 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 the usual first-line antihypertensive drugs [1]. If 3 antihypertensive drugs are needed, 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 [1,41]. 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 [1,42]. There is no evidence that any one class of antihpertensive drugs is better to treat hypertension in patients with peripheral arterial disease [1,42].

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 treatment [1,43]. Angiotensin-converting enzymes or angiotensin receptor blockers should be used for the treatment of diabetics with hypertension and persistent albuminuria [1,44]. Chlorthalidone was better than lisinopril, amlodipine, and doxazosin in decreasing cardiovascular disease and renal outcomes in nondiabetics with hypertension and the metabolic syndrome [1,45].

Beta blockers are the preferred antihypertensive drugs in patients with hypertension and thoracic aortic aneurysm [1,46]. 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 BP, ventricular rate, dP/dt, and stress on the aorta [46,47]. The SBP should be reduced to 100 to 120 mm Hg, and the ventricular rate should be decreased to less than 60 beats/minute by intravenous propranolol, metoprolol, labetalol, or esmolol [46,47].

Pregnant women with hypertension should not be treated 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 of resistant hypertension

Diagnose resistant hypertension if the 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 [1,48–50]. 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 [50]. Pseudohypertension and white coat hypertension must be excluded. before diagnosing resistant hypertension.

Pseudo hypertension in elderly patients is a falsely high SBP which results from markedly sclerotic arteries which do not collapse under the BP cuff [1,24]. Confirm pseudohypertension by measuring intra-arterial pressure [1,24]. White coat hypertension is diagnosed if patients have a persistently elevated office BP but a normal home BP or a normal 24-hour ambulatory blood pressure [1,24]. 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 [1,24,51].

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, non-steroidal 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 [1,24,50,52].

Patients with resistant hypertension also need screening for secondary causes of hypertension with treatment of these secondary causes [1,24]. 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 rresistant hypertension within a median of 1.5 years from initial treatment [53]. Over 3.8 years median follow-up, cardiovascular events were 47 % (33 % to 62 %)

higher in the patients who had resistant hypertension [53]. 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 [54]. The patients in this study 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 [54]. 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 [51]. Of 14.684 patients with hypertension randomized to amlodipine, chlorthalidone, or lisinopril, 11.4%, 9.6%, and 19.7%, respectively, had treatment-resistant hypertension [55]. The 2018 AHA Scientific Statement on resistant hypertension [56] stated that the prevalence of treatment-resistant hypertension among 4.158 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 [48] and 19.7% using the criteria for diagnosis recommended by the 2017 ACC/AHA hypertension guidelines [1]. Using the 2018 definition [1,56], 3.2% of US adults taking chlorthalidone or indapamide and 9.0% taking spironolactone or eplerenone had resistant hypertension.

Management of resistant hypertension includes improving compliance with use of medication, detection and therapy of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities [1,23]. If a fourth antihypertensive drug is necessary to control BP in patients treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the treatment regimen [1,49].

Patient non-adherence to both lifestyle measures and antihypertensive drug therapy is a major factor for treatment-resistant hypertension [57–62]. Methods for assessing patient non-adherence 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[57–62]. The prevalence of non-adherence to antihypertensive drug therapy in patients with treatment-resistant hypertension in a pooled analysis of 24 studies was 31.2% [63].

The prevalence of non-adherence to antihypertensive drug therapy in patients with treatment-resistant hypertension varies from 20.3% to 41.1% depending on the asessment method used [64]. In a study of 76 patients with treatment resistant hypertension prescribed at least 4 antihypertensive drugs who had urine screening for non-adherence, 40 patients (53%) were found to be non-adherent to taking their antihypertensive drugs [62]. Of these 40 patients, 30% had complete adherence and 70% had incomplete adherence to their antihyperensive drugs [62]. 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, systems interventions to offer case management, and patient-level educational interventions with behavioral support [59].

Antihypertensive drug therapy of resistant hypertension

Antihypertensive drug therapy of resistant hypertension should maximize diuretic therapy [1, 24] Excess sodium and fluid retention is an important cause of resistant hypertension [48, 65, 66]. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve BP control [1,67]. The beneficial effects of thiazide diuretics are decreased when the glomerular filtration rate is less than 40 cc/minute [1, 24, 48, 65, --68]. These patients should be treated with a loop diuretic such as furosemide every 12 hours [1, 24, 65].

Increased activation of the renin-angiotensin-aldosterone system also plays an important role in the development of treatment-resistant hypertension [65, 66, 69). Low dose eplerenone reduces aortic stiffness in patients with resistant hypertension [70]. The data available support the use of an mineralocorticoid receptor antagonist such as spironolactone or eplerenone as the fourth antihypertensive drug to use in patients with treatment-resistant hypertension [1, 24, 50, 65, 66, 69–76]. In the PATHWAY-2 trial, spironolacone was better than placebo, bisoprolol, and doxazosin in treating drug-resistant hypertension [73].

Patients should be treated with 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 drugs are needed, centrally active alpha agonists such as clonidine or methyldopa or direct vasodilators such as hydralazine and minoxidil are further options [1, 24, 50, 76].

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 found that 2.710 patients(19.2%) had resistant hypertension [77]. The optimal SBP goal for decreasing 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< 120 mm Hg [77].

Investigational drugs for treating resistant hypertension

Investigational drugs for treatment of resistant hypertension include aldosterone synthase inhibitors, activators of the angiotensin-converting enzyme2/ angiotensin (1–7)/ MAS receptor axis, centrally acting aminopeptidase inhibitors, vasopeptidase inhibitors, dual-acting angiotensin receptor-neprilysin inhibitors, dual-acting endothelin converting enzme-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 [69, 78–80]. None of these investigational drugs have been approved in the United States for treating resistant hypertension.

Sacubitril/valsartan was shown in a double-blind, randomized controlled trial to be better than olmesartan in lowering clinic and ambulatory cental aortic and brachial pressures in 454 patients, mean age 67.7 years, with systolic hypertension and stiff arteries [81]. A meta-analysis of 11 randomized controlled trial in 6.028 participants demonstrated that sacubitril/valsartan was better than angiotensin receptor antagonists for treating patients with hypertension [82]. Sacubitril/valsartan merits investigating therapy of resistant hypertension [81–83].

A phase 2, open-label, multicenter, dose-titrating study in 256 overweight or obese hypertensive patients (56% black or Hispanic) demonstrated that firibastat, a first-in-class brain aminopeptidase A inhibitor was effective in reducing BP [84]. Firibastat should also be investigated for treating resistant hypertension.

Device treatment of drug-resistant hypertension

Device therapy being investigated 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 [69, 78, 85–92]. None of these device therapies have been approved for treating resistant hypertension in the United States. The device therapy of greatest interest being investigated is sympathetic denervation of the renal arteries [85–90]. A sham-controlled trial of renal artery denervation in 535 patients with resistant hypertension found no significant reduction in SBP 6 months after renal artery denervation compared with the sham procedure [85]. This trial also did not find a benefit of renal artery denervation on reducing ambulatory BP in either the 24-hour or day and night periods 6 months after the procedure compared with the sham procedure [86]. However, an analysis of 6 trials with 977 patients suggested a benefit in lowering BP by this procedure [90]. The 2017 ACC/AHA hypertension guidelines do not recommend any device therapy for treating resistant hypertension [1]. These guidelines state that 2 randomized controlled trials of renal sympathetic nerve ablation have been negative [1, 85, 86, 93].

Conclusion

White coat hypertension and pseudohypertension must be excluded before diagnosing resistant hypertension. 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. 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, non-steroidal 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 non-adherence to both lifestyle measures and antihypertensive drug

therapy are major factors for treatment-resistant hypertension. Treating resistant hypertension includes improving compliance with use of medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treating 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 less when the glomerular filtration rate is lowered to less than 40 ml/minute/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 hours If a fourth antihypertensive drug is necessary to control BP in patients treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the drug treatment regimen. Further research is needed for investigational drugs and device therapy for treating resistant hypertension. Clinical trials should be performed investigating treatment of resistant hypertension by sacubitril/valsartan and also by firibastat.

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