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## Management of resistant hypertension – A review

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### Abstract

Hypertension is a worldwide health problem, which is a greatest attributor for the burden of cardiovascular diseases when BP remains resistant or refractory to therapeutic measures. Despite the advanced development in the antihypertensive therapy, the incidence of resistant hypertension is estimated to be less than 5% of the hypertensive population. Resistant hypertension is defined as blood pressure that remains above the goal in spite of the concurrent use of 3 antihypertensive agents of different classes. It increases the risk of stroke, congestive heart failure, myocardial infarction, renal failure and retinal haemorrhage. Resistant hypertension is always multifactorial in etiology. Pseudoresistance includes poor medication adherence or white coat hypertension. Secondary causes of hypertension are common with resistant hypertension which includes obstructive sleep apnea syndrome, primary aldosteronism, pheochromocytoma, cushing's syndrome, renal parenchymal disease, renal artery stenosis and diabetes. Successful management of resistant hypertension requires identification and reversal of life style factors, proper diagnosis and appropriate treatment of secondary causes of hypertension and use of effective multidrug regimens. The effective use of antihypertensive drugs reduces the occurrence of stroke by 30-40%, heart failure by 40-50%, coronary heart disease by 15%. The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to an acceptable level, with minimum inconvenience to the patient. Therefore the need for earlier and comprehensive intervention in the management of resistant hypertension must be emphasized in attaining this goal.

**Keywords:** Antihypertensive drugs, pseudoresistance, resistant hypertension.

### 1. Introduction

Hypertension is a major risk factor for coronary heart disease and ischemic as well as hemorrhagic stroke. The disease burden attributable to arterial hypertension is substantial, accounting for or contributing to 62% of all strokes and 49% of all cases of heart disease, culminating in an estimated 7.1 million deaths a year; equivalent to 13% of total worldwide deaths. [1] In addition to coronary heart diseases and stroke, complications of raised blood pressure include heart failure, peripheral vascular disease, renal impairment, retinal hemorrhage and visual impairment. Based on recent national data from 2011–2012, treatment of hypertension exceeded the Healthy People 2020 target goal of 69.5%. However, the control of hypertension has neither met the goal of the Healthy People 2020 (61.2% by 2020) nor the Million Hearts Initiative (65% by 2017). These results provide evidence for continued efforts to improve the management of hypertension in order to attain these goals. [2,3]

Only around half of all hypertensive patients are effectively managed on a single agent and studies, such as the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) suggest that 20% to 30% of all patients may be resistant to antihypertensive treatment.[4] According to the American Heart Association Professional Education Committee definition, a patient is “resistant” when they are unable to reach their blood pressure goal ( Table-1) despite optimal use of three or more anti-hypertensives, one of which must be a diuretic.[5] Most causes for poor control is well known, however a considerable percentage falls into a category known as ‘resistant hypertension’ of which pathophysiology and risk factors are not fully understood. [5] Studies have shown that older age, obesity and high sodium intake are strongly correlated with poor control of hypertension. [6, 7]

Patient factors such as compliance and knowledge and health care system factors like limitation of resources and lack of reminders of appointments also plays a major role in poor blood pressure control. [8-12] Managing resistant hypertension is difficult and involves expensive testing to look for underlying secondary causes. Furthermore, patients with uncontrolled blood pressure are more likely to have target organ damage and have higher cardiovascular risks than patients with well controlled blood pressure. Uncontrolled blood pressure affects patient’s mental, physical and social wellbeing, while also increasing the health care expenditure of a country. Exploring and enhancing our understanding of the causes of resistant hypertension paves way for more effective prevention and/ or treatment of the resistant hypertension.

**Table 1: JNC 7 classification of hypertension**

BP Classification	SBP, mm Hg		DBP, mm Hg
Normal	<120	and	< 80
Prehypertension	120 – 139	or	80-89
Stage 1 hypertension	140 – 159	or	90 – 99
Stage 2 hypertension	≥ 160	or	≥ 100

**BP** – blood pressure;

**DBP** – diastolic blood pressure;

**SBP** – Systolic blood pressure

**JNC7** – Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

## 2. Possible causes and Risk factors

The Prevalance of resistant hypertension is not uncommon. In a recent analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg.[13] The possible causes of refractoriness to Standard antihypertensive drug therapy should be evaluated properly. Resistant hypertension is almost multifactorial in etiology. Some of the factors like inaccurate measurement of blood pressure using poor blood pressure technique, poor adherence to antihypertensive therapy and white coat effect (when clinic blood pressure are persistently elevated while out-of-office values are normal or significantly lower) could give impression of treatment resistance but they are distinct from true treatment resistance. So they are said to be psuedo-resistance. This distinction is clinically important as patients with poorly controlled hypertension secondary to these causes need not be subjected to the evaluations and continued manipulations in treatment regimens that are undertaken for patients with true treatment resistance.

Therefore Successful treatment requires identification of causes and risk factors contributing to treatment resistance: diagnostic work up, proper evaluation and appropriate treatment with effective regimens. The risk factors and causes of resistant hypertension are in table-2.

**Table 2: Resistant hypertension: Risk factors and secondary causes**

	Common	Less common
Clinical risk factors	<ul style="list-style-type: none"> <li>• Pseudo – resistance (poor measurement technique, poor adherence, white – coat)</li> <li>• Older age</li> <li>• High baseline BP</li> <li>• Obesity</li> <li>• Excessive dietary salt ingestion</li> <li>• Chronic kidney disease</li> <li>• Diabetes</li> </ul>	<ul style="list-style-type: none"> <li>• Left ventricular hypertrophy</li> <li>• Female sex</li> </ul>
Medications interfering with BP control	<ul style="list-style-type: none"> <li>• Non – narcotic analgesics (NSAID, aspirin, COX2 Inhibitors)</li> <li>• Sympathomimetic agents</li> <li>• Stimulants</li> <li>• Alcohol</li> </ul>	<ul style="list-style-type: none"> <li>• Oral contraceptives</li> <li>• Cyclosporine</li> <li>• Erythropoietin</li> <li>• Herbal compounds and stimulants</li> </ul>
Secondary cause of resistant hypertension	<ul style="list-style-type: none"> <li>• Obstructive sleep apnea</li> <li>• Renal parenchymal disease</li> <li>• Renal artery stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Pheochromocytoma</li> <li>• Cushing’s disease</li> <li>• Hyperparathyroidism</li> <li>• Aortic coarctation</li> <li>• Takayasu’s disease</li> <li>• Intracranial tumor</li> </ul>

## 3. Evaluation and Investigations

Although the exact prevalence of resistant hypertension is unknown and it can be anticipated to increase, the evaluation of patients with resistant hypertension becomes most crucial in its management.Hence it should include confirming true treatment resistance, identification of causes contributing to treatment resistance, including secondary causes of hypertension and documentation of target-organ damage. Accurate assessment of treatment adherence and use of good BP measurement technique is required to exclude pseudo-resistance. In most cases, treatment resistance is multifactorial in etiology with obesity, excessive dietary sodium intake, obstructive sleep apnea, and CKD being particularly common factors. Target organ damage such as retinopathy, CDK and LVH supports a diagnosis of poorly controlled hypertension. [14, 15]

**3.1 Medical history:** The medical history should document duration, severity and progression of the hypertension; treatment adherence; response to prior medications, including adverse events; current medication use, including herbal and over-the counter medications; and symptoms of possible secondary causes of hypertension. Daytime sleepiness, loud snoring and witnessed apnea are suspicious for sleep apnea. A history of peripheral or coronary atherosclerotic disease increases the likelihood of renal artery stenosis. Labile hypertension in association with palpitations and/or diaphoresis, suggests the possibility of pheochromocytoma.

**3.2 Assessment of adherence:** Ultimately, adherence in a clinical setting can only be known by patient self-report.

Patients should be specifically asked, in a non-judgmental fashion, how successful they are in taking all of their prescribed doses, including discussion of adverse effects, costs, and dosing inconvenience, all of which can limit adherence. Family members will often provide more objective assessments of a patient’s adherence, but such input should generally be solicited in the presence of the patient. Electronic compliance monitoring also suggested nowadays to confirm the adherence to the treatment and helpful in rational therapeutic decisions of resistant hypertension. [16]

**3.3 BP measurement:** Use of good BP measurement technique is essential to the accurate diagnosis of resistant hypertension, including having the patient sit quietly in a chair with his or her back supported for 5 minutes before taking the measurement; use of the correct cuff size with the air bladder encircling at least 80% of the arm (the adult large cuff for the majority of patients); and supporting the arm at heart level during the cuff measurement. [17] A minimum of 2 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken to represent the patient’s BP. The BP should be measured carefully in both arms and the arm with the higher pressures generally should be used to make future measurements. Supine and upright BP should be measured during follow-up to detect orthostatic complications with treatment.

**3.4 Physical examination:** A fundoscopic examination should document the presence and severity of retinopathy. The presence of carotid, abdominal, or femoral bruits increases the possibility that renal artery stenosis exists. Diminished femoral pulses and/ or a discrepancy between arm and thigh BP suggest aortic coarctation or significant aorto-iliac disease. Cushing’s disease is suggested by abdominal striae, particularly if pigmented; moon facies; or prominent interscapular fat deposition.

**3.5 Ambulatory BP monitoring:** Documentation of a significant white-coat effect requires reliable assessment of out-of-office BP values. This is accomplished most objectively with the use of 24-hour ambulatory BP monitoring. Alternatively, work site measurements by trained health practitioners and/or out of- office assessments with use of manual or automated BP monitors can be relied on and Cuffs adequately sized for use with extremely obese patients. A significant white-coat effect should be suspected in patients with resistant hypertension in whom clinic BP measurements are consistently higher than out-of-office measurements; in patients who repetitively show signs of over treatment particularly orthostatic symptoms; and in patients with chronically high office BP values but an absence of target organ damage (LVH, retinopathy, CKD). In such cases, 24-hour ambulatory BP monitoring is recommended. A mean ambulatory daytime BP of >135/85 mm Hg is considered elevated.

**3.6 Biochemical evaluation:** Biochemical evaluation of the treatment-resistant hypertensive should include a routine

metabolic profile (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, and creatinine); urinalysis; and a paired, morning plasma aldosterone and plasma renin to screen for primary aldosteronism. [18] Even in the setting of ongoing antihypertensive treatment (excluding potassium-sparing diuretics), the aldosterone/renin ratio is an effective screening test for primary aldosteronism, having a high negative predictive value. A 24-hour urine collected during ingestion of the patient’s normal diet can be helpful in estimating dietary sodium and potassium intake, calculating creatinine clearance, and measuring aldosterone excretion. Measurement of 24-hour urinary metanephrines or plasma metanephrines is an effective screen for patients in whom pheochromocytoma is suspected.

**3.7 Non-invasive imaging:** Imaging for renal artery stenosis should be reserved for patients in whom there is an increased level of suspicion. This would include young patients, particularly women, whose presentation suggests the presence of fibromuscular dysplasia and older patients at risk of atherosclerotic disease. For patients with CKD, modalities that do not involve iodinated contrast may be preferred over CT angiography. Diagnostic renal arteriograms in the absence of suspicious non-invasive imaging are not recommended. Likewise, due to poor specificity, abdominal CT imaging is not recommended to screen for adrenal adenomas in the absence of biochemical confirmation of hormonally active tumors (hyperaldosteronism, pheochromocytoma, Cushing’s syndrome).

**4. Management**

Resistant hypertension is almost always multifactorial in etiology. Treatment (Table 3) is predicated on (i) identification and reversal of lifestyle factors contributing to treatment resistance (Table 4); (ii) accurate diagnosis and appropriate treatment of secondary causes of hypertension; and (iii) use of effective drugs combination.

**Table 3: Management strategies and principles of pharmacological therapy**

Strategies	Issues
Aggressive lifestyle changes	<ul style="list-style-type: none"> <li>• Assessment of adherence</li> <li>• Dietary salt restriction</li> <li>• Weight loss</li> <li>• Moderation / cessation of alcohol intake</li> <li>• Increased physical activity</li> <li>• Ingestion of high fibre, potassium and calcium containing diet</li> </ul>
Treatment of secondary causes	<ul style="list-style-type: none"> <li>• Treatment of obstructive sleep apnea</li> <li>• Renal artery stenosis management (angioplasty)</li> </ul>
Pharmacological treatment	<ul style="list-style-type: none"> <li>• Maximise diuretic therapy (e.g., chlorthalidone, thiazides)</li> <li>• Addition of mineralocorticoid receptor antagonist (e.g., spironolactone, amiloride, eplerenone)</li> <li>• Combine agents with different mechanisms of action</li> <li>• Use of loop diuretics in patients with chronic kidney disease</li> <li>• Refer to specialist</li> </ul>

**4.1 Maximize adherence:** Treatment adherence worsens with the use of an increasing number of pills, with increasing complexity of the dosing regimen, and increase in the cost as well adverse effects. Accordingly, prescribed regimens should be simplified as much as possible, including the use of a long-acting combination of products to reduce the number of prescribed pills and to allow for once-daily dosing. Adherence is also enhanced by more frequent clinic visits and by having patient’s record home BP measurements. Use of multidisciplinary treatment approach including nurse case managers, pharmacists, and nutritionists can improve treatment results. The objective monitoring of compliance using electronic devices may be a useful step in the management of resistant hypertension, as it enables physicians to take rational decision in the management.

**Table 4: Lifestyle Modification Recommendations**

Modification	Recommendation	AVG, SBP Reduction Range
Weight reduction	Maintain normal body weight (body mass index 18.5 – 24.9 kg / m <sup>2</sup> ).	5 – 20 mm Hg / 10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and low fat dairy products with reduced content of saturated and total fat.	8 - 14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to ≤ 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2 -84 mm Hg
Aerobic physical activity	Regular aerobic physical activity ( e.g., brisk walking ) at least 30 minutes per day, most days of the week	4 - 9 mm Hg
Moderation of alcohol consumption	Men: Limit to ≤ 2 drinks * per day. Women and lighter weight persons: limit to ≤ 1 drink * per day.	2 - 4 mm Hg
<ul style="list-style-type: none"> <li>• 1 drink – ½ oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz 80-proof whiskey). Effects are dose and time dependent.</li> </ul>		

**4.2 Non pharmacological treatment**

**4.2.1. Weight reduction:** A recent review of long-term weight loss studies indicated that a 10-kg weight loss is associated with a 6.0 mm Hg reduction in systolic and a 4.6mm Hg reduction in diastolic BP. [19] While difficult to achieve and even more difficult to maintain, weight loss should be encouraged in any patient with resistant hypertension who is either overweight or obese.

**4.2.2. Dietary salt restriction:** The benefit of dietary salt reduction is well documented in general hypertensive patients with observed reductions in systolic and diastolic BP of 5 to 10 and 2 to 6 mm Hg, respectively. Elderly patients tend to show larger benefit. Dietary salt reduction has not been specifically evaluated in patients with resistant hypertension. In an evaluation of patients whose BP was uncontrolled on a combination of an ACE inhibitor and hydrochlorothiazide a reduced-salt diet lowered systolic and diastolic BP at 1 month

follow-up by 9 and 8 mm Hg. [20] Accordingly, dietary salt restriction, ideally to less than 6 g salt/24-hour, should be recommended for all patients with resistant hypertension.

**4.2.3. Cessation of alcohol intake:** Whether by undoing negative physiological effects or improvements in medication adherence, cessation of heavy alcohol ingestion can significantly improve hypertension control. Daily intake of alcohol should be limited to no more than 2 drinks (1 ounce of ethanol) per day for most men and 1 drink per day for women or lighter-weight persons. [15] We would recommend complete cessation in patients with resistant hypertension.

**4.2.4. Increased physical activity:** In patients with severe hypertension (untreated systolic ≥180 or diastolic BP ≥110 mm Hg who received up to 3 antihypertensive agents to lower diastolic BP by 10 mm Hg and/or to <95 mm Hg), 16 weeks of an aerobic exercise regimen (stationary cycling 3 times a week) lowered diastolic BP by 5 mm Hg and systolic BP by 7 mm Hg. [21] In a meta-analysis that included studies of both normotensive and hypertensive cohorts, regular aerobic exercise produced average reductions of 4 mm Hg in systolic and 3 mm Hg in diastolic BP. [22] Based on these observed benefits, patients should be encouraged to exercise for a minimum of 30 minutes on most days of the week.

**4.2.5. Dietary interventions:** Ingestion of a diet rich in fruits and vegetables; high in low fat dairy products, potassium, magnesium, and calcium; and low in total saturated fats ( i.e., the Dietary Approaches to Stop Hypertension or DASH diet) reduced systolic and diastolic BP by 11.4 and 5.5 mm Hg more, respectively, than the control diet in hypertensive patients. [23] The benefit of ASH diet has not been separately evaluated in patients with resistant hypertension, but some degree of BP reduction seems likely. [24]

**4.3. Treatment of secondary causes of Hypertension:** When primary aldosteronism, pheochromocytoma, or Cushing’s disease is suspected or confirmed, referral to an appropriate specialist should be needed for an effective management.

**4.3.1. Treatment of obstructive sleep apnea:** Treatment of sleep apnea with continuous positive airway pressure (CPAP) likely improves BP control, although the benefit in CPAP intervention trials has been variable. In a well-controlled evaluation that included both normotensive and mildly hypertensive subjects, 9 weeks of CPAP use (5.5 hours per night) lowered 24-hour mean ambulatory systolic and diastolic BP by 10.3 and 9.5 mm Hg, respectively. [25]

**4.3.2. Treatment of renal artery stenosis:** Angioplasty of fibromuscular lesions almost always benefits and is often curative, of the associated hypertension and therefore is the recommended treatment of choice.[26] Whether endovascular revascularization is needed for most atherosclerotic lesions is controversial. In patients with either controlled BP or resistant hypertension, the relative benefit of intensive medical therapy versus angioplasty with stenting has not been clearly established. Poorly controlled hypertension imparts a

major level of cardiovascular risk, however, and endovascular angioplasty, with or without stenting, should be considered when drug therapy alone is unsuccessful.

#### 4.4. Pharmacological treatment

**4.4.1. Withdrawal of interfering medications:** Medications that may interfere with BP control, particularly NSAIDs, should be avoided or withdrawn in patients with resistant hypertension (Table 2). The acetaminophen may be preferable to other NSAIDs since it is less likely to worsen the blood pressure control. When initiating treatment with these agents, BP should be monitored closely while recognizing that adjustments to the antihypertensive regimen may become necessary.

**4.4.2. Diuretic therapy:** Evaluations of patients with resistant hypertension referred to specialty clinics have been consistent in finding that treatment resistance was in part related to a lack of, or underuse of, diuretic therapy. [18] It has been found that patients with resistant hypertension often had occult volume expansion underlying their treatment resistance. [27] BP control can be achieved through use of increased doses of diuretics. In most patients, use of a long-acting thiazide diuretic will be most effective. The JNC 8 panel strongly suggests thiazide type diuretic as initial therapy for the management of hypertension. Given the outcome benefit demonstrated with chlorthalidone and its superior efficacy compared with hydrochlorothiazide, chlorthalidone should be preferentially used in patients with resistant hypertension. In patients with underlying CKD (creatinine clearance <30 mL/min), loop diuretics may be necessary for effective volume and BP control. Furosemide is relatively short acting and usually requires at least twice-daily dosing. Alternatively, loop diuretics with a longer duration of action, such as torsemide, can be used.

**4.4.3. Combination therapy:** An abundance of studies demonstrate additive antihypertensive benefit by combining 2 agents of different classes. [18] This is particularly true of diuretics, which significantly improve BP control when used in combination with most if not all other classes of agents. Beyond studies of 2-drug combinations, there is little data assessing the efficacy of specific combinations of 3 or more drugs. Accordingly, recommendation of specific multi-drug combinations is largely empiric and/or anecdotal. Intuitively, it seems most appropriate to continue to combine agents of different mechanisms of action. In that regard, a triple drug regimen of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide diuretic is effective and generally well tolerated.

Although  $\beta$ -antagonists are indicated in the setting of coronary heart disease or congestive heart failure, combined  $\alpha$ - $\beta$ -antagonists, because of their dual combination of action, may be more effective antihypertensives. [28] Recent studies indicate an add-on antihypertensive benefit of aldosterone antagonists in patients uncontrolled on multidrug regimens. Centrally acting agents are effective

antihypertensive agents but have a higher incidence of adverse effects and lack outcome data. Lastly, potent vasodilators such as hydralazine or minoxidil can be very effective, particularly at higher doses, but adverse effects are common.

Ultimately, combinations of 3 or more drugs must be tailored on an individual basis taking into consideration prior benefit, history of adverse events contributing factors, including concomitant disease processes such as CKD or diabetes. Treatment recommendations in this setting cannot be overly standardized, particularly when going beyond 3 drugs. The widespread difficulty in controlling BP has led to a proliferation of treatment algorithms for prescription of antihypertensive agents as monotherapy and in combination. These algorithms rely primarily on the likely presence or absence of inappropriate volume expansion as suggested by suppressed renin levels.

Renin levels are recommended to be measured directly or presumed based on ethnicity and age. These algorithms have not been validated in large, diverse cohorts such that the recommendations are largely empiric. In addition, as suggested by the studies discussed above, patients with resistant hypertension typically have refractory volume expansion such that treatment recommendations dichotomized according to volume status are likely less relevant. Recent reports have suggested that the combined use of an ACE inhibitor and ARB or a dihydropyridine and non-dihydropyridine calcium channel blocker provides significant additional antihypertensive benefit compared with monotherapy with the different agents. [29, 30] These studies, however, have not generally used maximal doses of either of the combined agents, so it is not possible to know whether the additional BP reduction is really unique to the combination or simply a titration effect. The ONTARGET study reported that combination of ACE with ARB may be associated with greater hypotension and renal insufficiency.

**4.4.4. Mineralocorticoid Receptor Antagonists:** Consistent with high prevalence of primary aldosteronism in patients with resistant hypertension have been studies demonstrating that mineralocorticoid receptor antagonists provide significant antihypertensive benefit when added to existing multidrug regimens. Studies have reported that spironolactone lowered systolic and diastolic BP by 24 and 10 mm Hg, respectively, when added to the regimen of patients whose BP was uncontrolled with at least 2 medications. [31] That included an ACE inhibitor or ARB and diuretic. In a blinded comparison, amiloride 10 mg daily, spironolactone 25 mg daily, or a combination of both were used as add-on therapy in patients whose BP was uncontrolled on a 2-drug regimen consisting of a diuretic (a thiazide diuretic in 92% of the subjects and a loop diuretic in the remaining 8%) and a calcium channel blocker. The mean decreases in systolic and diastolic BP compared with placebo were, respectively, 12.2 and 4.8 mm Hg for amiloride, 7.3

and 3.3 mm Hg for spironolactone, and 14.1 and 5.1 mm Hg for the combination. Both spironolactone and amiloride are generally safe and well tolerated. The most common adverse effect of spironolactone is breast tenderness with or without breast enlargement in men. Hyperkalemia is uncommon with either agent, but it can occur, necessitating close monitoring. Risk of hyperkalemia is increased in older patients, patients with diabetes and/or CKD, or when added to ongoing treatment with ACE inhibitors, ARBs, and/or NSAIDs.

**4.4.5. Dosing:** A recent cross-sectional analysis of ambulatory BP control indicated that patients taking at least one of their hypertensive agents at bedtime had better 24-hour mean BP control and, in particular, lowers night-time systolic and diastolic BP values. This latter difference may be particularly relevant as recent studies have suggested that nocturnal BP levels better predict cardiovascular risk than do daytime values. It may be that twice-daily dosing of non-diuretic BP medications will improve control rates in patients with resistant hypertension. This potential benefit, however, would have to be reconciled with reductions in adherence that would likely occur with use of less convenient and potentially more expensive dosing regimens.

#### 4.5. JNC 8 Hypertension new guidelines

- In the patients 60 years of age or older who do not have diabetes or chronic kidney disease, the goal blood pressure level is now <150/90 mmHg.
- In patients 18 to 59 years of age without major comorbidities and in patients 60 years of age or older who have diabetes, chronic kidney disease, both conditions, the new goal blood pressure level is 130/90 mm Hg.
- First line and later line treatments should now be limited to 4 classes of medications- thiazide – type diuretics, calcium channel blockers (CCB), ACEIs and ARBS.
- Second – and third – line alternatives included higher doses or combinations of ACEIs, ARBs, thiazide – type diuretics, and CCBs
- Several medications are now designated as later – line alternatives, including the following:
  - Beta – blockers
  - Alpha – blockers
  - Alpha<sub>1</sub>-beta – blockers (eg, carvedilol)
  - Vasodilating beta – blockers (eg, nebivolol)
  - Central alpha<sub>2</sub> – adrenergic agonists (eg, clonidine)
  - Direct vasodilators (eg, hydralazine)
  - Loop diuretics (eg, furosemide)
  - Aldosterone antagonists (eg, spironolactone)
  - Peripherally acting adrenergic antagonists (eg, reserpine)
- When initiating therapy, patients of African descent without chronic kidney disease should use CCBs and thiazides instead of ACEIs
- Use of ACEIs and ARBs is recommended in all patients with chronic kidney disease regardless of either as first – line therapy or in addition to first – line therapy
- ACEIs and ARBs should not be used in the same patient simultaneously
- CCBs and thiazide – type diuretics should be used instead of ACEIs and ARBs in patients over the age of 75 with impaired kidney function due to the risk of hyperkalemia, increased creatinine, and further renal impairment.

## 5. Future Directions

Resistant hypertension is a specific subgroup that remains understudied. Experimental assessment of patients with resistant hypertension is complicated by associated high cardiovascular risk, which limits the safe withdrawal of medications and which restricts the types and duration of experimental interventions that can be used to explore proposed aetiologies. Studies are further limited by concomitant disease processes such as diabetes, CKD, sleep apnoea and atherosclerotic disease. These concurrent diseases and their treatments are difficult to systematically control for and confound interpretation of study results.

Even among patients with resistant hypertension, subgroups of patients with different aetiologies undoubtedly exist. As an extreme example, the young patient with combined systolic and diastolic resistant hypertension is undoubtedly different in terms of etiology, prognosis, and likely effective treatment than the elderly patient with severe, isolated, resistant systolic hypertension. Also likely different is the patient with true refractory hypertension, that is, whose BP is never controlled despite maximal medical therapy. The genetic assessments of patients with resistant hypertension are also limited. Some studies showed that a particular CYP3A5 allele (CYP3A5\*1) has been associated in African-American patients with higher systolic BP levels in normotensive participants and hypertension more resistant to treatment. Identification of genetic influences on resistance to current therapies might also lead to development of new therapeutic targets.

Electrical stimulation of the carotid sinus baroreceptor and catheter-based radio frequency renal denervation is another promising approach that currently is being studied to control blood pressure. Meaningful differentiation of these subgroups will likely speed identification of respective causes of treatment resistance and development of specific treatment strategies. The depth of knowledge is needed to better identify and treat patients with resistant hypertension. Efficacy assessments of specific multidrug regimens are needed to better guide therapy.

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