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**Review Article**

# Resistant hypertension: a review

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## ABSTRACT

Resistant hypertension is currently defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive medications, of which one is a diuretic. Several factors have been identified as contributors to resistant hypertension such as poor patient adherence, physician inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake, certain drugs and volume overload. Uncontrolled blood pressure is a considerable cardiovascular and neurological risk factor that can lead to possible end-organ consequences of untreated hypertension, including heart failure, stroke, ischemic heart disease and renal failure. A comprehensive history and physical examination are essential for pointing towards to an underlying diagnosis. A PubMed search was conducted for review articles and papers from 1955 to 2019 containing the keywords 'resistant hypertension', 'secondary hypertension', 'refractory hypertension', 'heart failure' and 'stroke', and the literature was compiled. Non-pharmacological measures chiefly include lifestyle modifications such as smoking cessation, reduction in alcohol intake, dietary sodium restriction, healthy eating plans, increased physical activity and weight loss. Among recommended drugs, spironolactone and beta blockers are the preferred fourth- and fifth-line drugs respectively, in patients unresponsive to ACE Inhibitors, calcium channel blockers as well as diuretics. Although most patients are well controlled on extended drug regimes, some develop refractory hypertension which does not even respond to the five-drug regimen. Interventional therapies such as renal denervation and carotid sinus stimulation have been developed for patients with refractory hypertension, but still require further research and follow up to ascertain their full potency and efficacy.

**Keywords:** Anti-hypertensive, Heart failure, Renal denervation, Resistant Hypertension, Stroke

## INTRODUCTION

Hypertension has become an extremely common presentation in the hospital setting today, and is presently one of the leading causes of cardiovascular and neurological morbidity and mortality. The latest European guidelines retain the previous definition of hypertension (i.e., BP >140/90 mm Hg) whereas the American guidelines have lowered the threshold to define hypertension to <130/80 mm Hg.[1,2] It is estimated that nearly 1.5 billion adults in the world will have hypertension in the decade ahead.[3] Early detection and treatment is important to prevent the possible end-organ consequences of untreated hypertension, which include heart failure, stroke, ischemic heart disease and renal failure.[4] Therefore, it becomes crucial to effectively diagnose and tackle this problem at the earliest, and reduce the ever-growing health burden on the community.

Some patients have difficulty achieving optimum blood pressure goals in spite of simultaneous use of several antihypertensive medications. Several terms have been used to describe this condition, but the term "resistant hypertension" has been most commonly used.[5] Resistant hypertension is currently defined as uncontrolled blood pressure despite the use of optimal doses of three anti-hypertensive medications, of which at least one is a diuretic.[6] Several factors have been identified as

contributors to resistant hypertension. Some of these important factors are poor patient compliance, physician inertia, inadequate doses or inappropriate combinations of anti-hypertensive drugs, excess alcohol intake, certain drugs and volume overload.[6-14] It is a relatively common phenomenon, with an estimated prevalence of 10-20% among treated hypertensive patients. Refractory hypertension is rare with a prevalence of about 5% of patients with uncontrolled resistant hypertension. It is defined as an uncontrolled blood pressure with the use of five or more anti-hypertensive medications, including a long-acting thiazide diuretic, such as chlorthalidone, and a mineralocorticoid receptor antagonist such as spironolactone.[15]

It is estimated that roughly one-tenth of hypertensive patients in westernized countries have resistant hypertension; higher rates seen in specialist centers as compared to primary and secondary centers.[15,16] Secondary hypertension represents another very important contributor to drug resistance (Tables 1 and 2).[5]

**Table 1: A general overview of the various conditions leading to secondary hypertension.[4,5,16]**

| S. no. | Causes |
|---|---|
| 1 | Endocrine disorders |
| 2 | Neurological disorders such as intracranial masses |
| 3 | Renal disorders such as chronic kidney disease |
| 4 | Stress |
| 5 | Drugs |
| 6 | Obstructive sleep apnea |
| 7 | Coarctation of aorta |

**Table 2: The various endocrinal causes of hypertension.[5]**

| S. no. | Endocrinal causes of secondary hypertension |
|---|---|
| 1 | Primary aldosteronism (Conn's syndrome) |
| 2 | Pheochromocytoma |
| 3 | Hyperthyroidism |
| 4 | Hypothyroidism |
| 5 | Cushing's syndrome |
| 6 | Acromegaly |
| 7 | Hyperparathyroidism |
| 8 | Carcinoid tumor |
| 9 | Congenital adrenal hyperplasia (CAH) |

## PREVALENCE AND RISK FACTORS

The prevalence of resistant hypertension shows a wide variation, with data from many clinical trials showing a relatively high prevalence in the general population (20-35%).[5-14] Higher prevalence is seen in patients with chronic kidney disease (CKD) or renal transplant patients (29%-56%), confirming the findings of previous studies that showed the prevalence of resistant hypertension to be almost three times higher among patients with CKD than the general hypertensive population.[17] The true prevalence of resistant hypertension is a bit challenging to measure due to the existence of 'pseudo-resistant' hypertension, which refers to poorly controlled disease that appears resistant but is actually attributable to other factors. The most common factors for apparent treatment resistance have been found to be either non-compliance to, or insufficient drug therapy.

Several lifestyle factors have been found to affect the resistance to anti-hypertensive treatment. Excessive dietary salt intake is a common contributor to resistant hypertension and acts by blunting the blood pressure reducing actions of most antihypertensive drugs, including diuretics and inhibitors of the renin-angiotensin system. Obesity also contributes to treatment resistance, and blood-pressure control has been found to be more difficult to achieve in obese hypertensive patients as compared to lean hypertensive patients. The factors implicated in the pathogenesis of obesity induced hypertension include Insulin resistance, sympathetic nervous system over-activity, sodium retention, and activation of the renin-angiotensin system. Heavy alcohol consumption is another important factor which has been shown to result in blood pressure elevation. In addition, blood pressure control might be more difficult in heavy drinkers due to poor adherence to anti-hypertensive medication.[6-14]

Some of the major non-pathological factors which are implicated in treatment resistant hypertension include poor patient compliance, short half-lives of prescribed drugs, faulty blood pressure measurement technique, 'white-coat' hypertension, unhealthy lifestyle practices (as mentioned above), and the use of medications that cause elevation of blood pressure (Table 3).

Table 4 gives an overview of the common causes of resistant hypertension and patient characteristics, according to the European society of cardiology (ESC) 2018 guidelines.[1]

**Table 3: An overview of the various drugs causing elevations in blood pressure.[4, 16]**

| S. no. | Drugs implicated in secondary hypertension |
|---|---|
| 1 | Non-steroidal anti-inflammatory drugs (NSAID) |
| 2 | Oral contraceptives (OCPs) |
| 3 | Tricyclic anti-depressants (TCAs) |
| 4 | Monoamine oxidase (MAO) inhibitors |
| 5 | Cyclosporine and tacrolimus |
| 6 | Cocaine |
| 7 | Sympathomimetic drugs (Epinephrine, nor-epinephrine, dopamine, amphetamine, ephedrine) |
| 8 | VEGF inhibitors |
| 9 | Erythropoietin (EPO) |
| 10 | Caffeine and alcohol |

**Table 4: An overview of the common causes of resistant hypertension and patient characteristics.[1, 18]**

| Characteristics of patients with resistant hypertension | Common causes of secondary hypertension | Drugs associated with secondary hypertension |
|---|---|---|
| **Ag>75 years and black population** | Chronic kidney disease | Oral contraceptives |
| **Obesity** | Atherosclerotic renovascular disease (Renal artery stenosis) | NSAIDs |
| **High sodium intake** | Primary hyper-aldosteronism | Tricyclic anti-depressants |
| **Co-morbidities such as CKD, atherosclerosis, diabetes, LVH, aortic stiffening.** | Obstructive sleep apnea | Monoamine oxidase (MAO) inhibitors |
| | Pheo-chromocytoma | Steroids |
| | Hyperthyroidism | Cyclosporine and tacrolimus |
| | Hyper-parathyroidism | Sympathomimetic drugs (Epinephrine, nor-epinephrine, dopamine, amphetamine, ephedrine) |
| | Cushing's disease | Cocaine |
| | Aortic coarctation | VEGF inhibitors |
| | Fibromuscular dysplasia | Erythropoietin |
| | | Caffeine and alcohol |

## CLINICAL FEATURES AND DIAGNOSIS

The patients usually present with headache, palpitations or chest pain but in few cases may be completely asymptomatic. End organ damage becomes highly likely in patients with prolonged uncontrolled blood pressure.[19] Possible end-organ consequences of untreated hypertension include ischemic heart disease, heart failure, stroke and renal failure.[4] Resistant hypertension is suspected in patients having persistently elevated blood pressure, which responds minimally to at least six months of therapy with three conventional anti-hypertensive agents.[20] Diagnosis is confirmed if the treatment is proven unsuccessful after completion of six months of treatment, the blood pressure is measured by proper technique and confounding factors such as pseudo-resistance have been ruled out.[4]

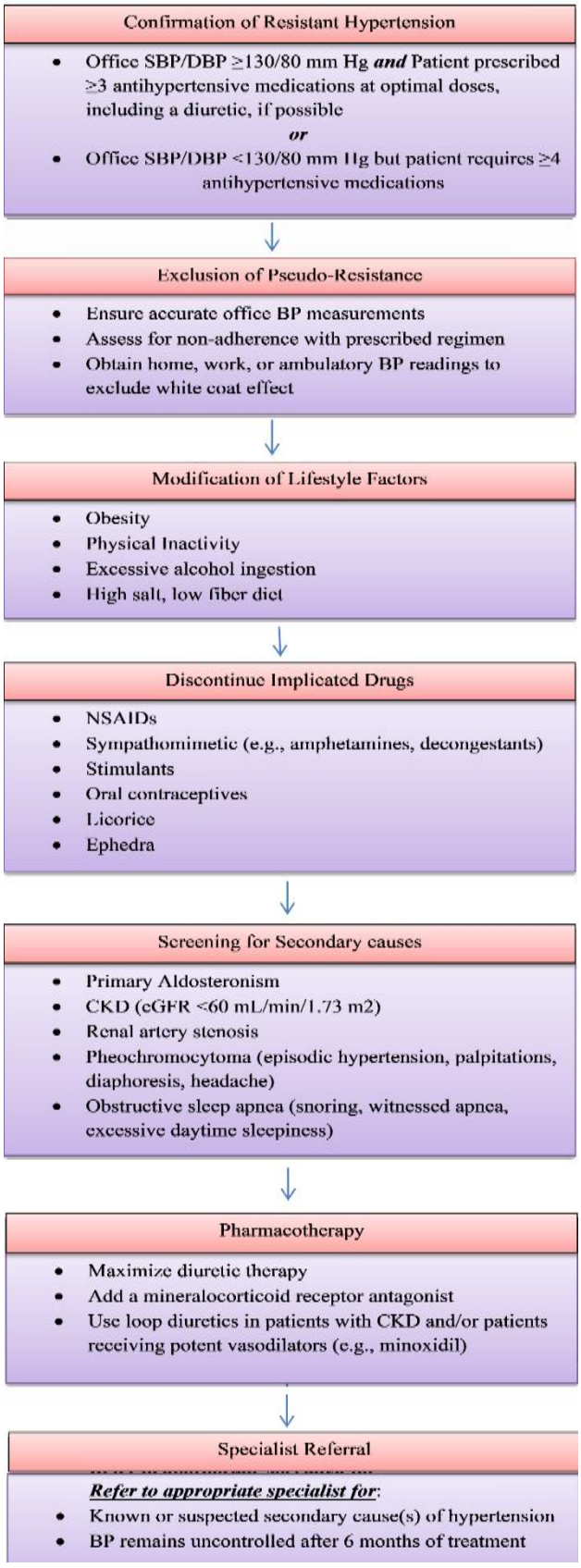


**Figure 1: American college of cardiology (ACC) 2017 guidelines for diagnosis, evaluation and treatment of resistant hypertension.[2]**

Patients with resistant hypertension require screening for secondary causes, (Table 1) such as obstructive sleep apnea, chronic kidney disease and primary hyper-aldosteronism.[21] A comprehensive history and physical examination is essential for pointing towards to an underlying diagnosis. The patient may have general tiredness and disturbance of sleep-wake cycle pathognomonic of obstructive sleep apnea/episodic palpitations with headaches suggestive of pheochromocytoma, while abdominal bruit might imply renal artery stenosis.[4] Many case reports have documented an asymptomatic presentation in these patients.

Patients with resistant hypertension should be investigated with kidney function tests such as serum creatinine levels, estimated glomerular filtration rate, urine dipstick analysis and a renal doppler ultrasound.[10,16] This is due to the high prevalence of chronic kidney disease in patients with resistant hypertension. 24-hour ambulatory blood pressure monitoring should also be undertaken to nullify the white coat effect as well as because the blood pressure readings from ambulatory monitoring correlate more closely with morbidity and mortality.[17,22,23] All patients with ongoing uncontrolled hypertension should also assessed for signs of end-organ compromise by means of yearly fundoscopy, electrocardiogram and urine dipstick analysis.[4]

The investigations for secondary causes of hypertension (Table 5) and a simple diagnostic algorithm as given by the American college of cardiology in 2017 for resistant hypertension has been depicted in Figure 1.[2]

**Table 5: Investigations for secondary causes of hypertension.[4,16,24]**

| Suspected secondary cause | Investigation |
|---|---|
| **Primary hyperaldosteronism** | Plasma aldosterone to renin ratio |
| **Thyroid dysfunction** | Thyroid function tests (T3, T4 and TSH) |
| **Pheochromocytoma** | 24-hour urinary catecholamine levels |
| | Plasma Metanephrines |
| **Cushing's syndrome** | Urinary cortisol |
| **Obstructive sleep apnea** | Polysomnography |
| **Renovascular disease** | Renal artery duplex scan |
| **Renal parenchymal disease** | Renal ultrasound scan |
| **Coarctation of aorta** | Cardiac ultrasound scan |

## MANAGEMENT

Treatment comprises of both non-pharmacological as well as pharmacological measures. Non-pharmacological measures chiefly include lifestyle modifications such as smoking cessation, reduction in alcohol intake, dietary sodium restriction, healthy eating plans, increased physical activity and weight loss. Lifestyle adjustments complement the efficacy of drug therapy and are often satisfactory in uncomplicated essential hypertension.[4] A brief overview of the treatment recommendations given by the ESC in 2018 has been shown below in Table 6.

**Table 6: European society of cardiology (ESC/ESH) 2018 recommendations for diagnosis and treatment of resistant hypertension.[1, 25]**

| Recommendations | | Class | Level of evidence |
|---|---|---|---|
| **Diagnosis** | It is recommended that hypertension be defined as resistant hypertension when: | **1** | **C** |
| | A Therapeutic regimen including optimal or best-tolerated doses of anti-hypertensives which include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, | | |
| | Inadequate control of BP has been confirmed by ABPM or HBPM; and | | |
| | Other causes of pseudo-resistant hypertension (e.g., poor medication adherence) and secondary hypertension have been ruled out. | | |
| **Treatment** | Recommended treatment of resistant hypertension is: | **1** | **B** |
| | Lifestyle modifications, especially dietary sodium restriction. | | |
| | Addition of low-dose spironolactone to the existing treatment regimen. | | |
| | Substitution by eplerenone, amiloride or higher doses of Thiazide/Thiazide-like or loop diuretics, if patient is intolerant to spironolactone. | | |
| | Or the addition of bisoprolol/ doxazosin. | | |

## NON-PHARMACOLOGICAL THERAPY

NSAID therapy needs to be terminated in patients with resistant hypertension, exacerbation of prior hypertension, or incident hypertension. Pain relief can be optimally achieved by acetaminophen in patients with osteoarthritis and pain of musculo-skeletal origin. In patients with chronic inflammatory arthritic diseases such as rheumatoid arthritis who respond better to anti-inflammatory agents, tramadol or nerve blocks might be of help, constituting effective alternatives to NSAIDs. In cases, however, where NSAIDs are indispensable, the lowest effective dose should be administered, since the existing data points towards dose-related effects of NSAIDs on blood pressure.[5]

Another class of drugs that are widely used and are capable of inducing hypertension are oral contraceptives.[26] Women using oral contraceptives have a much higher risk of developing hypertension compared to women that were not using such drugs ("pill"-induced hypertension). A study in hypertensive women revealed that those taking oral contraceptives had more severe hypertension and lower blood-pressure control rates than women using other contraceptive methods. However, withdrawal of oral contraceptives abolished this increased risk, underlining the need for close monitoring in women taking oral contraceptives.[5,27] Combined oral contraceptives (progestin and estradiol) were seen to be associated with higher and more frequent blood pressure elevations than progestin-only oral contraceptives. It can, therefore, be summarized that oral contraceptive may contribute to resistance in hypertensive women, but the underlying composition and type of oral contraceptive is also important.[5]

There has been a long-standing association between obstructive sleep apnea (OSA) and hypertension, which has been shown in epidemiological, longitudinal, and cross-sectional studies, as well as in studies from specialized clinics.[28] OSA in normotensive subjects has also been shown to be an important predictor of future development of hypertension.[5] Continuous positive airway pressure (CPAP) represents the treatment of choice for patients with OSA. In addition to decreasing the incidence of cardiovascular events in patients with OSA, CPAP also attenuates the blood pressure elevations during sleep.[29,30] However, the long-term effects of CPAP on blood pressure are not well documented.

Primary aldosteronism, which was initially described by Conn in 1955, is another common cause of resistant hypertension.[31] It is characterized by autonomous production of aldosterone by the adrenal glands and a subsequent decrease in renin levels though negative feedback. Aldosterone excess leads to hypertension, metabolic alkalosis, hypernatremia, and potassium loss resulting in hypokalemia. It can result from an aldosterone producing adenoma, bilateral adrenal hyperplasia or rare familial syndromes.[5] Medical therapy includes calcium channel blockers, mineralocorticoid antagonists such as spironolactone and eplerenone, angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs). Surgery is the treatment of choice for typical aldosteronomas, renin-responsive adenomas (RRAs), and primary adrenal hyperplasia (PAH). The present options are (1) Partial adrenalectomy, in which a wedge resection of the gland with the adenoma is performed along with aldosteronoma enucleation, and (2) Medulla-sparing adrenalectomy, in which the adrenal medullary tissue is retained, while removing the cortex.

Renovascular hypertension is another common form of secondary hypertension of atherosclerotic origin in the vast majority of cases. It is seen more frequently in older individuals, diabetics, smokers, and in patients with atherosclerotic lesions at other vascular beds.[32] Nearly one-fourth of patients who undergo cardiac catheterization are found to have higher than 70%renal artery stenosis (RAS).[33] On the other hand, Fibro-muscular dysplasia is a much less frequent cause of RAS (approximately 10%) than atherosclerosis; seen more frequently in younger females. Renovascular hypertension is quite common among patients with resistant hypertension, and the diagnosis can be confirmed by several methods which can detect RAS (duplex ultrasound, renal scintigraphy, and CT and MR angiography) with rather good sensitivity and specificity.[34,35] Treatment options include: Surgical treatment, Balloon angioplasty (with or without stenting), and conservative drug treatment. The surgical approaches (Percutaneous trans-luminal angioplasty (PTA), surgical revascularization and nephrectomy) are reserved for specific indications, while the remaining two approaches have been compared in the recently published ASTRAL study and the CORAL study, without any definite evidence of any one being superior over the other.[36] Pharmacological treatment includes Calcium channel blockers, ACE inhibitors and ARBs, diuretics, beta blockers and eplerenone.

For the Non-pathologic causes of resistant hypertension, treatment has to be individualized. Poor patient compliance has to be corrected and modified via proper guidance and counseling by the primary care physician. The patient needs to be made fully aware of the catastrophic effects of inadequate control of blood pressure. Anti-hypertensives need to be given in accordance with their half-lives and timings of peak effectivity. For example, amlodipine can be prescribed as once daily morning or evening dose for adequate and effective control whereas ACE inhibitors such as enalapril and ARBs such as telmisartan are seen to be more effective when given as a twice daily divided regimen. Better control of early morning and mid-day blood pressure spike can be achieved in young patients with bedtime dosing of anti-hypertensives instead of the usual morning dosing. Although much more effective, and also protective against risk of stroke and myocardial infarction, night time dosing is not advisable for elderly patients in view of the risk of late-night dizziness or fall leading to injury.

The physician should also be careful with his/her blood pressure measurement techniques as faulty techniques quite often lead to erroneous blood pressure readings and the patient becomes falsely labelled as a case of resistant hypertension. Many patients with 'white-coat' hypertension are also wrongly diagnosed as treatment resistant. This can be avoided by proper ambulatory blood pressure monitoring (ABPM) and re-assessment of the patient every 3-6 months to confirm the diagnosis. Blood pressure lowering medications are rarely required in these patients as most of them are quite well controlled by the initiation of a healthy lifestyle, diet modification with low salt intake and a high intake of fresh fruits, green vegetables and adequate fibre, proper exercise and weight loss, complete cessation of smoking and alcohol intake,

and the correction of hyperglycemia as well as dyslipidemia. Discontinuation of drugs/medications responsible for elevating blood pressure is strongly advised as has been discussed in detail above.

## PHARMACOLOGICAL THERAPY

The preferred initial drug choices are the same as for essential hypertension.[37] The guidelines of the national institute for health and clinical excellence (NICE) recommend initial treatment with an angiotensin-converting enzyme inhibitor (ACE inhibitor) in patients younger than 55 years of age, or a dihydropyridine calcium channel blocker (CCB) in patients older than 55 or black patients of any age.[38] Adequate monotherapy controls hypertension in almost 30% of cases, but the regimen can be modified by altering the dosage or adding an additional class of drug, if control is not optimized with a single drug.[48] Triple therapy must be reviewed before selecting further add-on therapy because optimal dosing and drug selection often normalizes the blood pressure in many patients.[4]

Among diuretics, superior blood pressure reduction is seen with chlorthalidone as compared to hydrochlorothiazide, especially in patients with resistant hypertension.[39-41] Chlorthalidone is a thiazide-like diuretic with a longer half-life and greater potency, and therefore a good initial step in controlling refractory hypertension is to switch patients from hydrochlorothiazide to chlorthalidone. The starting dose of chlorthalidone is 12.5 mg daily, taken in the morning, titrated if necessary to a maximum of 50 mg daily.[42] Indapamide may be used as an alternative in some elderly patients with renal insufficiency as chlorthalidone has a longer half-life and duration of action than indapamide, and is associated with a higher risk of renal impairment and hypokalaemia.[4,43] An appropriate starting dose is a 1.5 mg controlled-release tablet each morning. Patients with severe renal impairment (GFR below 30 ml/min) should be treated by a loop diuretic under specialist guidance.[20]

Spironolactone is recommended as the fourth antihypertensive drug.[20,44] Patients can be started on 25 mg per day, which can be increased gradually, preferably over several months, to a maximum of 100 mg daily if necessary.[4] The therapeutic effect of spironolactone is seen over two to three weeks and adverse effects of spironolactone usually appear at higher doses. These include gynecomastia and breast tenderness, menstrual irregularities and sexual dysfunction. Amiloride, a potassium-sparing diuretic, is a reasonable alternative to spironolactone, with a dose range from 2.5-10 mg daily. Careful monitoring is required during treatment with either spironolactone or amiloride in view of their propensity to retain potassium.[4] An increase in the thiazide dose should be considered if the blood potassium level exceeds 4.5 mmol/L.[45] Those patients who still have a persistently elevated blood pressure in spite of quadruple drug therapy, should be evaluated for secondary hypertension.

**Table 7: A list of the 'last resort' drug options for resistant hypertension.[4,44]**

| Drug | Remarks |
|---|---|
| **Alpha blockers** | Prazosin<br>-Initial dose 0.5 mg at bedtime, titrated to 1-10 mg twice daily as maintenance dose; few patients benefit from divided doses up to 40 mg per day.<br>-Beneficial in patients with benign prostatic hypertrophy (BPH) as well as lower urinary tract symptoms.<br>-May cause postural hypotension in some patients, caution advised in the elderly (risk of night-time dizziness and fall). |
| **Direct vasodilators** | Minoxidil<br>-Can be started at 5 mg once daily, with maintenance dose up to 40 mg twice daily (not to exceed 100 mg per day).<br>-Side effects include hypertrichosis, reflex tachycardia and fluid retention (contraindicated in women, caution advised in patients with coronary artery disease and heart failure respectively). |
| | Hydralazine<br>-Can be started with 10-12.5 mg every six hours, titrated to up to 200 mg in divided doses (some patients may require up to 300 mg per day).<br>-Safer than minoxidil, and preferred in females who present with hypertension refractory to any other drug treatment. |
| **Centrally acting sympatholytic** | Clonidine<br>-Initial dose is 0.05-0.1 mg twice daily, with maintenance doses up to 0.3 mg twice per day.<br>-Side effects may include dry mouth and dizziness/ sedation.<br>-Abrupt withdrawal may lead to rebound hypertension. |
| | Methyldopa<br>-Safe option in pregnant females.<br>-Initial dose is 125 mg twice daily, can be given up to 250 mg twice daily. |

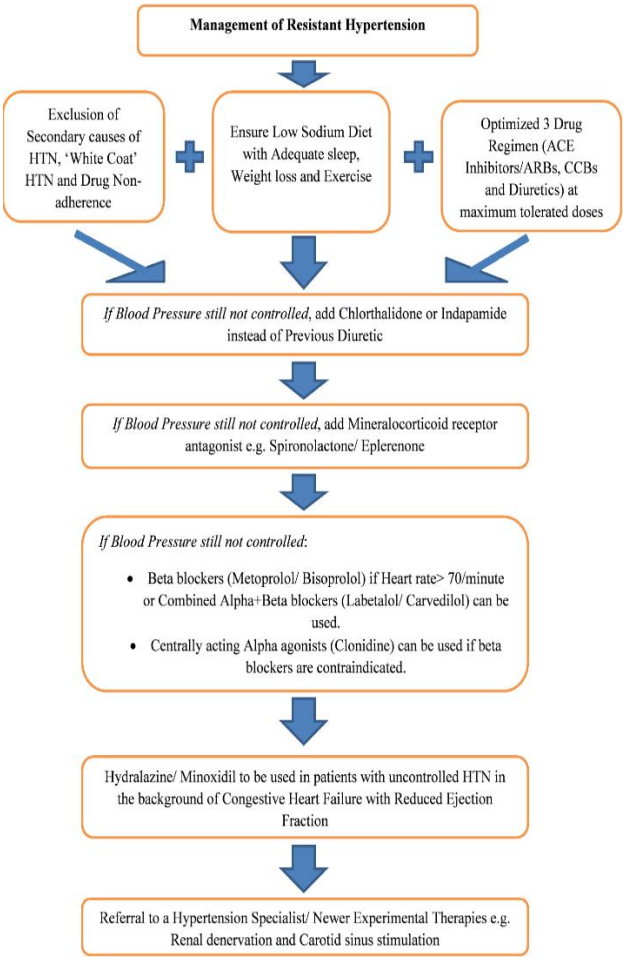


**Figure 2: Treatment of resistant hypertension (ACC 2017 recommendations).[2]**

Vasodilating beta blockers, such as carvedilol and labetalol, are a preferable next option as fifth-line drug therapy.[20] These agents offer less cardiovascular protection than other agents, and are associated with higher rates of stroke than with any of the CCBs, ACEIs or thiazides.[4,46] Carvedilol should be initiated at 12.5 mg daily, before increasing to a maximum dose of 50 mg per day. Labetalol is commenced initially at 100 mg twice daily and titrated to a maximum dose of 2400 mg daily; dose increments should not be faster than by 200 mg increments twice daily.[4] In some patients such as those with Diabetes, bronchial asthma, ischemic heart disease or peripheral vascular disease, traditional cardio-selective beta blockers like atenolol or metoprolol may instead be indicated.[4,20]

Some other 'last resort' drug options include alpha blockers, clonidine, methyldopa and direct vasodilators such as hydralazine or minoxidil. Although such agents are very efficacious in controlling blood pressure, their use must be moderated by patient co-morbidities and drug side-effects. These drugs have been summarized below in Table 7 and a general approach for the management of resistant hypertension (Figure 2).

## INTERVENTIONAL THERAPY

There are a certain percentage of refractory patients who remain hypertensive despite optimum medical therapy. Thus, some new therapies specifically designed for this subgroup of patients are now being assessed, namely renal sympathetic denervation and carotid sinus stimulation.[4]

In renal sympathetic denervation, the ablation of renal afferent and efferent nerves is done by a radiofrequency catheter through a minimally invasive, percutaneous intervention performed via femoral access. The thermal effect generated by the application of low-dose radiofrequency energy effectively disrupts large portions of nervous fibers located within the renal artery adventitia.[59] Normally, renin is released from the Juxtaglomerular apparatus via sympathetic stimulation, and causes vasoconstriction of the afferent renal vessels which leads to increased tubular reabsorption of sodium and elevated blood pressure. Renal denervation deactivates this sympathetic effect, causing decreased afferent vessel vasoconstriction and lowering of the blood pressure.[4] Furthermore, since other conditions, such as congestive heart failure, atrial fibrillation, sleep apnea, and diabetes mellitus are all associated with an overactive sympathetic drive, this procedure might also result in improvements in glycemic levels, sleep apnea, arrhythmias, and a decrease in oxidative stress.[47,48]

The other emerging intervention is carotid sinus stimulation, based on the theory that sustained electrical stimulation of carotid baroreceptors by an implantable device, should inhibit the sympathetic output.[4] A carotid sinus is a dilated area located at the bifurcation of the carotid artery, which contains numerous baroreceptors (stretch-sensitive mechanoreceptors) innervated by the carotid sinus nerve.[49] These baroreceptors can sense the endogenous blood pressure changes, and regulate the sympathetic tone via negative feedback towards the opposite direction.[50] These carotid baroreceptors are activated when the blood pressure is elevated, thereby transmitting inhibitory signals to the nuclei in the brain stem. This causes an attenuation of sympathetic tone and subsequently the blood pressure after a complex chain of signal reception and conversion process.[51]

According to recent studies, a major role of the baroreflex in the maintenance of sympathetic output has been suggested. It also participates in body fluid balance regulated by the kidney, as well as in the long-term regulation of blood pressure.[52] Several implantable devices for carotid baroreceptor stimulation have been developed, which have demonstrated good efficacy when used as an adjunct to regular anti-hypertensive drug treatment.[49, 53]

## CONCLUSION

Hypertension continues to pose an ever-growing challenge in the present clinical scenario. Resistant cases are much more common now, presenting with uncontrolled blood

pressure readings even on three anti-hypertensive agents which include at least one diuretic. Resistant hypertension needs to be correctly diagnosed and distinguished from pseudo-resistant hypertension which can be attributed to medication non-compliance, insufficient drug therapy, failure to adhere to lifestyle advice, poor measurement technique, 'white-coat' hypertension and the use of medications that interfere with blood pressure. Many of these patients have an underlying secondary cause which needs to be investigated promptly and treated accordingly to prevent further complications as well as end organ damage. Among recommended drugs, Spironolactone and vasodilatory beta blockers are the preferred 4$^{th}$-and 5$^{th}$-line drugs respectively, in patients unresponsive to ACE inhibitors, calcium channel blockers as well as diuretics. Although most patients are well controlled on extended drug regimes, some develop refractory hypertension which does not respond even to the 5-drug regimen. For these cases, drugs such as alpha blockers, clonidine, methyldopa, minoxidil and hydralazine may be employed under careful monitoring. Interventional therapies such as renal denervation and carotid sinus stimulation have also been developed for such patients with refractory hypertension, but still require further research and follow up to ascertain their full potency and efficacy over the long term.

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