Resistant Hypertension
Sanjeev Gulati*, Shrea Gulati**

Introduction
Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. The exact prevalence of resistant hypertension is unknown. In various studies its prevalence has been reported to be 20% to 30% of study participants.1

Case Definitions
It is important to clearly understand and differentiate resistant hypertension from others.

a. Resistant hypertension: Resistant hypertension is defined in the 2008 American Heart Association scientific statement as blood pressure that remains above goal in spite of concurrent use of three antihypertensive agents of different classes.1

b. Refractory hypertension: Some patients with resistant hypertension cannot be controlled, even with maximal medical therapy (four or more drugs with complementary mechanisms given at maximal tolerated doses) under the care of a hypertension specialist. Such patients are referred to as having refractory hypertension. Non responsiveness in such patients may be due to neurologic mechanisms (e.g., sympathetic overactivity).

c. Apparent resistant hypertension: Patients with apparent resistant hypertension have uncontrolled clinic blood pressure (i.e., greater than or equal to 140/90 mmHg) despite being prescribed three or more antihypertensive medications, or require prescriptions of four or more drugs to control their blood pressure.2,3 However, such patients may have pseudoresistant hypertension.

d. Pseudoresistant hypertension: Pseudoresistance refers to poorly controlled hypertension that appears resistant to treatment but is actually attributable to other factors.

However, before we label a patient as resistant hypertension it is important to ensure that we follow the standard guidelines for measuring blood pressure in our patients. These state that:
- Proper blood pressure measurement technique must be used
- The size of the blood pressure cuff should be double checked for accuracy
- The blood pressure readings must be recorded on 2 separate occasions

The measurement of blood pressure should be conducted after a patient has been seated quietly for 5 minutes and his or her arm should be at heart level. Then, using a properly calibrated and appropriately sized cuff, blood pressure should be measured. Too narrow or too short a cuff may give an erroneously high reading (usually more than 5–15 mmHg elevation in case of systolic pressure). The patient should be encouraged to avoid smoking before 15–30 min of the blood pressure measurement, because smoking may elevate systolic blood pressure up to 5–20 mmHg. It is also suggested to avoid drinking of coffee, although this may cause only a small elevation in blood pressure.

True resistant hypertension – Patients with true resistant hypertension are those who have uncontrolled clinic blood pressure despite being compliant with an antihypertensive regimen that includes three or more drugs (including a diuretic, and each at optimal doses i.e., 50 percent or more of the maximum recommended antihypertensive dose), and who also have uncontrolled blood pressure confirmed by 24-hour ambulatory blood pressure monitoring. Pressure is controlled with four or more medications should be considered to have resistant hypertension. Although arbitrary in regard to the number of medications required, resistant hypertension is thus defined in order to identify patients who are at high risk.
Inappropriate combinations of agents

Poor adherence to antihypertensive therapy. In one study, for example, 40 out of 76 patients with unexplained resistance to four or more antihypertensive drugs were determined to be either nonadherent or only partially adherent to therapy. Poor adherence to therapy is a common cause of apparent treatment resistance. Retrospective cohort studies suggest that ~0% of patients with newly diagnosed hypertension will discontinue treatment during the first year, and only 40% will continue with therapy during the first 5 or 10 years of follow-up.

Suboptimal antihypertensive therapy. In a large series of 468,877 patients seen in an outpatient clinic, 44,684 (9.5 percent) had apparent resistant hypertension. Of these, however, only 22,189 (half of those with apparent resistant hypertension) were prescribed optimal antihypertensive therapy (defined as a diuretic and two or more additional drugs, each at 50 percent or more of the maximal recommended antihypertensive dose). Two additional causes of pseudo-resistance are related to the antihypertensive regimen itself:

a. inappropriate combinations of agents
b. clinician inertia, a failure to change or increase dose regimens in order to obtain adequate treatment of poorly controlled hypertension despite awareness of the condition

Poor adherence to lifestyle and dietary approaches such as a reduced sodium intake. An increased salt intake is one of the commonest causes of apparent treatment resistance in our day to day practice.

5. White coat hypertension: White coat hypertension (also called isolated clinic or office hypertension) refers to patients who have office readings that average more than 140/90 mmHg and reliable out of office readings that average less than 140/90 mmHg. Having the BP in the office taken by a nurse or technician, rather than the physician, may minimise the white coat effect. White coat hypertension is present in as many as 20 to 30 percent of patients, possibly leading to an erroneous diagnosis of either hypertension or, in a patient with known hypertension, resistant disease. It is more common among patients with resistant hypertension.

**Prevalence**

The exact prevalence of resistant hypertension is unknown. This is in part due to the non-feasibility of conducting a large, forced titration study to answer this question appropriately. However, cross-sectional studies and hypertension outcome studies suggest that it is not uncommon. Data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2008 suggest that 12.8% of the antihypertensive-treated population meets the criteria for resistant hypertension; this number may rise to > 50% in patients with kidney diseases. In a study of 300 hypertensive chronic kidney disease (CKD) patients, 38% met the definition of resistant hypertension after 6 months of blood pressure management, with a higher prevalence of diabetic nephropathy and higher levels of proteinuria emerging among the patients with resistant hypertension. A number of factors may contribute to the pathogenesis and higher prevalence of resistant hypertension in CKD, including impaired sodium handling, increased activity of the renin-angiotensin-aldosterone (RAAS) and sympathetic systems, impaired nitric oxide synthesis and endothelium-mediated vasodilation, and increased arterial stiffness (Table 1).

**Genetics/Pharmacogenetics**

As resistant hypertension represents an extreme phenotype, it seems reasonable to predict that genetic factors may play a greater role in these patients than in the general hypertensive population. However, genetic studies of patients with resistant hypertension are limited. In one of the few studies of patients with resistant hypertension in Finland, 347 patients with resistant hypertension were screened for mutations of the β and γ subunits of the epithelial sodium channel (ENaC). Mutations of these subunits can cause Liddle’s syndrome, a rare monogenic form of hypertension. Compared with normotensive controls, 2 β ENaC

**Table 1: General characteristics of patients with resistant hypertension**

- Old age
- Female Sex
- Smoking
- Excessive Salt Consumption
- Chronic Consumption of Interfering Drugs (NSAIDs, steroids, etc)
- Obesity
- High baseline Blood Pressure (BP)
- Chronic Kidney Disease (CKD)
- Diabetes Mellitus
- Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.8%</td>
<td>Hypertension</td>
</tr>
<tr>
<td>38%</td>
<td>Resistant hypertension</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>CKD patients</td>
</tr>
</tbody>
</table>
and γ ENaC gene variants were significantly more prevalent in the patients with resistant hypertension. The presence of the gene variants was associated with increased urinary potassium excretion relative to plasma renin levels but was not related to baseline plasma aldosterone or plasma renin activity.

The CYP3A5 enzyme (11β-hydroxysteroid dehydrogenase type 2) plays an important role in the metabolism of cortisol and corticosterone, particularly in the kidney. A particular CYP3A5 allele (CYP3A5*1) has been associated in African-American patients with higher systolic blood pressure levels in normotensive participants and hypertension more resistant to treatment. Although based on a very small number of patients, these results are provocative and support additional attempts to identify genotypes that may relate to treatment resistance. Identification of genetic influences on resistance to current therapies might also lead to development of new therapeutic targets.

**Lifestyle Factors**

**Obesity**

Obesity is associated with more severe hypertension, a need for an increased number of antihypertensive medications, and an increased likelihood of never achieving blood pressure control. Mechanisms of obesity-induced hypertension are complex and not fully elucidated but include impaired sodium excretion, increased sympathetic nervous system activity, and activation of the renin-angiotensin-aldosterone system.

**Dietary Salt**

Excessive dietary sodium intake contributes to the development of resistant hypertension both through directly increasing blood pressure and by blunting the blood pressure-lowering effect of most classes of antihypertensive agents. In an analysis of patients referred to a university hypertension centre for resistant hypertension, average dietary salt ingestion based on 24-hour urinary sodium excretion exceeded 10 g a day.

**Alcohol**

Heavy alcohol intake is associated with both an increased risk of hypertension, as well as treatment-resistant hypertension. Prospectively, cessation of heavy alcohol ingestion by a small group of patients reduced 24-hour ambulatory systolic blood pressure by 7.2 mm Hg and diastolic blood pressure by 6.6 mm Hg while dropping the prevalence of hypertension from 42% to 12%.

**Drug-Related Causes**

Several classes of pharmacological agents can increase blood pressure and contribute to treatment resistance. Nonnarcotic analgesics, including nonsteroidal anti-inflammatory agents (NSAIDs), aspirin, and acetaminophen and, are probably the most common offending agents in terms of worsening blood pressure control. Meta-analyses of the effects of NSAIDs have indicated average increases in mean arterial pressure of approximately 5.0 mm Hg.

Other medication classes that may worsen blood pressure control include antituberculous therapy and sympathomimetic compounds such as decongestants and certain diet pills, amphetamine-like stimulants, modafinil, and oral contraceptives. Glucocorticoids, such as prednisone, induce sodium and fluid retention and can result in significant increases in blood pressure. Herbal preparations containing ephedra (or ma huang) have been associated with worsening blood pressure. Licorice, a common ingredient in oral tobacco products, can raise blood pressure by suppressing the metabolism of cortisol, resulting in increased stimulation of the mineralocorticoid receptor. In anaemic patients with CKD, erythropoietin therapy may increase blood pressure in both normotensive and hypertensive patients.

**Evaluation**

The evaluation of patients with resistant hypertension should be directed toward 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 blood pressure measurement technique is required to exclude pseudo-resistance. In most cases, treatment resistance is multifactorial in aetiology with obesity, excessive dietary sodium intake, obstructive sleep apnoea, and CKD being particularly common factors. Target-organ damage such as retinopathy, CKD, and LVH supports a diagnosis of poorly controlled hypertension and in the case of CKD will influence treatment in terms of classes of agents selected as well as establishing a blood pressure goal of < 140/90 mm Hg.

**ABPM and resistant hypertension**

Confirmation of true resistant hypertension should include the accurate measurement of office blood pressure, with attention to environment, body and arm position, appropriate cuffs, and the recommendation that multiple measurements be obtained at least 1 min apart and averaged out. Use of clinic blood pressure measurements has shortcomings. Hence for the diagnosis of Resistant hypertension it is absolutely essential that the clinician uses out-of-office monitoring including home and 24-h ambulatory blood pressure monitoring (ABPM).

ABPM, which involves readings taken at preset intervals throughout the day and night to capture the diurnal rhythm and variability of blood pressure
over 24 h, can help detect ‘white-coat’ hypertension, an elevation in blood pressure that occurs during clinic visits, with normal blood pressure in non-clinic settings and absence of target organ damage. The confirmation of white-coat hypertension, a common cause of pseudo-resistance, identifies patients who are relatively low risk and therefore unlikely to benefit from additional antihypertensive therapy. In one study of patients with apparent resistant hypertension, 28% were found to have normal awake ambulatory blood pressure when ABPM was used to complement office BP measurements.

Twenty-four-hour ABPM has, in fact, been shown to be the best method for estimating a patient’s hypertension-related cardiovascular risk. ABPM can identify patients with ‘masked’ hypertension, (elevated ambulatory blood pressure but normal clinic blood pressure), and has been associated with an increased risk of cardiovascular events. In a study of 466 patients with apparent responder hypertension based on clinic measurements, ambulatory BP monitoring found 27% to have ‘masked’ hypertension, which over a follow-up period of 5 years was associated with a relative risk of 2.28 (95% CI, 1.1–4.7; P < 0.05) of fatal and nonfatal cardiovascular events, compared with true responder hypertension. Moreover, ABPM provides clinicians with the ability to capture nighttime blood pressures and to identify the presence of a ‘non-dipping’ pattern, which is the diminution or reversal of the normal 10–20% nocturnal fall in blood pressure that occurs in both normotensive and hypertensive individuals. Several studies have shown that both of these are independent CVS risk factors. ABPM takes on greater importance in the CKD population with hypertension, as both non-dipping and masked hypertension are more common among patients with CKD. In the AASK Cohort Study, a remarkable 80% of the participants were non-dippers, and of the 377 participants with controlled clinic BP, 70% had masked hypertension. Higher nighttime BP and masked hypertension were associated with increased severity of target organ damage, including higher prevalence of left ventricular hypertrophy (LVH) and proteinuria and lower estimated GFR. Accordingly, in a large cohort of 436 hypertensive patients with CKD, ABPM has been shown to be a better predictor of renal and cardiovascular end points compared with office BP measurements, the components of ABPM.

As this study suggests, the prognostic role of ABPM is superior to that of office BP among CKD patients.

Investigations and Laboratory evaluation

Basic laboratory testing in patients with resistant hypertension includes measurement of serum electrolytes, glucose, and creatinine, and a urinalysis with estimation of proteinuria (e.g., urine albumin-to-creatinine ratio).

Screening for primary aldosteronism is also warranted since, in a large series of 1616 patients with resistant hypertension, 11 percent fulfilled criteria for primary aldosteronism, only 46 percent of whom were hypokalaemic. Screening for primary aldosteronism begins with a paired, morning measurement of the plasma aldosterone concentration (PAC) and plasma renin activity (PRA) to determine whether the patient has an elevated or high-normal PAC, suppressed PRA, and elevated PAC/PRA ratio. Certain antihypertensive drugs can alter the ratio, some of which should be discontinued prior to testing. If the ratio suggests primary aldosteronism, further evaluation is necessary to confirm the diagnosis. These issues are discussed in detail elsewhere.

In addition to blood testing, a 24-hour urine collection should be obtained on the patient’s usual diet for determination of sodium excretion, creatinine clearance, and aldosterone excretion. Urinary sodium excretion permits estimation of dietary sodium intake unless the patient has been recently (within the past two weeks) started on a diuretic or there has been a recent dose increase.

Patients with resistant hypertension should also be evaluated for phaeochromocytoma if they have suggestive manifestations such as episodic hypertension, palpitations and/or diaphoresis, or tremor. Noninvasive imaging — Most patients with resistant hypertension should undergo noninvasive imaging for renal artery stenosis. This is particularly important in patients with known atherosclerotic disease in other vascular beds, including peripheral artery disease, coronary artery disease or cerebrovascular disease, an abdominal bruit, a rise in serum creatinine after initiation of an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, or, onset of hypertension at a young age which could represent fibromuscular dysplasia.

Among patients with resistant hypertension who have none of these risk factors, we delay screening for renovascular disease until the remainder of the evaluation for resistant hypertension is negative. The preferred methods of screening are discussed elsewhere. Because of low specificity, imaging studies should not be performed to screen for adrenal adenomas in the absence of biochemical evidence of hormonally active tumours.

Treatment Recommendations

Resistant hypertension is almost always multifactorial in aetiology. Treatment is predicated on identification and reversal of lifestyle factors contributing to treatment resistance; accurate diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multidrug regimens. When primary aldosteronism,
phaeochromocytoma, or Cushing’s disease is suspected or confirmed, treatment will be specific for that particular disorder. Treatment of sleep apnoea with continuous positive airway pressure (CPAP) likely improves blood pressure control.

In chronic kidney disease, the approach to treatment of resistant hypertension should aim to address the multitude of factors that contribute to the pathogenesis of hypertension in this population, including impaired handling of sodium and volume expansion, increased activity of the renin-angiotensin-aldosterone system, enhanced sympathetic activity and reduced endothelium-dependent vasodilation. Particular focus should be lent to patterns of elevated blood pressure that have been found to be more prevalent in this population and to increase the risk of target organ damage, including elevated nighttime BP and the presence of non-dipping.

Lifestyle changes, including weight loss; regular exercise; ingestion of a high-fibre, low-fat, low-salt diet; and moderation of alcohol intake should be encouraged where appropriate. Potentially interfering substances should be withdrawn or down-titrated as clinically allowable.

Maximise Adherence

Treatment adherence worsens with the use of an increasing number of pills, with increasing complexity of the dosing regimen, and as out-of-pocket costs increase. 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 patients record home blood pressure measurements. Involving the patient by having him or her maintain a diary of home blood pressure values should improve follow-up and enhance medication adherence, while involvement of family members will likely enhance persistence with recommended lifestyle changes.

Night time dosing

A recent cross-sectional analysis of ambulatory blood pressure control indicated that patients taking at least one of their hypertensive agents at bedtime had better 24-hour mean blood pressure control and, in particular, lower nighttime systolic and diastolic blood pressure values.

Salt restriction (ndT)

Salt restriction has been shown to lower blood pressure in patients with and without hypertension. In the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial, sodium reduction from 100 to 50 mmol per day generally had twice the effect on blood pressure as reduction from 150 to 100 mmol per day. The effect of dietary sodium restriction on the degree of BP reduction appears to be particularly robust in patients with resistant hypertension. In a small, randomised crossover trial of patients with resistant hypertension, a low (50 mmol/day) compared with high (250 mmol/day) sodium diet decreased mean office systolic BP (SBP) by 22.7 mm Hg and led to significant reductions in daytime, nighttime and 24-h ambulatory blood pressure.

Thus, patients with resistant hypertension, as well as those with CKD, demonstrate particularly salt-sensitive hypertension. Patients with CKD have an impaired ability to effectively excrete sodium and will respond to a sodium load by raising blood pressure in order to re-establish salt balance; this ‘pressure natriuresis’ comes at the expense of hypertension-related target organ damage. In addition, dietary sodium intake has been shown to interact with the RAAS, particularly aldosterone, in both animal models and human studies, to mediate hypertension, vascular and tissue damage and kidney disease. In a study of patients with resistant hypertension and high 24-h urinary aldosterone, urinary protein excretion increased significantly with progressively greater salt intake, suggesting that aldosterone excess and high dietary sodium intake interact to increase proteinuria. Indeed, in a randomised, double-blind, placebo-controlled crossover study in proteinuric patients without diabetes, salt restriction itself exerted an antihypertensive and antiproteinuric effect and further enhanced the antiproteinuric effects of RAAS blockade to nearly the same magnitude as, and in an additive manner with, diuretics.

Diuretics

The salt-excreting handicap of CKD and resulting extracellular volume expansion also provides the basis for treating hypertensive CKD patients with diuretics. Studies of resistant hypertension suggest that, even in the absence of CKD, this group of patients manifest increased extracellular volume, as measured by brain-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP). Therefore, use of appropriate diuretics is a cornerstone of therapy in patients with CKD and resistant hypertension. Nonetheless, diuretics remain underutilised and underdosed, and a change in diuretic therapy may help a significant proportion of patients with resistant hypertension achieve BP goals. For example, while the major trials supporting the use of diuretic therapy used chlorthalidone at 25 mg/day, the weaker hydrochlorothiazide (HCTZ) at doses of 12.5–25 mg/day remains the most commonly prescribed antihypertensive medication worldwide. However, when evaluated with 24-h ambulatory BP monitoring, the antihypertensive efficacy of HCTZ at doses of 12.5–25 mg/day has been shown to be inferior to that of other commonly prescribed drug classes. Chlorthalidone is approximately twice as potent as HCTZ with a much longer duration of action (8–15 h for HCTZ compared with > 40 h for chlorthalidone).
In clinical studies using 24-h ABPM, chlorthalidone 25 mg/day results in greater reductions in 24-h mean SBP compared with HCTZ 50 mg/day, primarily due to its effect on reducing nighttime mean SBP. Therefore, strong consideration should be given to using chlorthalidone over HCTZ, especially given the growing importance of nocturnal blood pressure on cardiovascular outcomes and kidney disease progression in patients with CKD.

Thiazide diuretics are most effective in patients with a GFR > 50 mL/min/1.73 m², although chlorthalidone can be effective to a GFR of 30–40 mL/min/1.73 m² in the absence of severe hypoalbuminaemia. A loop diuretic is preferred for patients with advanced CKD (GFR < 30 mL/min). Typically, loop diuretics such as furosemide and bumetanide should be dosed at least twice daily given their short duration of action and the potential for intermittent natriuresis leading to a reactive increase in the RAAS (with ensuing sodium retention) if dosed once daily. The longer-acting torsemide can be dosed once or twice daily. Consideration should also be given to combining the loop diuretic with a diuretic that acts more distally in the nephron, such as a thiazide or a low-dose potassium-sparing diuretic.

Amiloride antagonises the epithelial sodium channel in the distal collecting duct of the kidney, thereby functioning as an indirect aldosterone antagonist. In a study of 38 patients with low-renin hypertension whose blood pressure was uncontrolled with multiple drugs, including a diuretic, substitution with the combination of amiloride 2.5/hydrochlorothiazide 25 mg daily for the prior diuretic lowered systolic and diastolic blood pressure by 31 and 15 mm Hg, respectively. In 26 patients, the amiloride/hydrochlorothiazide doses were doubled with an additional reduction in systolic and diastolic blood pressure of 11 and 4 mm Hg, respectively.

**Adequate RAAS blockade**

Targeting the RAAS with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) is a well-established therapeutic strategy to target hypertension, slow the progression of CKD and reduce morbidity and mortality in heart failure. However, many patients progress despite treatment, and clinical trials of ACE inhibitors and ARBs suggest that after an initial decline, plasma aldosterone levels will increase in 30–40% of patients over the long term, a phenomenon known as ‘aldosterone breakthrough’. Aldosterone breakthrough has been linked to adverse outcomes such as LVH, impaired exercise capacity, urinary albumin excretion and a more rapid decline in GFR.

One therapeutic option to target incomplete blockade of the RAAS is dual blockade with the combination of ACE inhibitors and ARBs, which has been shown to confer modest BP reductions of an average of 4/3 mm Hg compared with monotherapy as well as proteinuria reductions of 30 and 39% compared with monotherapy with ACE inhibitors and ARBs, respectively. However, improved cardiovascular and renal outcomes have not been consistently demonstrated despite these additional reductions in BP and proteinuria. An alternative strategy is to use ‘ultrahigh’ doses of ACE inhibitors or ARBs. Several small, short-term clinical studies in patients with hypertension and CKD have found significant incremental reductions in proteinuria after treatment with ARBs at higher than conventional doses, albeit without additional blood pressure changes.

Suppressing the RAAS with mineralocorticoid receptor blockers (MRBs), such as spironolactone and eplerenone, has gained renewed interest as a treatment for resistant hypertension in patients with and without CKD. Recent studies have found significantly higher aldosterone levels and an elevated aldosterone to renin ratio (ARR) in over a third of patients with resistant hypertension, despite persistent extracellular volume expansion. In this setting, MRBs have emerged as effective therapy for patients with resistant hypertension, with and without CKD. The strongest evidence for the efficacy of MRBs in resistant hypertension comes from two studies. In 2007, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed that fourth-line add-on therapy with spironolactone, at a median treatment duration of 1.3 years and a starting dose of 25 mg/day, resulted in a mean reduction in SBP of 21.9 mm Hg (95% CI: 20.8–23.0 mm Hg) and in diastolic BP of 9.5 mm Hg (95% CI: 9.0–10.1 mm Hg). Subsequently, the randomised, double-blind, placebo-controlled addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) trial demonstrated a mean decrease in daytime systolic ambulatory BP of 5.4 mm Hg (P = 0.02), as well as significant decreases in ABPM nighttime systolic (8.6 mm Hg, P = 0.01), 24-h ABPM systolic (9.8 mm Hg, P = 0.004) and office systolic BP values (6.5 mm Hg, P = 0.01), with spironolactone 25 mg/day at 8 weeks of therapy. These patients need to be monitored for hyperkalaemia. In a cohort of 46 patients with mean eGFR 56.5 ± 16.2 mL/min/1.73 m² who had spironolactone (25 mg/day) or eplerenone (50 mg/day) added to a stable antihypertensive regimen, including a maximally dosed RAAS blocker and an appropriately dosed diuretic, a baseline eGFR ≤ 45 mL/min/1.73 m² and a baseline serum potassium > 4.5 mEq/L were the strongest predictors of hyperkalaemia (defined as serum potassium > 5.5 mEq/L). With close monitoring of potassium, the use of MRBs in patients with early stage CKD, or with later stage CKD and a low baseline potassium level and/or concomitant use of diuretics,
they can potentially neutralise some of the adverse metabolic effects of diuretics. The alpha-blockers are effective in treating benign prostatic hypertrophy, and so can be a valuable part of hypertension treatment regimens in older men who have this condition.28

**Combination Therapy**

An abundance of studies demonstrate additive antihypertensive benefit by combining 2 agents of different classes. This is particularly true of thiazide diuretics, which significantly improve blood pressure control when used in combination with most if not all other classes of agents. In the Veterans Affairs Single Drug Therapy Cooperative Study, patients not controlled (diastolic blood pressure ≥ 90 mm Hg) on one randomly assigned antihypertensive medication (thiazide diuretic, ACE inhibitor, β-blocker, calcium channel blocker, α-blocker, or a centrally acting α agonist) were then randomised to one of the other medications. If diastolic blood pressure was still not controlled, the first medication was added back in to test the various 2-drug combinations: the combinations that included a thiazide diuretic were consistently more effective than combinations that did not include the diuretic.

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 multigang 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. This triple regimen can be accomplished with 2 pills with use of various fixed-dose combinations.

Although β-blockers are indicated in the setting of coronary heart disease or congestive heart failure, combined α-β-blockers, because of their dual combination of action, may be more effective antihypertensives, although head-to-head comparisons of maximal doses are lacking. 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. With minoxidil especially, reflexive increases in heart rate and fluid retention occur such that concomitant use of a β-blocker and a loop diuretic is generally necessary.

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, and patient financial limitations. Treatment recommendations in this setting cannot be overly standardised, particularly when going beyond 3 drugs.

**Newer drug therapy**

The antagonism of endothelin receptor is a newer approach for the treatment of hypertension using antihypertensive medications which is currently under evaluation. Among the several endothelin receptor antagonist, darusentan is a selective antagonist for type A endothelin receptors which causes vasoconstriction and proliferation of vascular smooth muscle]. But findings from other study failed to meet its beneficial effect on blood pressure reduction and the drug’s future remains uncertain. Atrasentan, another highly selective endothelin receptor antagonist exhibited blood pressure reduction while study conducted on 72 patients. Another interesting approach for the management of resistant hypertension is administration of nitric oxide donors. Small clinical study conducted on 6 patients with resistant hypertension reveals that the combination of nitrates with phosphodiesterase-5 inhibitors resulted in significant blood pressure reduction (Figure 1).

**Interventional management of resistant hypertension**

**Renal denervation**

Efferent sympathetic outflow to the kidney stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow; afferent signals from the kidney modulate central sympathetic outflow and contribute to neurogenic hypertension. Based on the evidence of the role of renal sympathetic nerves in various aspects of blood pressure control, a catheter based approach using radiofrequency energy to selectively target and disrupt the renal nerves has been developed.

Following observational safety and feasibility studies, the Simplicity HTN-2 Trial, a multicentre, prospective randomised trial, was performed in patients who had a baseline systolic blood pressure > 160 mm Hg (> 150 mm Hg for patients with type 2 diabetes) despite taking three or more antihypertensive drugs. There were no serious procedure related or device related complications and occurrence of adverse events did not differ between groups. There were no adverse effects on the kidney, and this was also the case for patients with impaired renal function. In summary, the available evidence indicates that catheter based renal denervation has a favourable safety profile and results in potentially substantial and sustained blood pressure reduction in patients with drug resistant hypertension. In pilot studies, no loss of antihypertensive response was evident with follow-up of 2 years. Effects on cardiovascular morbidity and mortality are currently unknown.

**Carotid baroreflex activation**

Another device based therapy of resistant hypertension is carotid baroreflex activation, in which stimulating electrodes are implanted in the perivascular space around the carotid sinuses. The Rheos Baroreflex Hypertension Therapy System enhances afferent nerve traffic from the baroreceptors to the cardiovascular control centres of the brain, which subsequently reduce sympathetic outflow and blood pressure. Initial results justify further development and investigation of baroreflex activation therapy.

**Prognosis**

The prognosis of patients with resistant hypertension compared with patients with more easily controlled hypertension has not been specifically evaluated. Presumably, prognosis is impaired as such patients typically present with a long-standing history of poorly controlled hypertension and commonly have associated cardiovascular risk factors such as diabetes, obstructive sleep apnoea, left ventricular hypertrophy (LVH), and/or CKD. The degree to which cardiovascular risk is reduced with treatment of resistant hypertension is unknown. The benefits of successful treatment, however, are likely substantial as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which demonstrated a 96% reduction in cardiovascular events over 18 months with use of triple antihypertensive regimens compared with placebo in patients with severe hypertension (diastolic blood pressure 115 to 129 mm Hg). How much of this benefit occurs with successful treatment of resistant hypertension is unknown.

**References**


