Resistant Hypertension: A Clinical Perspective

Rajeev Gupta

HYPERTENSION IN INDIA

In India cardiovascular diseases (CVD) are epidemic and the largest cause of deaths. The Million Death Study in India reported that in years 2000-2003 CVD’s caused 20% of the more than 10.5 million annual deaths. The absolute numbers of deaths (about 2.1 million) are highest in the world and significantly greater than USA and other large countries. Major CVD risk factors are as important in India as in other countries. Both INTERHEART and INTERSTROKE studies have reported that common risk factors are important. Population-based epidemiological studies have reported that all major risk factors especially smoking, obesity, hypertension, hypercholesterolemia and diabetes have increased by 2-5 times in the country over last 50 years. Hypertension is a major risk factor and recent studies have reported a high prevalence in both urban and rural areas. In urban areas the prevalence varies from 30%-45% in different regions (Figure 1). These findings are consistent with other developing countries in Asia and elsewhere where it has been reported that, at any one time, about half of all individuals have high blood pressure (BP). Epidemiological studies report that currently 70% of hypertension in India is stage I or mild hypertension diagnosed by systolic BP 140-159 and/or diastolic BP 90-99 mm Hg while rest of the subjects have stage II hypertension. These studies also show that there are more than 65 million hypertensive subjects in India with more than 20 million stage II hypertensives requiring aggressive therapies.

RESISTANT HYPERTENSION: DEFINITION AND EPIDEMIOLOGY

Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. American Heart Association has provided guidelines for proper evaluation and management of this condition. It is defined as BP that remains above goal (>140 and/or >90 mm Hg) in spite of concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose. 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 of having reversible causes of hypertension and patients who may benefit from special diagnostic and therapeutic considerations. Patients whose BP is controlled but require 4 or more medications to do so should also be considered resistant to treatment. Other definitions also exist.
The prevalence of resistant hypertension is unknown. Clinical trials data suggest that it is not rare involving perhaps 20% to 30% of study participants. Cross-sectional studies and hypertension outcome studies suggest, however, that it 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. In a cross-sectional analysis of Framingham Heart Study participants, only 48% of treated participants were controlled to <140/90 mm Hg and less than 40% of elderly participants (>75 years of age) were at a goal BP. Among higher-risk populations and, in particular, with application of the lower goal BP recommended in the JNC-7 report for patients with diabetes mellitus or chronic kidney disease (CKD), the proportion of uncontrolled patients is even higher. Of NHANES participants with CKD, only 37% were controlled to <130/80 mm Hg and only 25% of patients with diabetes were controlled to <130/85 mm Hg. In absence of any large data from India the exact prevalence of resistant hypertension is unknown. The status of hypertension awareness, treatment and control status is very low in India especially in rural subjects. In a nationwide study among women in different regions of the country a low level of awareness, treatment and control status was observed, more in rural areas (Figure 2). This suggests a significant prevalence of resistant hypertension as among other populations where control rates are low have high prevalence.

CAUSES AND RISK FACTORS
BP remains uncontrolled most often because of persistent elevations in systolic BP. In an analysis of Framingham study data, the strongest predictor of lack of BP control was older age, with participants >75 years being less than one fourth as likely to have systolic BP controlled compared with participants 60 years of age. The next strongest predictors of lack of systolic BP control were the presence of obesity. In terms of diastolic BP control, the strongest negative predictor was obesity, with BP being controlled about one third less often compared with lean participants. In a prospective analysis of Framingham participants, in addition to older age, higher baseline systolic BP was associated with increased risk of never reaching goals.

As resistant hypertension represents an extreme phenotype, it seems reasonable to predict that genetic factors may play a greater role than in the general hypertensive population. However, genetic assessments of patients with resistant hypertension are limited. 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 BP levels in normotensive participants and hypertension more resistant to treatment. 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. Apart from the genetic factors there are others that influence development of resistance (Table I).

PSEUDO-RESISTANCE
This is the most common form of resistance in clinical practice. It implies absence of true resistance to drugs and is due to either measurement errors, poor adherence to treatment or white-coat effect.

Poor BP measurement technique
Inaccurate measurement of BP can result in the appearance of treatment resistance. Two of the most common mistakes; (i) measuring the BP before letting the patient sit quietly and (ii) use of too small a cuff; will result in falsely high BP readings. Although the degree to which inaccurate measurement of BP results in falsely labelling patients as having uncontrolled hypertension is unknown, assessments of office BP measurement technique suggest that it is likely a common clinical problem.
Table I. Resistant hypertension: Risk factors and secondary causes

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
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<tbody>
<tr>
<td>Clinical risk factors</td>
<td></td>
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<tr>
<td>• Pseudo-resistance (poor measurement technique,</td>
<td>• Left ventricular hypertrophy</td>
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<tr>
<td>poor adherence, white-coat effect)</td>
<td>• Female sex</td>
</tr>
<tr>
<td>• Older age</td>
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<tr>
<td>• High baseline BP</td>
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<tr>
<td>• Obesity</td>
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<tr>
<td>• Excessive dietary salt ingestion</td>
<td></td>
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<tr>
<td>• Chronic kidney disease</td>
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<tr>
<td>• Diabetes</td>
<td></td>
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<tr>
<td>Medications interfering with BP control</td>
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<tr>
<td>• Non-narcotic analgesics (NSAIDs, aspirin, COX-2</td>
<td>• Oral contraceptives</td>
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<tr>
<td>inhibitors)</td>
<td>• Cyclosporine</td>
</tr>
<tr>
<td>• Sympathomimetic agents</td>
<td>• Erythropoietin</td>
</tr>
<tr>
<td>• stimulants</td>
<td>• Herbal compounds and stimulants</td>
</tr>
<tr>
<td>• Alcohol</td>
<td></td>
</tr>
<tr>
<td>Secondary causes of resistant hypertension</td>
<td></td>
</tr>
<tr>
<td>• Obstructive sleep apnea</td>
<td>• Phaeochromocytoma</td>
</tr>
<tr>
<td>• Renal parenchymal disease</td>
<td>• Cushing’s disease</td>
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<tr>
<td>• Primary aldosteronism</td>
<td>• Hyperparathyroidism</td>
</tr>
<tr>
<td>• Renal artery stenosis</td>
<td>• Aortic coarctation</td>
</tr>
<tr>
<td></td>
<td>• Takayasu’s disease</td>
</tr>
<tr>
<td></td>
<td>• Intracranial tumor</td>
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</table>

Poor adherence
Poor adherence to antihypertensive therapy is a major cause of lack of BP control. Retrospective analyses indicate that approximately 40% of patients with newly diagnosed hypertension will discontinue their antihypertensive medications during the first year of treatment. This may be a greater problem in Indian patients. During 5 to 10 years of follow-up, less than 40% of patients may persist with their prescribed antihypertensive treatment. While poor adherence is common at the primary care level, it may be less common among patients who are seen by specialists. In a retrospective analysis at a hypertension specialty clinic, it was estimated that poor adherence was a significant contributing factor to the lack of BP control in only 16% of evaluated patients. Lack of BP control is distinct from treatment resistance. For an antihypertensive regimen to have failed, it has to have been taken correctly. This distinction is clinically important as patients with poorly controlled hypertension secondary to lack of adherence need not be subjected to the evaluations and continued manipulations in treatment regimens that are undertaken for patients with true treatment resistance.

White-coat effect
Studies indicate that a significant white-coat effect (when clinic BP are persistently elevated while out-of-office values are significantly lower) is as common in patients with resistant hypertension as in the more general hypertensive population, with a prevalence in the range of 20% to 30%. Patients with resistant hypertension on basis of “white coat” resistance phenomenon manifest less severe target organ damage and appear to be at less cardiovascular risk compared with those patients with persistent high BP during ambulatory monitoring.

Fragmented health services
An important issue in India and many developing countries is lack of access to chronic care. Patients change their physicians at will and most primary and secondary physicians have no system to track patients'. This results in inappropriate care, poor lifestyle advise and changing pharmacological therapy with poor BP control.

LIFESTYLE FACTORS AND DRUGS

Obesity
Obesity is associated with more severe hypertension, a need for an increased number of antihypertensive medications, and an increased likelihood of never achieving BP control. As a consequence, obesity is a common feature of patients with resistant hypertension. Mechanisms of obesity-induced hypertension are complex and 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 BP and by blunting the BP lowering effect of most classes of antihypertensive agents. These effects tend to be more pronounced in typical salt-sensitive patients, including the elderly, African Americans and (possibly) South Asians and patients with CKD. Although excessive dietary sodium is fairly widespread, it has been specifically documented as being common in patients with resistant hypertension.

**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 reduced 24-hour ambulatory systolic BP by 7.2 mm Hg and diastolic BP 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 BP and contribute to treatment resistance (Table 1). Given their widespread use, nonnarcotic analgesics, including nonsteroidal antiinflammatory agents (NSAIDs), aspirin, and acetaminophen, are probably the most common offending agents in terms of worsening BP control. Meta-analyses of the effects of NSAIDs have indicated average increases in mean arterial pressure of approximately 5.0 mm Hg

Studies indicate that NSAIDs can blunt the BP-lowering effect of several antihypertensive medication classes, including diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers. Similar effects have been described with the selective cyclooxygenase-2 (COX-2) inhibitors. Other medication classes that may worsen BP control include sympathomimetic compounds such as decongestants and certain diet pills, amphetamine-like stimulants, modafinil and oral contraceptives. Glucocorticoids induce sodium and fluid retention and can result in significant increases in BP. Corticosteroids with the greatest mineralocorticoid effect (eg, cortisone, hydrocortisone) produce the greatest amount of fluid retention, but even agents without mineralocorticoid activity (eg, dexamethasone, triamcinolone, betamethasone) produce some fluid retention. Herbal preparations containing ephedra or strychnine and many Indian herbal preparations have been associated with worsening BP. Licorice, a common ingredient in oral tobacco products, can raise BP by suppressing the metabolism of cortisol, resulting in increased stimulation of the mineralocorticoid receptor.

**SECONDARY CAUSES**
Secondary causes of hypertension are common in patients with resistant hypertension although the overall prevalence is unknown. The likelihood of a readily definable secondary cause of hypertension is greater in older patients because of a greater prevalence of sleep apnea, renal parenchymal disease, renal artery stenosis, and primary aldosteronism. Uncommon secondary causes of hypertension include pheochromocytoma, Cushing’s syndrome, hyperparathyroidism, aortic coarctation, and intracranial tumors (Table I).

**Obstructive sleep apnea**
Untreated obstructive sleep apnea is strongly associated with hypertension and in normotensive persons predicts development of hypertension. Sleep apnea is particularly common in patients with resistant hypertension. In an evaluation of 41 consecutive patients (24 men, 17 women) with treatment-resistant hypertension, 83% were diagnosed with unsuspected sleep apnea based on an apnea-hypopnea index ≥10 events/h. Cross-sectional studies indicate that more severe the sleep apnea, less likely is BP controlled despite the use of an increasing number of medications. The mechanisms by which sleep apnea contributes to the development of hypertension have not been fully elucidated. A well-described effect is that the intermittent hypoxemia, and/or increased upper airway resistance associated with sleep apnea, induces a sustained increase in sympathetic activity. Sleep apnea has been associated with increases in reactive oxygen species.

**Renal parenchymal disease**
CKD is both a common cause and complication of poorly controlled hypertension. Population studies in USA indicate that 3% of the population have increased serum creatinine above 1.6 mg/dL, corresponding to more than 5.6 million of general population. In another cross-sectional study of patients with CKD being followed in nephrology clinics, less than 15% had their BP controlled to <130/80 mm Hg despite of the use on average of 3 different antihypertensive agents. Treatment resistance in patients with CKD is undoubtedly related in large part to increased sodium and fluid retention and consequential intravascular volume expansion.

**Renal artery stenosis**
Renovascular disease is a common finding in hypertensive patients undergoing cardiac catheterization, with more
than 20% of patients having unilateral or bilateral stenoses with obstruction 70%. Studies of treatment-resistant hypertension commonly reveal a high prevalence of previously unrecognized renovascular disease, particularly in older patient groups. The former series suggested that 12.7% of patients ≥ 50 years of age referred to a hypertension centre had a secondary cause of hypertension, the most common of which (35%) was renovascular disease. More than 90% of renal artery stenoses are atherosclerotic in origin. Bilateral renal artery stenoses should be suspected in patients with a history of “flash” or episodic pulmonary edema, especially when echocardiography indicates preserved systolic heart function. Renal artery stenosis can be difficult to identify with noninvasive studies. Duplex ultrasound, magnetic resonance angiography, renal scintigraphy, and computed tomography angiography have good test characteristics in published studies but the true positive and negative predictive value will vary both with the populations at risk and the level of expertise at each institution.

**Primary hyperaldosteronism**
Recent studies indicate that primary aldosteronism is a much more common cause of hypertension than had been demonstrated historically. In an evaluation of more than 600 patients with hypertension, the prevalence of primary hyperaldosteronism was found to be 6.1%. Primary aldosteronism is common in patients with resistant hypertension with a prevalence of approximately 20%.

**Pheochromocytoma**
Pheochromocytoma represents a small but important fraction of secondary causes of resistant hypertension. The prevalence of pheochromocytoma is 0.1% to 0.6% of hypertensives in a general ambulatory population. The exact prevalence of pheochromocytoma as a cause of resistant hypertension is unknown, but the literature is replete with case reports of malignant and difficult-to-control hypertension secondary to pheochromocytoma. Although the clinical presentation of pheochromocytoma is highly variable, approximately 95% of patients demonstrate hypertension and 50% have sustained hypertension. Furthermore, pheochromocytoma is characterized by increased BP variability which is an additional independent risk factor beyond increased BP itself for cardiovascular morbidity and mortality. The diagnosis of pheochromocytoma should be entertained in a hypertensive patient with a combination of headaches, palpitations, and sweating, typically occurring in an episodic fashion, with a diagnostic specificity of 90%. The best screening test for pheochromocytoma is plasma free metanephrines (normetanephrine and metanephrine), which carries a 99% sensitivity and an 89% specificity.

**Diabetes**
Diabetes and hypertension are commonly associated, particularly in patients with difficult-to-control hypertension. Clinical trials have indicated that in order to achieve the lower BP goal recommended for patients with diabetes, an average range of 2.8 to 4.2 antihypertensive medications will be needed. The degree to which insulin resistance directly contributes to the development of hypertension versus simply being associated with hypertension because of common underlying causes has not been determined.

**EVALUATION AND INVESTIGATIONS**
The evaluation of patients with resistant hypertension should be directed toward (i) confirming true treatment resistance, (ii) identification of causes contributing to treatment resistance, including secondary causes of hypertension, and (iii) documentation of target-organ damage. Accurate assessment of treatment adherence and use of good BP measurement technique is required to exclude pseudoresistance. In most cases, treatment resistance is multifactorial in etiology with obesity, excessive dietary sodium intake, obstructive sleep apnea, and CKD being particularly common.

**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.

**Assessment of adherence**
Ultimately, adherence in a clinical setting can only be known by patient self-report. Patients should be specifically asked, in a nonjudgmental 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.

**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. 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.

**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 aortoiliac disease. Cushing’s disease is suggested by abdominal striae, particularly if pigmented; moon facies; or prominent interscapular fat deposition.

**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. In the case of patient self-assessments, use of good BP technique with validation of the accuracy of readings is essential. Cuffs adequately sized for use with extremely obese patients are generally not available with ambulatory or home automated monitors. 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 overtreatment, 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.

**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. 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.

**Noninvasive 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. The preferred imaging modality will vary by institution, depending on the level of training and experience. 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 noninvasive 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).

**MANAGEMENT**

Resistant hypertension is almost always multifactorial in etiology. Treatment (Table II) is predicated on (i) identification and reversal of lifestyle factors contributing to treatment resistance; (ii) accurate diagnosis and appropriate treatment of secondary causes of hypertension; and (iii) use of effective multi-drug regimens.
Table II. Management strategies and principles of pharmacological therapy

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Issues</th>
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<tr>
<td>Aggressive lifestyle changes</td>
<td>• Assessment of adherence</td>
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<tr>
<td></td>
<td>• Dietary salt restriction</td>
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<tr>
<td></td>
<td>• Weight loss</td>
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<td></td>
<td>• Moderation / cessation of alcohol intake</td>
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<td></td>
<td>• Increased physical activity</td>
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<td></td>
<td>• Ingestion of high fibre, potassium and calcium containing diet</td>
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<tr>
<td>Treatment of secondary causes</td>
<td>• Treatment of obstructive sleep apnea</td>
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<tr>
<td></td>
<td>• Renal artery stenosis management (angioplasty)</td>
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<tr>
<td>Pharmacological treatment</td>
<td>• Maximise diuretic therapy (e.g., chlorthalidone, thiazides)</td>
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<td></td>
<td>• Addition of mineralocorticoid receptor antagonist (e.g., spironolactone, amiloride, eplerenone)</td>
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<td>• Combine agents with different mechanisms of action</td>
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<td></td>
<td>• Use of loop diuretics in patients with chronic kidney disease</td>
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<td></td>
<td>• Refer to specialist</td>
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</table>

Maximize adherence
Treatment adherence worsens with the use of an increasing number of pills, with increasing complexity of the dosing regimen, and as 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 BP measurements. Use of multidisciplinary treatment approach including nurse case managers, pharmacists, and nutritionists can improve treatment results. There are ongoing studies in India to test efficacy of such strategies using low-cost alternatives.

Weight loss
Weight loss, although not specifically evaluated in patients with resistant hypertension, has a clear benefit in terms of reducing BP and often allows for reduction in the number of prescribed medications. 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 4.6 mm Hg reduction in diastolic BP. 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.

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. Accordingly, dietary salt restriction, ideally to less than 6 g salt/24-hour, should be recommended for all patients with resistant hypertension.

Moderation/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. We would recommend complete cessation in patients with resistant hypertension.

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. 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. Based on these observed benefits, patients
should be encouraged to exercise for a minimum of 30 minutes on most days of the week.

**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 (ie, 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. The benefit of DASH diet has not been separately evaluated in patients with resistant hypertension, but some degree of BP reduction seems likely.

**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.

**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. 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.

**Withdrawal of interfering medications**
Medications that may interfere with BP control, particularly NSAIDs, should be avoided or withdrawn in patients with resistant hypertension (Table I). However, as this is often clinically difficult, the lowest effective dose should be used with subsequent down titration whenever possible. When initiating treatment with these agents, BP should be monitored closely while recognizing that adjustments to the antihypertensive regimen may become necessary.

**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. It has been found that patients with resistant hypertension often had occult volume expansion underlying their treatment resistance. 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. Given the outcome benefit demonstrated with chlorothalidone and its superior efficacy compared with hydrochlorothiazide, chlorothalidone 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.

**Combination therapy**
An abundance of studies demonstrate additive antihypertensive benefit by combining 2 agents of different classes. 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 multidrug 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. Use of British National Institute of Clinical

**ABCDE Algorithm in Hypertension**

<table>
<thead>
<tr>
<th>Younger &lt; 50 yrs</th>
<th>Older &gt; 50 yrs</th>
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<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 2</strong></td>
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<tr>
<td>A or B (if sympathetic hyperactivity)</td>
<td>A or B (if sympathetic hyperactivity) +C or D or both</td>
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<tr>
<td>Mono</td>
<td>Two</td>
</tr>
<tr>
<td>A and/or C</td>
<td>Add D</td>
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<tr>
<td>A and/or C</td>
<td>A and C, and/or D, add B or E</td>
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</table>

A-ACE inhibitors/angiotensin receptor blockers; B-beta blockers; C-calcium channel blockers; D-diuretics; E-extra drugs (spironolactone, central adrenergic agonists, direct vasodilators, alpha blockers, etc.)

**Fig.3: Hypertension management guidelines and drug combinations**
Excellence ABCD algorithm or our ABCDE modification\textsuperscript{10} can provide basic guidelines (Figure 3).

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. 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 lead 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. 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.

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\begin{tabular}{|c|c|c|}
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Agent & Titratable Dose & Maximal Dose \\
\hline
\(\beta\)-blocker & 20 to 40 mg daily & 40 mg daily \\
Dihydropyridine & 10 to 20 mg daily & 20 mg daily \\
Aldosterone & 2.5 mg daily & 25 mg daily \\
Spironolactone & 2.5 mg daily & 50 mg daily \\
\hline
\end{tabular}
\caption{Dosing Schedules for Antihypertensive Medications}
\end{table}

**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\textsuperscript{11}. 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. 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.

**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, lower 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 nondiuretic 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.

**FUTURE DIRECTIONS**

Resistant hypertension is a specific subgroup that remains understudied\textsuperscript{4}. 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. Meaningful differentiation of these subgroups will likely speed identification of respective causes of treatment resistance and development of specific treatment strategies. Much additional knowledge is needed to better identify and treat patients with resistant hypertension.

REFERENCES