Review Article

Resistant Hypertension: Detection, Evaluation, and Management

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ABSTRACT

Treatment resistant hypertension (RH) is an important clinical problem. Its prevalence in clinical practice ranges from 10-20%. It has been defined as failure to achieve target blood pressure (BP), usually >140/90 mmHg after taking 3 or more anti-hypertensive medicines, one of which is a diuretic, in appropriate dose. It also includes patients whose BP achieves target values on 4 or more antihypertensive medications. The diagnosis of RH requires confirmation of medication adherence and exclusion of white-coat effect. The importance of RH is due to the associated risk of adverse outcomes. Once antihypertensive medication adherence is confirmed and out-of-office BP recordings exclude a white-coat effect, evaluation includes identification of contributing lifestyle behaviours, identification of drugs interfering with BP medication effectiveness, screening for secondary hypertension including obstructive sleep apnoea, and assessment of target organ damage. Management of RH includes maximization of lifestyle interventions, use of long-acting thiazide-like diuretics (Chlorthalidone or Indapamide), addition of a mineralocorticoid receptor antagonist (Spironolactone or Eplerenone), and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP.

Key words: Hypertension management, Obstructive sleep apnea, Polytherapy, White coat hypertension.

INTRODUCTION

Hypertension is the world's leading risk factor for cardiovascular diseases (CVD), stroke, disability, and death. It is the most important non-communicable disease risk factor in India and important cause of mortality and morbidity.[1] Recent studies have reported high prevalence of this condition in both urban and rural populations in India.[2,3] Hypertension control rates are however low despite the fact that it can be managed in primary care by simple and inexpensive medicines. A meta-analysis reported that less than 20% of patients with hypertension in India have their blood pressure (BP) under control.[4] On the other end of the BP control spectrum are patients with hypertension who are not well controlled despite multiple medications, a condition known as resistant hypertension.[5]

Resistant hypertension: Resistant hypertension (RH) has been defined by American Heart Association (AHA) as above goal elevated BP (>140 and/or 90 mmHg) in a patient despite concurrent use of three antihypertensive drug classes commonly including a long acting calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and a diuretic.[5,6] The drugs should be administered at maximum or maximally tolerated daily doses.[6] Resistant hypertension also includes patients whose BP achieves target values on ≥ 4 antihypertensive medications.

European Society of Cardiology (ESC) 2018 Hypertension Guidelines have made more stringent definition while retaining AHA criteria.[7] Accordingly, it is defined when recommended treatment strategy fails to lower office BP to <140 mmHg and/or <90 mmHg, the control of BP is confirmed by ambulatory or home blood pressure measurement and good adherence is demonstrated. ESC recommends that BP control strategy should include lifestyle measures and treatment with optimal or best tolerated doses of three or more drugs, which should include a diuretic, typically an ACEI/ARB, and a CCB. Moreover, these guidelines recommend that pseudo-resistance and secondary causes should be excluded.

Prevalence and prognosis of resistant hypertension: The term apparent treatment RH (aTRH) is used when ≥1

of the following data elements are missing: medication dose, adherence, or out-of-office BP; thus, pseudo-resistance cannot be excluded. Among treated adults with hypertension, prevalent aTRH occurs in ≈12% to 15% of population-based and 15% to 18% of clinic-based reports.[6] The prevalence of aTRH estimated from selected population-based, clinic-based, and clinical trial-based reports done at different time period ranges from 9.4 to 40.4 percent.

In a meta-analysis, that included more than 3.4 million patients with hypertension in high- and middle income countries, Noubiap et al reported true resistant hypertension in 10.3%, apparent resistant hypertension in 14.7 % with greater prevalence of resistant hypertension among the elderly (12.3%) and in chronic kidney disease (22.9%). There are only limited and small studies from India and other South Asian countries that have determined prevalence of resistant hypertension using variable criteria. Prevalence of resistance has been reported in 10-20% patients with hypertension in secondary and tertiary level clinical practices.[8-10] In a recent study on prevalence of resistant hypertension in clinical practice in India (Jaipur Heart Watch), Gupta et al[11] reported prevalence of resistant hypertension using two definitions. According to the first definition, uncontrolled BP (>140/90 mmHg) using any three drug classes, one of which was a diuretic, was observed in 19.4% (95% confidence interval [CI] 18.0-20.8%) while according to second definition, uncontrolled BP with use of any 4 drugs was observed in 6.3% (CI 5.3-7.0%) (Figure 1).

Patients with RH have a 32% increased risk of developing end-stage renal disease, a 24% increased risk of an ischemic CVD event, a 46% increased risk of heart failure, a 14% increased risk of stroke, and a 6% increased risk of death.[6] Prospective studies using ambulatory BP measurement (ABPM) have suggested an almost 2-fold increased risk of CVD events in patients with true RH. In the REGARDS study (Reasons for Geographic and Racial Differences in Stroke), uncontrolled RH was associated with a 2-fold increased risk of coronary heart disease compared with controlled RH.[12] In another study of >118,000 treated hypertensive adults, including >40,000 individuals with RH and 460,000 observation-years, BP control was associated with significantly lower rates of incident stroke and coronary heart disease with no difference in rates of incident heart failure.[6] BP control reduced the risk of incident stroke, coronary heart disease, or heart failure by 13% among those with RH compared with a 31% lower risk of these outcomes among patients without resistant hypertension.[6]

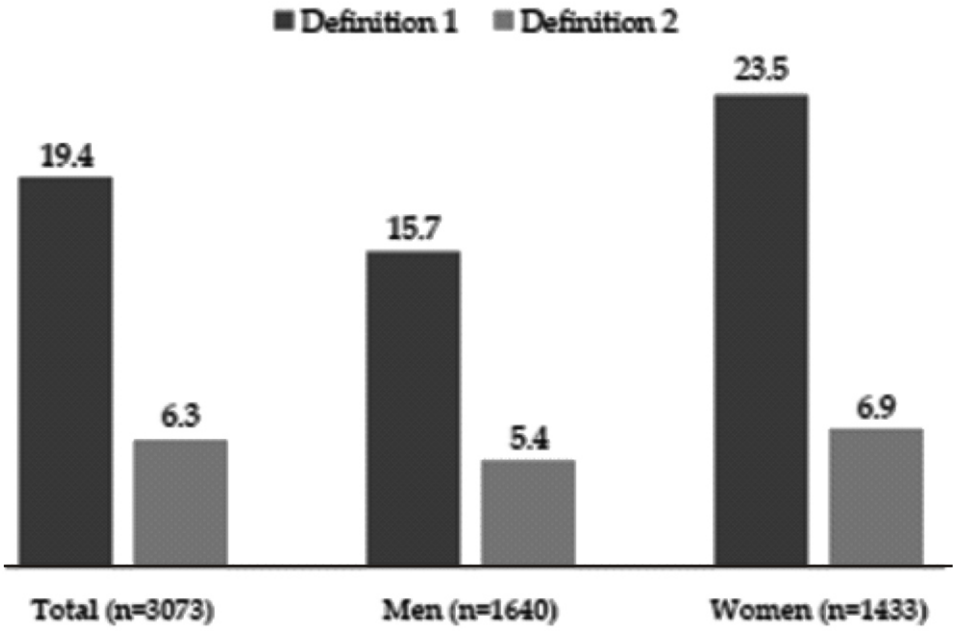

Figure 1: Prevalence of resistant hypertension in an Indian secondary care practice.
Prevalence was defined using 2 definitions: first was use of 3 or more drugs including a diuretic and second was use of any 4 drugs.

RISK FACTORS FOR RESISTANT HYPERTENSION

Patient Characteristics: AHA guidelines have reported that important demographic correlates of RH are black race (African Americans), older age, and male sex.[6] Associated comorbidities include obesity, left ventricular hypertrophy, albuminuria, diabetes mellitus, CKD, higher Framingham10-year risk score, and obstructive sleep apnoea (OSA).[6] It has been observed that very high proportions (60-80%) of individuals with RH have sleep apnea.[13] The normal nocturnal decline in BP is also attenuated in a high proportion (43-65%) of individuals with RH. This is a marker of sympathetic overactivity. Associated metabolic derangements, including hyperuricemia, aldosterone excess, and suppressed circulating renin levels are seen in about 60% patients.[6]

Medication Non-adherence: The term adherence is defined as remaining attached (to the medication regimen) and medication adherence is an important determinant of hypertension control.[6-8] Only 1 in 5 patients has sufficiently high adherence to achieve the benefits observed in clinical trials. Adequate adherence is defined as taking at least 80% of doses, although the scientific basis for this cut off is unclear.

Identification of patients with inadequate adherence among those with aTRH will avoid unnecessary and potentially harmful treatment intensification and allow implementation of strategies to improve adherence and more cost-effective allocation of health resources. Clinician assessment of adherence is poor.[6,7] Clinician impression and techniques such as pill count often are inaccurate. There is no gold standard for measuring adherence. Indirect methods such as pill count, self-report, and prescription refill data are simple, inexpensive, and widely used.[7] However, they can easily be manipulated to overestimate adherence. A direct method such as urine or blood measurement of drug or metabolites is considered more robust but is relatively expensive, of limited availability, and does not perfectly reflect level of adherence. All methods have limitations and inaccurate assessment of adherence should involve a combination of approaches.

No single intervention is uniquely effective, and a sustained approach using multiple strategies, including health system solutions and those that target the individual patient's barriers to adherence, is likely to be most effective. Key recommendations include using visual, interactive education and providing a medication list or pictorial medication schedule. Another approach, the teach back method, offers clinicians a nonthreatening way to confirm whether patients understand what has been explained to them. If a patient understands, he/she is able to "teach back" the information accurately.

Improper BP Measurement Technique: Proper BP measurement technique entails: (1) preparing the individual by emptying a full urinary bladder and then sitting with legs uncrossed and back, arm, and feet supported in a quiet room, ideally 5 minutes before the first reading is obtained; (2) choosing a BP cuff with a bladder length of at least 80% and width of at least 40% of the arm circumference; (3) placing the cuff directly on the skin of the upper arm at the level of the heart on the supported arm; and (4) obtaining a minimum of 2 readings 1 minute apart.[14]

White Coat Effect: The white-coat effect has been attributed to an alerting reflex triggered by the healthcare provider or the clinic environment that activates the sympathetic nervous system. A clinically significant white-coat effect may be present in 28% to 39% of individuals with aTRH by office BP measurement. BP measurement by automated office BP attenuates the white-coat effect.[7,14]

Treatment Inertia: Suboptimal antihypertensive therapy accounts for a large subset of patients not achieving BP targets. Overcoming clinician treatment inertia can be accomplished through an integrated health system model of care. Identifying patients with hypertension, standardizing BP measurements, and using a stepwise treatment algorithm have led to an increase in BP control rates from 54% in 2004 to 84% in 2010 in the Kaiser Permanente Southern California health system. Multipronged strategies with interventions at health system level, healthcare level, and patient level have been suggested for India.[15]

Obesity: Visceral adiposity in particular plays a fundamental role in causing high BP through enhanced salt sensitivity, vascular dysfunction, and activation of the sympathetic nervous system and renin-angiotensin system. Body mass index (BMI$\geq$30 kg/m^2) approximately doubles the risk for aTRH. In a large data set (>470 000) from the

Kaiser Permanente Southern California health system, obesity (BMI ≥30 kg/m^2) was also found to be an independent risk factor for RH (odds ratio, 1.62; 95% CI, 1.42-1.51).[5]

Lifestyle Factors: Relatively large inter-individual variations exist in "salt sensitivity" of BP. Few clinical trials demonstrated marked reductions in BP among patients with RH following a reduced sodium diet. Heavy alcohol intake (>30-50 g/d) is a well-established risk factor for hypertension. Both reduced physical activity and lower physical fitness are independent risk factors for hypertension. Further studies are needed to clarify the precise role of poor diet in the pathogenesis of RH. Psychosocial stressors (eg, occupational stress, low social support), negative personality traits (anxiety, anger, depression), and reduced sleep duration/quality have also been associated with high prevalence of RH.

Drug Related Factors: Several classes of pharmacologic agents can increase BP and contribute to drug-induced RH (Table 1). However, the effects of these agents are found to be highly individualized, with the majority of individuals manifesting little or no effect and others demonstrating severe elevations in BP levels.

Sleep Disorders and Pseudopheochromocytoma: Important contributing causes of resistant hypertension are sleep disorders and a related problem called pseudopheochromocytoma. This is a syndrome characterized by the presence of paroxysmal hypertension with 3 distinct features: abrupt elevation of BP, equally abrupt onset of distressful physical symptoms, and absence of reported fear or panic at the onset of attacks.[6] The original description involved patients with a history of emotional trauma from an event that they had denied; poor sleep quality, if long term, yields the same symptomology of paroxysmal hypertension and elevated BP, especially during the afternoon and evening hours. Poor sleep quality is not the result of just OSA but a host of sleep disorders, including restless leg syndrome and insomnia of various causes. The mechanism of poor sleep quality is activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system,which is supported by SYMPLICITY-HTN 3 trial.[16] The relationship between self-reported sleep duration and prevalent hypertension follows a U-shaped association with the nadir of the U being between 7 and 8 hours of uninterrupted sleep per night. As sleep time is either reduced or increased from this range, there is higher prevalence of hypertension.[6] Sleep quality and duration are critically important in the control of BP in RH. Clinicians should ask frequently about sleep quality and duration because they clearly affect BP control by activating both the sympathetic and renin-angiotensin systems and will further mitigate against controlling BP in RH. Many of these patients will have elevated heart rate disproportionate to their BP, a clinical clue that may be related to sleep quality. Diuretic use produce sleep disturbance at night by

Table 1: Drug that induce or exacerbate resistant hypertension

Drug class	Comments
Non-steroidalanti-inflammatory drugs (NSAIDs)	All non-topical NSAIDs in doses adequate to reduce inflammation and pain can affect BP levels in both normotensive and hypertensive individuals.The BP effect appears to be dose-dependent, involving the inhibition of COX-2 in the kidneys, with a reduction in sodium excretion and an increase in intravascular volume.
Oral contraceptives	Combined oral contraceptives have higher BP elevation effect. It is linked to activation of RAAS.
Sympathomimetics	Include Amphetamines, Pseudoephedrine, Ephedrine
Anti-organ rejection medicines	Cyclosporine, Tacrolimus. Increase BP by inducing systemic and renal vasoconstriction and sodium retention.
Erythropoietin	Dose dependent effect on BP
Alcohol, cocaine, and other psychoactive substances	Multiple mechanisms
Antidepressants	Tranylcypromine is the most likely of the agents to raise BP compared with Moclobemide and Bbrofaromine.
Glucocorticoids, mineralocorticoids	Multiple mechanisms

producing nocturnal micturition and by increasing sympathetic activity.

Obstructive Sleep Apnoea: OSA is extremely common in patients with RH, with prevalence rates as high as 70% to 90%, and when present, OSA is often server.[6] The high occurrence of OSA in patients with RH has been attributed to increased fluid retention and accompanying upper airway edema, as suggested by studies positively relating the presence and severity of OSA to aldosterone excess and high dietary sodium intake. Patients without OSA who suffer from sleep deprivation, defined as less than a minimum of 6 hours of uninterrupted sleep, also have increased sympathetic activity.

Evaluation of Resistant Hypertension: Diagnosis of resistant hypertension requires detailed information about multiple factors using careful history, physical examination, and investigations.[7,8] Following factors are important to guide therapy:

- Patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances, and sleep history.
- The nature and dosing of the antihypertensive treatment.
- A physical examination, with a particular focus on determining the presence of hypertension mediated organ damage and signs of secondary hypertension.
- Confirmation of treatment resistance by out-of-office BP measurements using ambulatory home-based measurement using validated devices (ABPM or HBPM).
- Laboratory tests to detect electrolyte abnormalities

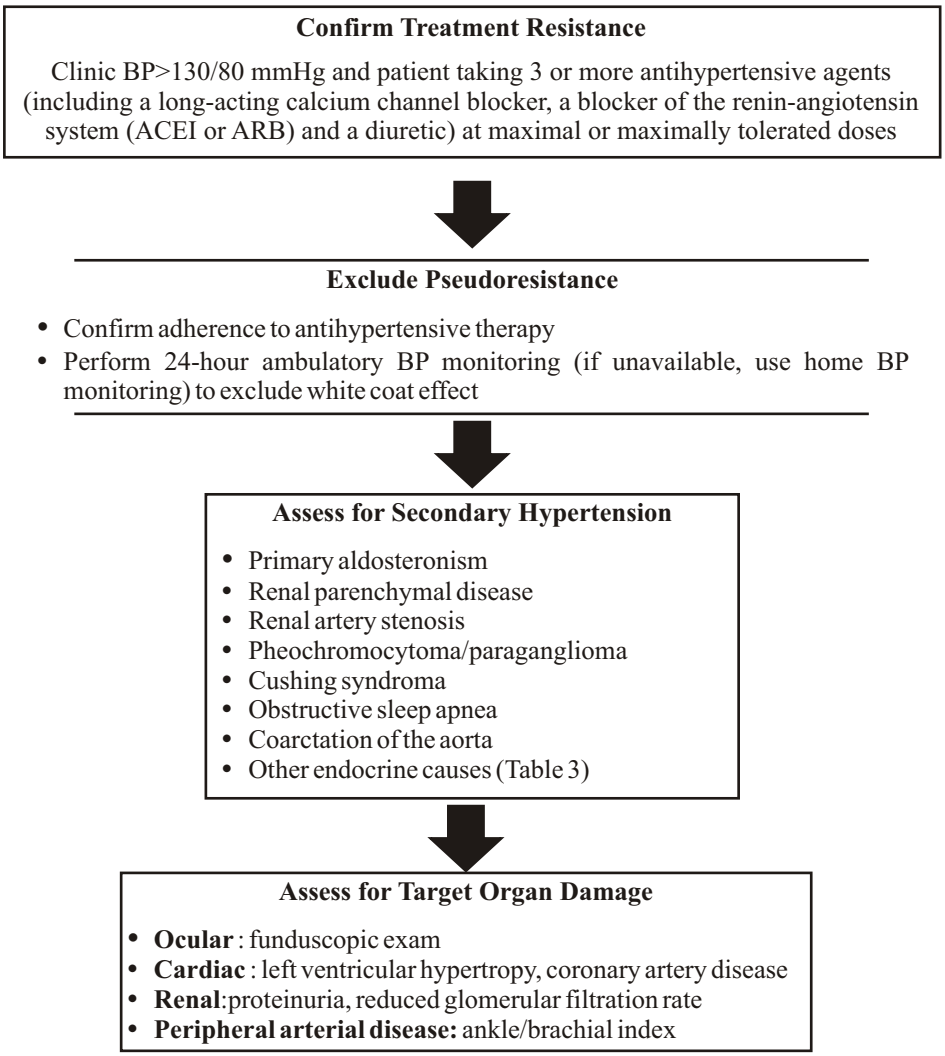

Figure 2: Evaluation of resistant hypertension according to AHA algorithm.[6]

(hypokalaemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction), and secondary hypertension.

- Confirmation of adherence to BP-lowering therapy.

The patients should also be screened for a secondary cause of hypertension, especially primary aldosteronism which has prevalence rate of around 20% in confirmed resistant hypertension, renal paranchymal disease, renal artery stenosis, pheochromocytoma, paraganglioma, Cushing's syndrome, coarctation of aorta, and others.[7] Figure 2 depicts the algorithm for evaluation of resistant hypertension according to AHA.

MANAGEMENT OF RESISTANT HYPERTENSION

Management of resistant hypertension is a complex issue

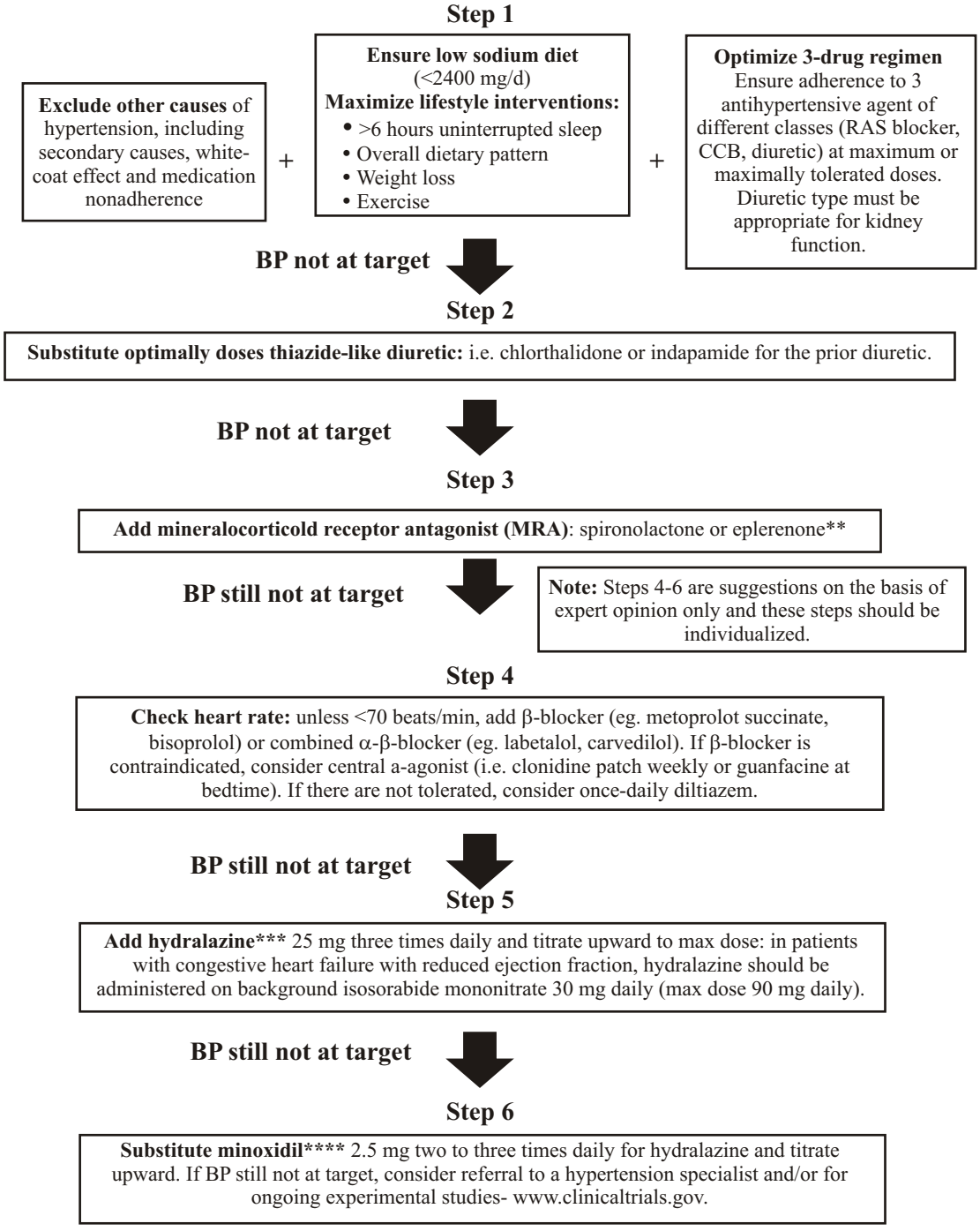

Figure 3: Resistant hypertension management algorithm from AHA guidelines.

and a care assessment is needed before embarking on appropriate therapy. Almost all the guidelines suggest similar approaches summarised in figure 3. Multifaceted interventions focus on healthy lifestyles and appropriate drug therapyare important.

Lifestyle Intervention: Important components of lifestyle changes are weight loss, dietary salt restriction, healthy diet, and regular physical activity. Guidelines suggest a healthy lifestyle (including caloric restriction), aiming for a >5% to 10% body weight loss among patients with RH to help lower BP. In patients with true RH (taking 3 to 4 antihypertensive medications), a low-sodium (50 mmol/d) versus a high-sodium (250 mmol/d) diet resulted in a profound reduction in average office BP (−22.7/−9.1 mm Hg) over a 7-day period. The available studies and AHA recommendation suggest that sodium restriction, even to low levels <65 to 100 mmol/d (1.53.0 g/d), yields significant linear reductions in BP among patients with high BP and RH.

Patients with RH should follow the established dietary recommendations promoted by the AHA. Patients with RH should follow current exercise recommendations which include ≥150 min/week (in 35 sessions of 30-40 minutes) of moderate to intense aerobic activity, optimally supplemented with 2 to 3 sessions of light resistance training per week.

Pharmacological Treatment: Once all identifiable forms of hypertension been excluded and contributions from the white-coat effect and masked uncontrolled hypertension are considered, therapeutic approaches for improved BP control in RH can begin. In second step, substitute the ongoing diuretic by Indapamide or Chlorthalidone. If the target BP is not achieved then add mineralocorticoid receptor antagonists (Spironolactone or Eplerenone). If BP is still not controlled the choice of a fifth drug (to add) depends on sympathetic drive as assessed in part by heart rate, patients with heart rates >80 bpm had higher mortality. Thus, agents such as β-blockers or, if medically contraindicated, central α-2 agonists such as transdermal Clonidine or Guanfacine should be considered. If BP is still not controlled, the addition of Hydralazine should be considered and combined with nitrates in cases of heart failure. Nitrates are preferred in this setting because they help restore calcium (Ca^{2+}). Moreover, Hydralazine reduces nitrate tolerance in this setting. Note that Hydralazine causes increased sympathetic tone and sodium avidity and therefore should be used in the presence of background appropriate diuretic and β-blocker therapy. Total daily doses of Hydralazine should be <150 mg to avoid drug-induced systemic lupus erythematosus. Lastly, Minoxidil may be tried if Hydralazine fails. Minoxidil is not well tolerated. It induces hirsutism, which in women can lead to discontinuation of the agent. Minoxidil must be given a minimum of twice daily and causes profound sodium avidity with fluid retention and increased sympathetic tone. Thus, a loop diuretic and β-blocker are required in virtually all cases (Figure 3).

Device Based Therapies

Renal Nerve Ablation: Several studies are ongoing, but presently there are no conclusions. The DENER-HTN trial (Renal Denervation for Hypertension) recently demonstrated a statistically significant reduction in daytime ambulatory SBP (−5.9 mm Hg; p=0.03) in patients on 3 antihypertensive drugs randomized to renal denervation versus those on 4 antihypertensive drugs.[6] At present, renal denervation procedures to treat RH have been discontinued in most countries unless patients are in research programs.

Carotid Baroreceptor Activation Therapy: Carotid baroreceptor activation therapy is a system that electronically activates baroreceptors that signal the brain to orchestrate a multisystemic response for disorders associated with sympathetic over activity such as hypertension, heart failure, and arrhythmias.[6] Consequently, reduced sympathetic nervous system activity and enhanced vagal activity. Hence, the heart rate slows, allowing greater left ventricular filling time and reducing cardiac workload and energy demands. A number of trials are in progress and the results may be available in 1-2 years.

CONCLUSIONS

Resistant hypertension is an important clinical problem and patients with this condition are at high risk of cardiovascular events. Secondary hypertension may be the underlying cause of resistant hypertension and, because a specific, and sometimes definite, treatment is available, a thorough investigation is mandatory in patients with uncontrolled BP despite treatment with multiple antihypertensive medications. If seated office BP >140/90

mmHg in patients managed with three or more anti-hypertensive medications at optimal (or maximally tolerated) doses including a diuretic, first exclude causes of pseudo-resistance (poor BP measurement technique, white-coat effect, non-adherence, and suboptimal choices in antihypertensive therapy), sleep deprivation, sleep apnea, pseudopheochromocytoma, and substance-induced increases in BP.

The basic principles of management include (a) consider screening patients for secondary causes as appropriate (b) optimize the current treatment regimen including health behaviour change and diuretic-based treatment (maximally tolerated doses of diuretics, and optimal choice of diuretic: use of thiazide-like rather than thiazide diuretics, and initiation of loop diuretics for eGFR<30 ml/min/1.73 m^2 or clinical volume overload) (c) add a low dose of Spironolactone as the fourth line agent in those whose serum potassium is <4.5 mmol/l and whose eGFR is >45 ml/min/1.73 m^2 to achieve BP targets. If Spironolactone is contraindicated or not tolerated, Amiloride, Doxazosin, Eplerenone, Clonidine, and β-blockers may be prescribed; and (d) interventional therapies with renal nerve ablation or carotid baroreceptor activation need further evaluation in randomised studies.

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