Consensus paper on the evaluation and treatment of resistant hypertension by the Turkish Society of Cardiology

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Introduction

Background

Hypertension is one of the major cardiovascular risk factors, closely related to the major cardiovascular, neurological, and renal adverse events (1, 2). Resistant hypertension (RHT), characterized by uncontrolled blood pressure (BP) despite intensive treatment, was shown to have 3 times more cardiovascular risk compared with controlled BP (3, 4). Moreover, this higher risk is not limited only to cardiovascular events, but also to end-organ damage. It is well documented that effective control of high BP in patients with RHT provides a significant decrease in major adverse events including cardiovascular and renal problems (5, 6).

Why a consensus document is required?

Considering the magnitude of the problem and its consequences, effective treatment of RHT is very important to reduce this higher risk and requires better diagnosis and sophisticated treatment. However, there is no consensus on how to achieve this goal. Current guidelines are inconsistent in the definition of RHT and far away from suggesting effective management strategies since they do not focus specifically on RHT (7-11). There is therefore a need for a brief up-to-date consensus, that explains the potential mechanisms leading to resistance in the control of high BP, and suggests effective structured treatment approaches for patients with RHT.

Aim of the proposed consensus document

This consensus paper reviews the major suggested mechanisms underlying RHT and determines specific diagnostic pathways for these patients. It also proposes structured, evidence-based treatment strategies to achieve adequate BP control. The main purpose of this document is to provide an algorithmic approach for the diagnosis of RHT, and recommend clear evidence-based recommendations for the management of high BP and related end-organ damage.

Definition

Current guidelines generally define RHT as an office measurement of BP >140/90 mm Hg despite three antihypertensive medications from different groups at ≥50% of the maximum dose, of which one of them is a diuretic (7-11). However, this definition

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Consensus Statements for Resistant Hypertension	Recommendation	References
Definition		
Failure to achieve adequate BP control determined by properly made office BP measurements and an ABPM, despite regularly taken three antihypertensive medication from different groups at ≥50% of the maximum dose, with one of them being a diuretic should be defined as RHT.	❤	11, 14, 15
Diagnosis		
The differential diagnosis of RHT should include pseudo-resistance, WCH, pseudohypertension, and secondary hypertension; and these conditions should be excluded before starting treatment.	❤	14, 15, 32, 36, 39
Ambulatory BP monitoring should be included in the diagnostic workup of RHT to avoid misdiagnosis due to WCH.	❤	36, 50
All patients with RHT should undergo basic laboratory tests including fasting blood glucose, serum sodium, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine with eGFR, complete blood count, lipid profile, thyroid-stimulating hormone, urinalysis, urinary albumin-to-creatinine ratio, and 12-lead electrocardiogram.	❤	7-10
Measurement of serum 25(OH)D concentration may be considered in patients with RHT.	❤	80, 81
Transthoracic echocardiography and a urinary USG should be performed in all patients with RHT.	❤	7-10
All patients with RHT should be screened for potential causes of secondary hypertension.	❤	43, 44, 46, 47, 57, 63, 65, 67, 68, 70, 71, 77-82
Patients with sudden onset or worsening hypertension under the age of 30 or over the age of 55, murmur over renal artery locations, unexplained asymmetry between two kidney sizes, increased serum creatinine level by more than 30% with the use of RAAS blockers or recurrent pulmonary edema associated with hypertensive fluctuations should undergo renal Doppler ultrasonography for screening renovascular disease.	❤	52, 53
All patients with truly confirmed RHT should be screened for PA.	❤	57-59
Hypertensive patients with hypokalemia, adrenal incidentaloma, sleep apnea, a family history of early-onset hypertension, or cerebrovascular accident at a young age should be screened for PA.	❤	57-59
Hypertensive first-degree relatives of patients with PA should be screened for PA.	❤	59
Hypertensive patients with lone AF may benefit from screening for PA.	❤	61, 62
A paired morning plasma aldosterone and plasma renin activity should be measured to calculate aldosterone-to-renin ratio in patients with RHT to screen for PA.	❤	58, 59
Hypertensive patients with features of Cushing syndrome such as proximal muscle weakness, easy bruisability, abnormal body fat distribution should be evaluated for Cushing syndrome.	❤	64
All patients with RHT should be questioned about symptoms related to OSA and examined for increased neck circumference. The patients with a clinical suspicion of OSA should be referred to a specialist for a definitive evaluation.	❤	70-73
Treatment		
Intense treatment of BP should be forced to reach adequate BP control to improve poor prognosis seen in patients with RHT compared to other hypertensive patients.	❤	5, 18
Lifestyle modification including reaching and keeping optimum body mass index, intensifying physical activity, moderation of alcohol ingestion, cessation of smoking, sleeping adequately, restriction of salt intake, and being nourished by the DASH diet should be advised to all patients with RHT.	❤	50, 92-95

Consensus Statements for Resistant Hypertension	Recommendation	References
The patients with RHT should be informed about the potential consequences of their disease, and the importance of pharmacological treatment, potential side effects of the drugs, and drug interactions to increase adherence to therapy. All patients should be encouraged to take their medications regularly.		5, 16, 18, 38, 39, 105
The first-line pharmacological treatment should include a combination of a RAAS blocker, a long-acting CCB, a potent diuretic.		30, 99, 106
Mineralocorticoid receptor antagonist should be preferred as the fourth drug in patients with uncontrolled BP despite first-line treatment to provide better BP control if eGFR ≥ 45ml/min and serum potassium levels <4,5 mmol/l. The fifth drug should be chosen among beta-blockers or alpha-blockers according to heart rate.		30, 115, 116, 118
Rilmenidine may be preferred for add-on treatment in patients whose BP is not controlled despite the above medication because of its positive metabolic effects especially in patients with diabetes and dyslipidemia.		122-124
Beta-blockers should be added at any treatment step, when there is a specific indication, such as heart failure, angina pectoris, post-myocardial infarction, atrial fibrillation, or younger women with or planning a pregnancy.		7, 8
Loop diuretics should be preferred in patients with an eGFR <30 ml/min to provide more effective diuresis.		104
Eplerenone or amiloride may be used as an alternative to spironolactone in patients with side effects such as breast tenderness or gynecomastia.		112-114
The effective treatment combination determined for each patient should be given by using a minimum number of pills containing these antihypertensive agents in adjustable doses to increase treatment adherence.		105
Routine application of renal denervation therapy, baroreceptor activation therapy, or arteriovenous anastomosis is contraindicated until convincing data accumulates.		135-146

BP - blood pressure, ABPM - ambulatory blood pressure monitoring, RHT - resistant hypertension, WCH - white coat hypertension, eGFR - estimated glomerular filtration rate, USG - ultrasonography, RAAS- renin-angiotensin-aldosterone system, PA - primary hyperaldosteronism, AF - atrial fibrillation, OSA - obstructive sleep apnea, DASH diet - Dietary Approaches to Stop Hypertension Diet, CCB - calcium channel blocker

does not discriminate between pseudo-resistance and true resistance since it also includes patients with white coat hypertension (WCH) and patients who are non-adherent to medication. It also does not consider inaccurate BP measurements. Recent studies suggested the term 'apparent RHT' for office measurement of BP >140/90 mm Hg despite three different antihypertensive medications (12, 13). Thus, to better discriminate true RHT, the present consensus paper suggests that the following definition: failure of achieving adequate BP control, determined by properly made office BP measurements and an ambulatory BP monitorization (ABPM), despite of regularly taken three antihypertensive medications from different groups at ≥50% of the maximum dose, with one of them being a diuretic.

Epidemiology

The prevalence of RHT shows a significant diversity among different studies. This diversity in prevalence seems to result from the different definitions. If the definition does not exclude pseudo-resistance, pseudo-hypertension, and WCH, the result may overestimate the true prevalence of RHT. Although, early studies using a broader definition for RHT report the prevalence as high as 21% (14), in a recent meta-analysis of 91 studies reporting the results of 3,207.911 patients on antihypertensive treatment, the prevalence of true RHT was 10.3% (15).

Prognosis

It is a well-known fact that increased BP is related to decreased survival (16, 17). Moreover, patients with RHT have a worse prognosis compared to other hypertensive patients. In a retrospective cohort study on 205,750 hypertensive patients, cardiovascular event rates were higher in patients with RHT (5). A prospective study including 470,386 hypertensive patients showed that RHT was strongly associated with end-stage renal disease (ESRD), ischemic heart event, congestive heart failure, cerebrovascular accident, and all-cause mortality (18). In this study, investigators further divided the RHT group into 2 subgroups: RHT controlled with ≥4 medications and RHT uncontrolled despite ≥3 medications. They found that the uncontrolled RHT group had more ESRD and cerebrovascular accidents compared to the controlled RHT group (18).

Pathophysiology

Although, RHT and controlled HT have the same risk factors such as older age, high body mass index, chronic kidney disease

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(CKD), and diabetes, which lead to endothelial dysfunction, arterial stiffness, and vascular damage; the exact pathophysiology responsible for resistance is unclear. In a normal healthy system, BP is maintained by the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), both of which function in coordination. Thus, overactive SNS and hyperaldosteronism, which result in volume overload and increased arterial stiffness, are the leading hypotheses in the pathophysiology of RHT (19).

Overactivation of SNS is an important contributor to RHT (20, 21). A selective increase in cardiac and renal sympathetic stimulation has been demonstrated in hypertensive patients (22). In the case of RHT, this stimulation is more powerful. Dudenbostel et al. (20) showed that 24-hour urinary normetanephrine levels are greater in RHT patients than in control subjects. Moreover, these patients had greater arterial stiffness, higher heart rate, and higher systemic vascular resistance (20). SNS also affects the kidney directly (23). It can directly increase renin secretion from juxtaglomerular granular cells in the kidney, inducing sodium reabsorption by renal tubular epithelial cells, and reducing renal blood flow through its impact on renal vasculature. In a healthy system, these effects are counter-regulated by negative feedback. However, in RHT, these feedback systems do not operate properly since afferent renal signals from the kidneys directed to the rostral ventrolateral medulla in the brain stem further potentiates the sympathetic outflow (24).

The other important mechanism in RHT pathophysiology is volume overload by RAAS overactivity (25, 26). Factors associated with volume overload are excess aldosterone, obesity, high dietary salt intake, and CKD (19, 27, 28). Recently the role of aldosterone in RHT pathogenesis became more apparent. Aldosterone plays a key role in sodium reabsorption and causes vasoconstriction in renal afferent and efferent arterioles (29). It also induces myocardial fibrosis and cardiac hypertrophy. The PATHWAY-2 (Prevention and Treatment of Hypertension With Algorithm-Based Therapy) trial demonstrated the superiority of spironolactone in RHT treatment compared to bisoprolol and doxazosin (30). A substudy of the PATHWAY-2 trial concluded that the antihypertensive effect of spironolactone was related to a significant reduction in thoracic fluid content. Based on this relationship, the authors suggested that RHT was attributable mainly to excess fluid retention, mediated by excess aldosterone (31). High dietary salt intake may also lead to volume overload. There is robust evidence of the association between dietary salt intake and RHT (29, 32, 33). Increased salt intake also promotes the adverse effects of vasoconstrictors on the vascular wall and contributes to arterial stiffness (34).

Different diseases and factors may lead to RHT via these pathophysiological mechanisms. Common reasons that should be considered in the etiology of RHT are given in Table 1.

Table 1. Causes of resistance to hypertension treatment

Inaccurate measurement
White coat hypertension
Pseudohypertension
Pseudoresistant hypertension
Hypervolemia
Sympathetic nervous system overactivation
Renal problems
Endocrine disorders
Obstructive sleep apnea
Drugs
Vitamin D deficiency

Differential diagnosis

Determining the exact reason for resistance in RHT may provide more effective control of BP and prevent the consequences of hypertension. Thus, establishing a differential diagnosis is an important step to understand the problem and choose the best treatment. Figure 1 shows an algorithm for the differential diagnosis of RHT.

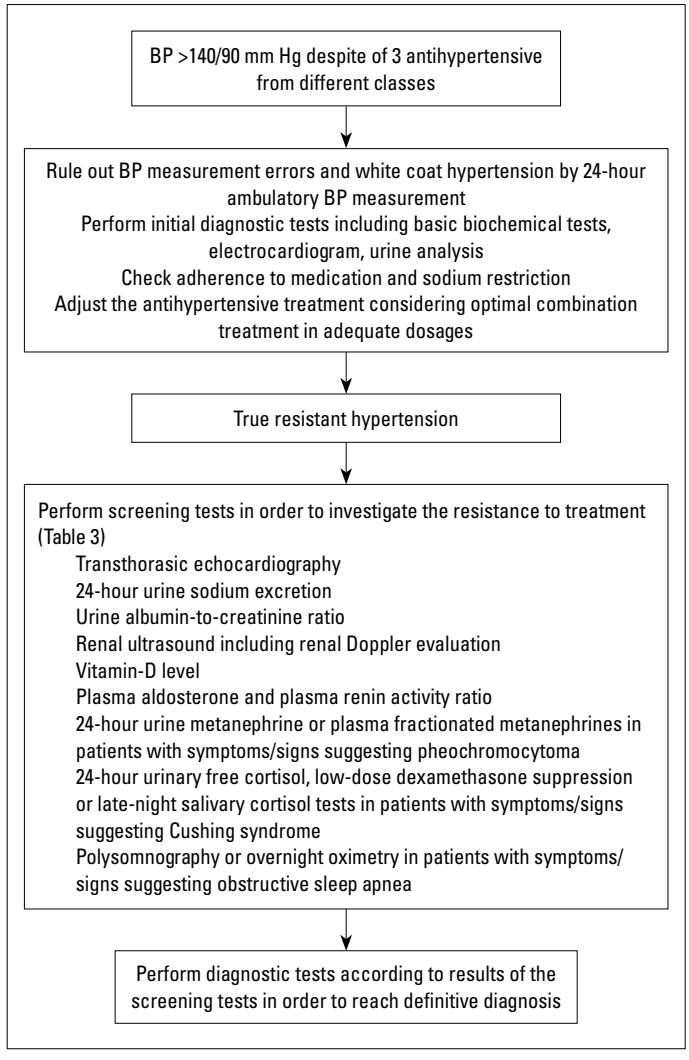

Figure 1. Algorithm for differential diagnosis of resistant hypertension

a. Inaccurate measurement

Inaccurate measurement of BP may lead to an incorrect diagnosis of RHT (35). Blood pressure should be measured in a quiet environment, after the patient has been seated for at least 5 minutes, using a sphygmomanometer of an appropriate size for the patient's arm, and calibrated according to standard protocols (7). A minimum of 2 readings, one minute apart should be obtained for an accurate BP measurement (7, 8).

b. White coat hypertension

White coat hypertension is defined as high office BP measurements despite controlled BP levels on home BP measurements or ABPM. Several studies report that more than one-third of patients diagnosed with RHT using office BP measurements have normal ABPM values (36).

c. Pseudohypertension

Pseudohypertension is defined as a false measurement of elevated BP using a sphygmomanometer in elderly people, because of artery incompressibility from intense calcification (37). This false measurement may cause misdiagnosis of RHT, and lead to unnecessary additional drug prescription resulting in orthostatic hypotension and syncope. This is diagnosed by invasive arterial BP measurement.

d. Pseudo-resistance

Pseudo-resistance resulting from non-adherence to lifestyle measures and drug treatment is an important problem in the misdiagnosis of true RHT. The studies using 24-hour urinary sodium excretion to measure sodium intake suggest that most patients diagnosed with RHT do not follow sodium restriction recommendations (38). The particularly high amount of sodium consumption in the Turkish population (14.8 g/day on average) may be a very important factor in the failure of hypertensive treatment in our country (28). Non-adherence to drug treatment is also a very common problem. Strauch et al. (39) found that 47% of patients were non-adherent to their medications by measuring serum levels of antihypertensive drugs, using liquid chromatography-mass spectrometry. Strikingly, in this study, the investigators could not detect any antihypertensive drug in the serum of 24% of patients (39). The frequent misinformation on drugs in media and the common misbeliefs on the side effects of drugs may be some of the reasons for the high incidence of non-adherence. Also, complex drug regimens with multiple drugs and multiple daily doses for the treatment of hypertension, as well as polypharmacy due to other chronic diseases may be other important barriers to adherence. Solutions to improve adherence must be multifactorial. Thus, using agents administered once daily and fixed-dose combination agents when available is recommended. Educating the patients, their families, and caregivers on hypertension, its consequences, and the possible adverse effects of drugs may improve adherence (8).

On the other hand, physicians' therapeutic inertia may also lead to treatment failure in patients with hypertension resulting in pseudo-resistance. Extensive data suggests that many doctors are reluctant to start and intensify drug treatment in patients with hypertension (40, 41). The delay in the proper management of high BP using correct combinations of antihypertensive drugs in adequate doses may be responsible for resistance to treatment. Thus, physicians should not neglect to start effective antihypertensive treatment and provide sufficient effort and time for therapeutic and lifestyle recommendations in each patient, to control BP.

Secondary hypertension

Secondary hypertension (SHT) is very common among patients with RHT. Potential causes of SHT should be screened in these patients. The frequency of diseases that cause hypertension differs with age. While the main reasons for SHT are endocrine disorders and obstructive sleep apnea in middle-aged patients, renal causes are more frequent in young adults and older patients (7).

a. Renal problems

Renal diseases are among the most common causes of RHT. Therefore, all hypertensive patients who remain resistant to medical treatment should be examined for potential renal diseases. Generally, a careful history and physical examination may help to detect kidney problems in a patient. The frequent diagnostic tools used in these patients are serum biochemistry, urine analysis, imaging techniques, and more rarely, renal biopsy and histopathological examinations.

1) Renal parenchymal diseases

Markers of kidney damage include a history of renal transplantation, presence of albuminuria or urinary sediment abnormalities, structural abnormalities revealed by imaging techniques (such as cortical scarring, contracted or polycystic kidneys), presence of renal tubular disorders (such as renal tubular acidosis, nephrogenic diabetes insipidus), and the presence of glomerular, tubular or vascular abnormalities on kidney biopsy (such as systemic lupus erythematosus). The presence of either of these markers (with or without a decrease in glomerular filtration rate (GFR)) or having a GFR <60 ml/min/1.73 m^2 (with or without markers of renal damage) for ≥3 months is defined as CKD.

Pathogenesis is multifactorial and varies according to the cause, type, and degree of kidney damage. Impaired sodium excretion, increased intravascular volume, and RAAS overactivity are the predominant pathophysiological mechanisms in many forms of CKD such as diabetic nephropathy, obstructive nephropathy, glomerulonephritis, pyelonephritis, and polycystic kidney disease (42). All these mechanisms are also responsible for hypertension seen in most patients with CKD.

The prevalence of RHT in patients with renal parenchymal diseases is more than 20% (43, 44), which is significantly higher

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than in the general hypertensive population (15). The prevalence increases with more advanced CKD and albumin/creatinine ratio >300 mg/g (45-47). Given that CKD affects more than 15 % of adults in the Turkish population (48), the magnitude of the epidemiological impact of RHT detected in this group can be estimated. Moreover, CKD may obstruct the response to antihypertensive treatment and promote resistance, which causes further damage to the kidneys, resulting in a vicious cycle (49). Thus, the diagnosis of RHT in patients with CKD requires special attention. An important dilemma is to determine whether RHT is a cause or a consequence of CKD. Other secondary causes should be evaluated and excluded before identifying CKD as the cause of RHT (50). Another important point concerns the individualization of treatment in these patients. The efficacy and safety of some antihypertensives, such as thiazide diuretics, spironolactone, hydralazine, and minoxidil should be evaluated by considering the etiology of CKD and the GFR of the patients (7).

2) Renovascular hypertension

Renal vascular hypertension (RVH) is defined as high systemic BP that occurs when blood flow to the kidneys decreases due to partial or complete obstruction of at least one renal artery or its branches. Persistent occlusion of the renal artery lumen of 80% or more disrupts baroreceptor signals in afferent arterioles, leading to the activation of the RAAS and the sympathoadrenergic system (51, 52).

Atherosclerotic renal artery stenosis is one of the most common causes of RVH and should be considered among the potential causes of RHT, especially in elderly patients who smoke, have dyslipidemia, or already have atherosclerotic vascular lesions in other anatomical sites. In relatively young, non-obese women without atherosclerosis, RVH is often associated with fibromuscular dysplasia (8, 11).

Sudden onset or worsening hypertension under the age of 30 or over the age of 55, presence of murmur over renal artery locations, unexplained asymmetry in kidney sizes, increased serum creatinine levels by more than 30% with the use of RAAS blockers, or recurrent pulmonary edema associated with hypertensive fluctuations could be used for RVH screening (7, 11). Renal Doppler ultrasonography should be the first-line technique used for diagnosis. Although the results of randomized studies are discouraging, renal artery stenting may be useful in RHT patients who are refractory to maximum medical therapy and have progressive renal function deterioration or multiple flash pulmonary edema attacks (53-55).

b. Endocrine disorders

1) Primary hyperaldosteronism

Primary hyperaldosteronism (PA), one of the most common causes of RHT, is due to inappropriately secreted aldosterone from the adrenal cortex (56). Although the prevalence of PA varies among studies, it is generally reported to be about 20% in patients with RHT (57). Since delayed diagnosis may have a significant impact on patient outcome, all patients with confirmed RHT should be screened for PA (58, 59). Also, hypertensive patients with spontaneous or diuretic-induced hypokalemia, adrenal incidentaloma, or sleep apnea should be screened for PA. A family history of early-onset hypertension or cerebrovascular accident at a young age should alert the physicians on PA. Moreover, the familial clustering of PA exists, suggesting a genetic susceptibility of PA. Thus, in some cases, PA is hereditary and first-degree hypertensive relatives of patients with PA should also be screened (59). PA patients with positive family history also have an increased risk of major cardiovascular events compared to those without a family history (60). Questioning for family history of PA is important in this context. Recent evidence suggests a connection between PA and atrial fibrillation (61, 62). Thus, patients presenting with lone atrial fibrillation may also benefit from screening tests for PA. Although hypokalemia is an important sign of PA, many of the patients with PA have normokalemia (63). The ratio of plasma aldosterone concentration to plasma renin activity (ARR) is therefore recommended as an initial screening test (58). Patient preparation before measuring ARR is very important to avoid inaccurate results (58). The patient's position (patient should be in a supine or sitting position for at least 60 minutes before sampling), diet (patient should be on an unrestricted salt diet), and potassium level (potassium deficiency should be corrected) before testing are important factors to take into account for accurate measurements. Commonly used antihypertensive medications can also affect ARR testing (58, 59). Mineralocorticoid receptor antagonists should be withdrawn for at least 4 weeks before testing (59). Calcium channel blockers and doxazosin may be used to control BP during this period. An ARR of >30 is the most adopted cut-off value, and >20 may be used if plasma aldosterone concentration is >16 ng/dL (59). If clinical suspicion is high, the patient should be referred to an endocrinologist for further evaluation no matter the results of the initial screening test. Patients with positive screening tests should undergo confirmatory tests, such as saline infusion, captopril challenge, oral sodium loading, or fludrocortisone suppression tests to definitively confirm the diagnosis of PA. However, patients with spontaneous hypokalemia, plasma renin below detection levels, and plasma aldosterone concentration above 20 ng/dl may be exempted from confirmatory testing (59). After the diagnosis of PA is established, it is crucial to investigate the specific etiology of PA, to decide on the appropriate treatment, which can either be surgical or medical. Imaging modalities and adrenal venous sampling are used if necessary, to distinguish between unilateral and bilateral diseases (58, 59).

2) Cushing syndrome

Hypertensive patients with features of Cushing syndrome such as proximal muscle weakness, easy bruisability, and abnormal body fat distribution should be evaluated for Cushing syndrome (64). Low-dose dexamethasone suppression, 24-hour

urinary free cortisol, or late-night salivary cortisol tests are screening tests for autonomous cortisol production. If two of these screening tests are positive, then the etiology of hypercortisolism should be investigated with further tests. If test results are abnormal or if there is a high suspicion of Cushing syndrome despite normal test results, the patient should be referred to an endocrinologist for further evaluation (65, 66).

3) Pheochromocytoma

Although the prevalence of pheochromocytoma is relatively low, it is higher in patients referred for RHT (67). Patients should be questioned on paroxysmal hypertension, palpitation, perspiration, pallor, and pounding headache. If there is clinical suspicion of pheochromocytoma, screening tests like the measurement of catecholamine metabolites in an appropriately collected 24-hour urine (fractionated urinary metanephrines) or plasma free metanephrines should be done (68). If the screening test is positive, patients should be referred for further evaluation and treatment. Imaging studies should be initiated to locate the lesion only after clear biochemical evidence of pheochromocytoma. A multidisciplinary approach with experts in endocrinology, cardiology, radiology, nuclear medicine, anesthesiology, and surgery is needed to evaluate, diagnose, treat and follow-up patients with pheochromocytoma, to ensure favorable outcomes (68, 69).

4) Other endocrine disorders

Hypo/hyperthyroidism, hyperparathyroidism/hypercalcemia, apparent mineralocorticoid excess disorders other than PA and acromegaly should also be suspected and evaluated accordingly in patients with RHT, according to the patient's clinical and laboratory findings (50).

c. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is more prevalent among hypertensive patients, and its prevalence reaches 71-83% in patients with RHT (70-72). OSA is shown to be one of the major risk factors for RHT (73). Therefore, all patients with RHT should be questioned on snoring, daytime sleepiness, morning headache, choking, and gasping in sleep (72). Screening questionnaires can be helpful to identify adult patients with increased risk of OSA. Increased neck circumference is also an important finding in OSA. If there is clinical suspicion of OSA, referral to a specialist should be considered for further evaluation. Patients suspected of having OSA should be evaluated with overnight polysomnography to diagnose OSA, and this should be treated accordingly (72).

d. Aortic coarctation

Aortic coarctation is one of the most common congenital heart diseases presenting with upper extremity hypertension resistant to treatment. It is an important cause of childhood hypertension and is characterized by a narrowing in the descending thoracic aorta, usually occurring distal to the left subclavian artery origin (74). The definitive diagnosis relies on imaging by echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI). Surgical or transcatheter correction of aortic coarctation which results in significant obstruction to blood flow is recommended in patients with hypertension (74). Despite the correction of coarctation using the methods aforementioned, hypertension persists in up to one-third of patients (75). All patients with aortic coarctation and hypertension should therefore get an effective medical treatment to prevent long term complications such as left ventricular hypertrophy, renal dysfunction, and intracranial aneurysms.

e. Drugs

Several classes of pharmacological agents may contribute to RHT (76). Nonsteroidal anti-inflammatory drugs, oral contraceptive agents, erythropoietin, estrogen/progesterone hormone replacement therapies, immunosuppressive agents such as cyclosporine and tacrolimus, and sympathomimetic amines may increase BP via a variety of mechanisms (50). Also, antineoplastic agents such as tyrosine kinase inhibitors and antidepressants can exacerbate hypertension. Therefore, a comprehensive history of medications and over the counter agents should be obtained in all patients with RHT (77). Common drugs that may lead to RHT are given in Table 2.

f. Vitamin D deficiency

Vitamin D deficiency is known to be related to hypertension (78, 79). Recently, it was also found to be related to RHT (80). Moreover, in a study evaluating 101 patients with RHT treated with renal denervation, those with significant vitamin D deficiency showed a blunted decrease in SBP in response to treatment (81). Although the evidence is still building, this relationship seems to result from increased activation of RAAS (82, 83). Vitamin D deficiency is very common in Turkey with a reported prevalence of almost 75% (84, 85). Thus, patients with RHT may benefit from serum 25(OH)D concentration measurement.

Table 2. Common drugs causing resistant hypertension

Non-steroidal anti-inflammatory drugs
Sympathomimetics (nasal decongestants)
Glucocorticoids, mineralocorticoids
Alcohol
Vascular endothelial growth factor inhibitors
Cyclosporine, tacrolimus
Oral contraceptives
Erythropoietin
Cocaine
Amphetamines
Antidepressants (monoamine oxidase-1 inhibitors)

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Basic diagnostic workup for the etiology of resistance to antihypertensive therapy

a. Basic laboratory tests:

Basic laboratory tests should include fasting blood glucose, serum sodium, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, serum creatinine with estimated GFR (eGFR), complete blood count, lipid profile, thyroid-stimulating hormone, urine analysis, urinary albumin-to-creatinine ratio, and 12-lead electrocardiogram. These tests aim to establish a cardiovascular risk profile, screen for SHT, and guide in the selection of antihypertensive medications (7). Serum uric acid levels may also be measured optionally. An eGFR value of <60 ml/min/1.73 m^2 and/or urine albumin-to-creatinine ratio of ≥300 mg/g should raise suspicion of CKD (8). If non-adherence to salt restriction is suspected, a 24-hour urine sodium excretion measurement may give an idea on the patient's sodium intake, sodium-sparing drugs, and several subtypes of CKD (86). In patients with RHT, a paired morning plasma aldosterone and plasma renin activity should be obtained to calculate the ARR, recommended as the first-line screening tool for PA. An ARR of >30 is the most commonly adopted cut-off value and >20 may be accepted if plasma aldosterone concentration is >16 ng/dL (50). Although sensitive, a positive ARR is not always diagnostic and further evaluation by a salt suppression test and non-suppression of aldosterone secretion in response to salt loading is required. Failure to suppress plasma aldosterone concentration to < 10 ng/dL with adequate salt loading is consistent with PA (87). If the initial evaluation and physical examination raise the suspicion of pheochromocytoma/paraganglioma, 24-hour urinary fractionated metanephrines or plasma free metanephrines should be evaluated (68). When Cushing syndrome is suspected, 24-hour urinary free cortisol (repeated at least twice), late-night salivary cortisol (repeated at least twice), or 1-mg overnight dexamethasone suppression tests may be used (87, 88). Basic tests used for screening and diagnosis of RHT are summarized in Table 3.

b. Imaging:

Transthoracic echocardiography should be performed in all patients with RHT (7). Disparities between in-office and out-of-office BP can be adjudicated by an ABPM (4). Urinary ultrasonography (USG) should be the first examination to determine the structural anatomy of the urinary system, including the kidneys (86). Imaging for renal artery stenosis in patients with RHT should be reserved for those with a high likelihood of RVH. Calculation of aortic and renal artery velocities by duplex USG of the renal arteries is preferred over CT and magnetic resonance angiography as a screening tool. Selective renal angiography in the absence of suspicious noninvasive imaging is not recommended (50). Once blood tests establish the presence of PA, an adrenal CT scan is the first-line imaging tool to distinguish adrenal ade-

Table 3. Diagnostic workup for the etiology of resistance to antihypertensive therapy

Etiology	Laboratory test	Imaging
High salt intake	24-hour urine sodium excretion	-
Renal parenchymal disease	Serum creatinine, electrolytes, eGFR, urinalysis for blood and protein, urine albumin-to-creatinine ratio	Renal ultrasound
Renovascular disease	Rise in serum creatinine during ACE/ARB treatment	Renal duplex ultrasonography Abdominal CTA/MRA Selective renal angiography
Primary hyperaldosteronism	Serum potassium (may be normal) Plasma aldosterone and plasma renin activity Salt loading test	Adrenal CT scan Selective adrenal venous sampling
Pheochromocytoma/paraganglioma	Plasma free metanephrines Urinary fractionated metanephrines Clonidine suppression test	CT/MRI scan of the abdomen/pelvis I^{123}-MIBG scan (functional imaging for metastasis) ^{18}F-FDG PET/CT scan for metastasis
Cushing syndrome	24-hour urinary free cortisol levels (2 sets) Late-night salivary cortisol (2 sets) 1-mg overnight dexamethasone suppression test Longer low dose dexamethasone (2 mg/d for 48 h) test	Pituitary MRI CT/MRI scan of the thorax/abdomen Nuclear imaging Adrenal CT/MRI
Obstructive sleep apnea	-	Polysomnography Overnight oximetry
Aortic coarctation	-	TTE Thoracic/abdominal CTA/MRA

noma from bilateral adrenal hyperplasia. This distinction will influence the decision for medical or surgical treatment. Selective adrenal venous sampling can be used to make the distinction between unilateral and bilateral adrenal disease (58, 87). CT or MRI of the abdomen/pelvis can be performed for the diagnosis of pheochromocytoma/paraganglioma (68). Once the diagnosis of ACTH-dependent Cushing syndrome is confirmed by laboratory tests, a high-resolution pituitary MRI with a gadolinium-based contrast agent should be performed. The ectopic source of the ACTH can be sought by thoracic or abdominal CT, MRI, or nuclear imaging. In ACTH-independent Cushing syndrome, adrenal imaging with CT or MRI is recommended (89). Polysomnography or overnight oximetry is diagnostic for OSA. Aortic coarctation can be evaluated by echocardiography, thoracic and abdominal CT, or magnetic resonance angiogram (90, 91).

Treatment

a. Nonpharmacological approach

Lifestyle modification is a component of nonpharmacological treatment and is an important aspect of RHT management. Adhering to healthy lifestyle behaviors was found to be related to a significant reduction in cardiovascular events in patients with RHT. The cardiovascular event rate was significantly lower in RHT patients practicing ≥2 healthy lifestyle behaviors compared to patients practicing 0 or 1 healthy lifestyle behavior (92). Patients should always be recommended to modify their lifestyle by losing weight, intensifying physical activity, smoking cessation, alcohol intake moderation, and starting a low sodium diet [Dietary Approaches to Stop Hypertension (DASH)] (93). The DASH diet pattern was developed to lower BP without medication by the National Institute of Health (94). It encourages people to reduce the amount of sodium in their diet and eat a variety of foods rich in nutrients that help lower BP such as potassium, calcium, and magnesium. DASH diets include lots of whole grains, fruits, vegetables, and low-fat dairy products. There is great evidence suggesting a strong association between dietary salt intake and RHT (95, 96). Salt restriction [low sodium diet (1.75 g of sodium/day)] may decrease BP by 5.4/2.8 mm Hg in hypertensive patients (95). This benefit may be greater in the case of aldosterone-induced sodium and fluid retention. The World Health Organization recommends the restriction of salt intake to <5 g/day in adults (97).

Patients with HT should also have ≥6 h uninterrupted sleep for better BP control (50). Vitamin D deficiency is significantly common in our country and patients with RHT should be encouraged to sunbath properly in natural sunshine (98).

Maximizing lifestyle interventions may help to decrease the number and dosage of pharmacological treatments in patients with RHT.

b. Pharmacological treatment

The combination of a RAAS blocker, a long-acting calcium channel blocker (CCB), and a diuretic at maximally tolerated doses is the optimal option in the treatment of RHT since these three classes provide complementary mechanisms of action, safety, tolerability, and efficacy. Long-acting compounds from these three classes are available. Among CCB, dihydropyridines may be preferred because of greater evidence from randomized clinical trials (RCT) and better side effect profile compared to non-dihydropyridines (99). Randomized controlled trials showed that volume overload (especially in CKD patients) or sympathetic tonus increase are the most common underlying mechanisms of RHT. Although there is limited evidence for RHT treatment, the addition of a potent diuretic to sodium restriction with the aim of removing volume overload is accepted as the most effective strategy, especially in patients with CKD. Increasing the diuretic dose or changing it with a potent thiazide-like diuretic (indapamide or chlorthalidone) may help in BP control. There is significant evidence that shows that chlorthalidone and indapamide decrease cardiovascular outcomes. Furthermore, switching from hydrochlorothiazide to the same dose of chlorthalidone provides 7-8 mm Hg additional reduction in systolic BP (100-102). Thiazide diuretics cannot provide natriuresis when eGFR <45 ml/min but chlorthalidone is effective up to an eGFR <30 ml/min for natriuresis (103). Below an eGFR of 30 ml/min or in cases with hypo-albuminemia, long-acting loop diuretic torsemide should be used for effective diuresis (104). All these different classes of diuretics should be used in maximally tolerated doses (hydrochlorothiazide 50 mg, chlorthalidone 25 mg, indapamide 2.5 mg, and torsemide 2.5-5 mg). CCB and RAAS blockers should also be used at their maximally tolerated doses (50).

Another important issue is the maintenance of adherence to antihypertensive drugs. Once an effective treatment combination has been found, switching to a single pill containing these antihypertensive agents in adjustable doses is an important step to ensure treatment adherence (105).

If BP targets cannot be reached despite all these treatment strategies, recent evidence suggests the addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone) to the treatment as the fourth antihypertensive drug. The placebo-controlled, double-blinded randomized PATHWAY-2 trial demonstrated that spironolactone is more effective than alpha-blocker doxazosin and beta-blocker bisoprolol for decreasing BP in RHT (30). In the Resistant Hypertension Optimal Treatment (ReHOT) trial, investigators compared a potent diuretic chlorthalidone with spironolactone. Both drugs decreased BP in patients with RHT, but spironolactone at 50 mg/day dose provided greater reduction in 24-hour and daytime ambulatory BP (106). Many other studies and meta-analysis suggest the superiority of spironolactone especially in low renin activity and salt-sensitive hypertensive states (107-112). Tolerability is an important problem with spironolactone because of more common side effects including breast tenderness and gynecomastia in men. Amiloride 10-20 mg/day or eplerenone 50-100 mg/day may be an alternative to spironolactone in these patients (30, 113). Eplerenone should be administered twice daily for optimal effect because of its shorter half-life (114). The risk of hyperkalemia is high in patients with eGFR <45 ml/min and/

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or serum potassium level >4.5 mmol/L. Therefore, spironolactone should not be preferred in these patients.

Despite their inferior efficacy compared to spironolactone in comparative studies, another pharmacological option in RHT is specific alpha-1 blockers. In this group, doxazosin decreases BP by an average of 12/7 mm Hg in hypertensive patients and is usually well tolerated (115). In RHT, the decrease in BP with doxazosin may be greater (116). However, in the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT), doxazosin-induced heart failure was more common compared to chlorthalidone and should be used cautiously in patients with heart failure (117). Sympathetic activity may be the underlying mechanism of RHT, and a heart rate >80 beats/min may reflect it. Thus, the decision of a fifth drug should consider heart rate as a reflection of sympathetic tonus (118). Bisoprolol 5-10 mg/day or doxazosin modified release 4-8 mg/day may be used in RHT when spironolactone is contraindicated or not tolerated according to PATHWAY-2 trial evidence (30). Beta-blockers could be added at any treatment step when there is a specific indication such as heart failure, angina pectoris, post-myocardial infarction, atrial fibrillation, or younger women with or planning pregnancy (7).

Central vasodilator hydralazine with nitrate combination may be used in patients with heart failure. Minoxidil may be considered if BP could not be controlled with the above-described measures (50, 119). It should be noted that hydralazine can cause increased sympathetic tone and sodium retention, and minoxidil induces hirsutism. Another central vasodilator rilmenidine shows selective binding to I1 imidazoline receptors. It results in an antihypertensive effect mainly through reduced total peripheral resistance by a reduction in sympathetic activity (120, 121). Evidence from studies with a limited number of patients supports that it does not have the classical adverse effects of centrally acting agents. Moreover, rilmenidine has positive metabolic effects especially in patients with diabetes and dyslipidemia (122-124).

Vitamin D deficiency is highly prevalent in Turkey (84, 85) and is shown to be related to RHT (81-83). However, there is no data regarding the effects of pharmacologically corrected Vitamin D deficiency in RHT. Until convincing evidence accumulates, correction of vitamin D deficiency by nonpharmacological measures should be preferred. In patients who do not respond or respond inappropriately to these measures, pharmacological supplements may be given to correct vitamin D levels. The algorithm for the treatment of RHT is given in Figure 2.

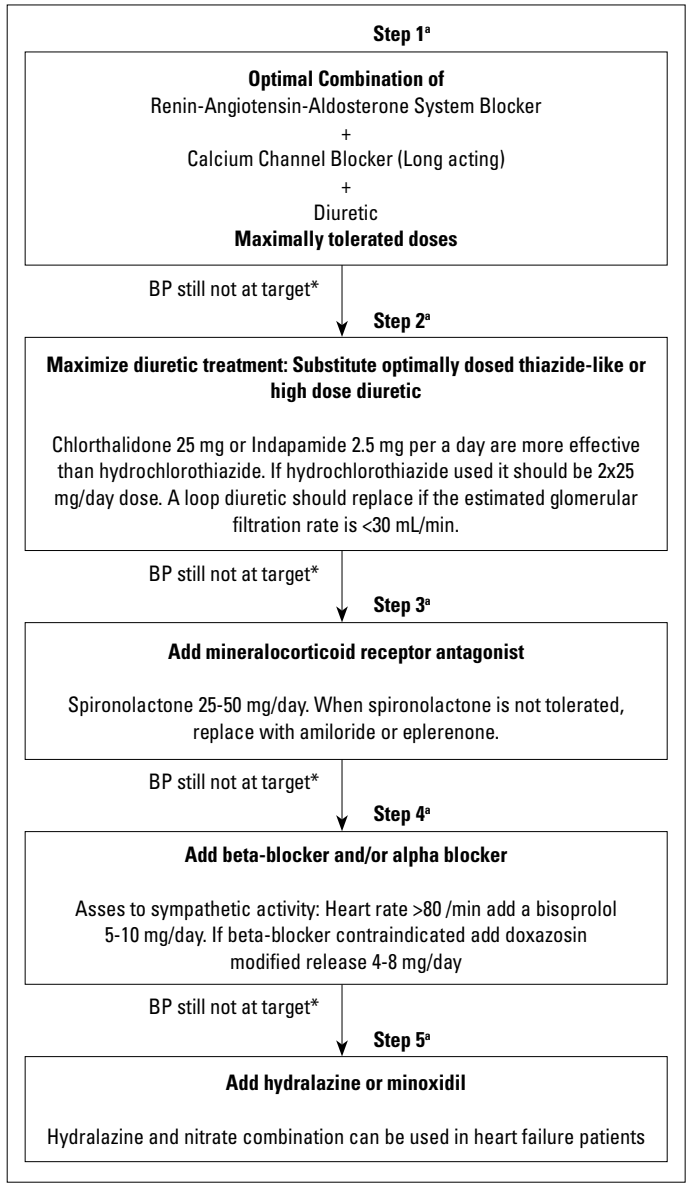

Figure 2. Algorithm for treatment of resistant hypertension
[a]: Beta blocker treatment can be add at any step presence of specific indication eg. heart failure, angina, post-MI, atrial fibrillation, younger women with, or, planning pregnancy
*: Combination tablets with adjustable doses considered when effective treatment has been found for maintenance drug adherence at any level

c. Investigational drugs

1) Firibastat

Aminopeptidase A is the enzyme responsible for the conversion of angiotensin II to angiotensin III in the brain. Inhibition of aminopeptidase A down-regulates the brain renin-angiotensin system and decreases sympathetic outflow (125). In the NEW-HOPE study, firibastat was shown to decrease BP significantly in patients with stage-2 hypertension with a good safety profile (126). Although there is no data on its role in RHT treatment, firibastat was found to be effective in patients who are at high risk for RHT in a sub-analysis of the NEW-HOPE study. Thus, firibastat may be a promising molecule in patients with RHT. However, more data is needed before using firibastat in routine daily practice.

2) Empaglifozin

Empaglifozin is a sodium-glucose cotransporter-2 inhibitor that is mainly indicated in Type II diabetes mellitus for glycemic control. In the EMPA-REG OUTCOME study, empaglifozin provided a mortality benefit and a decrease in heart failure hospitalizations (127). These positive effects on cardiovascular outcomes

are speculated to result from its effects on BP and weight control (128). Moreover, empaglifozin was tested in diabetic African American patients with hypertension in a short-term prospective study and provided a significant decrease in BP (129). Further randomized, long-term studies are required to understand the effect of empaglifozin in the treatment of hypertension.

3) Sacubitril/valsartan

Sacubitril/valsartan, a combination of an ARB and a neprilysin inhibitor provided a mortality and morbidity benefit compared to ARB alone in patients with heart failure, with the inconvenience of more significant hypotensive attacks resulting from extensive vasodilatation (130). However, this feature of sacubitril/valsartan may be an advantage in the treatment of hypertension. Compatible with this view, several studies investigated the potential of sacubitril/valsartan in hypertension treatment and found positive results (131-133). Sacubitril/valsartan decreased BP significantly and was found to be superior compared to ARBs, especially in elderly patients with arterial stiffness (133, 134). However, it has not been studied in patients with RHT. Thus, despite the potential benefit of sacubitril/valsartan as an antihypertensive, more qualified data is required on its usefulness in patients with RHT.

d. Invasive treatment

1) Renal denervation therapy

The sympathetic nervous system increases renal vascular resistance, renin release, and sodium absorption from the kidneys. Radiofrequency, ultrasound, and neurotoxin agents are used for renal denervation (RDN). The results of RDN are confusing in terms of efficacy and safety. Effective BP decrease with RDN has been detected in some observational studies and Symplicity-HTN 1 and 2 studies (135, 136). However, the lack of sham groups in these studies received great criticism. Therefore, two RCTs with a sham procedure control, one of which was Symplicity-HTN 3, were planned to complete this deficit. In these two studies, RDN was not found to be superior to medical treatment in terms of BP decrease, and no difference was found in terms of safety (137, 138). The inability to measure the decrease in sympathetic activity, the complex physiopathology of hypertension, and the lack of knowledge of the long-term consequences of decreased sympathetic activity limits the practice of RDN. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies performed with multielectrode catheters seem promising to achieve effective BP reduction with RDN in patients with and without pharmacotherapy (139, 140). However, the present data is still not adequate to recommend RDN in the treatment of RHT with confidence.

2) Baroreceptor activation therapy

In the baroreceptor activation therapy, the electrodes placed in the carotid artery stimulate the receptors via stimuli from the chest pulse generator. As a result, sympathetic activation is reduced by the vagus nerve. Although the second-generation device seems safe (141), the lack of RCT, its cost, and the necessity of complicated surgery restrict its development. The less invasive endovascular stent-like device inserted into the carotid artery was found to effectively reduce BP in the first human data (142). However, there is a need for RCTs to prove its safety and efficacy.

3) Arteriovenous anastomosis

In patients with advanced chronic obstructive pulmonary disease and hypertension, an arterio-venous (AV) shunt created to increase cardiac output and oxygen delivery causes an immediate decrease in BP (143). The creation of an AV fistula in patients with ESRD for hemodialysis results in a significant decrease in BP (144). Thus, the creation of such an AV anastomosis between central vessels may help to control BP in patients with RHT by providing a low resistance area to remove extensive pressure from the arterial system. The benefit of AV anastomosis in RHT has been investigated in prospective, randomized, controlled ROX-CONTROL HNT study. Despite a significant decrease in BP at 6 months and 1 year, a remarkable number of patients developed venous iliac stenosis related to the procedure (145, 146). Moreover, the effects of a permanent AV shunt on cardiac hemodynamics is not known.

Conclusion

RHT shows a significant prevalence and is related to significant mortality and morbidity. The development of guidelines specifically targeting this issue may help to decrease these adverse effects. The exact diagnosis of RHT may provide better usage of sources and prevent the negative consequences of over-treatment. Determining the underlying cause may increase the success of treatment. In the case of resistant essential hypertension, treatment should be changed to a combination of RAAS blocker, CCB, and a powerful diuretic in addition to proper nonpharmacological treatment as first-line. Spironolactone should be the first agent for add-on treatment in patients without contraindications. In patients who are resistant to these drugs, alpha-blockers, beta-blockers, I1 imidazoline receptor agonists, or peripheral vasodilators may be used. Further studies are required to understand the exact pathophysiological mechanisms causing resistance to treatment, and to choose the best drug combination to increase success rates in the treatment of RHT.

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