# REVIEWS

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# Resistant Hypertension*

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**A** – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

## Abstract

Resistant hypertension is a severe medical condition which is estimated to appear in 9–18% of hypertensive patients. Due to higher cardiovascular risk, this disorder requires special diagnosis and treatment. The heterogeneous etiology, risk factors and comorbidities of resistant hypertension stand in need of sophisticated evaluation to confirm the diagnosis and select the best therapeutic options, which should consider lifestyle modifications as well as pharmacological and interventional treatment. After having excluded pseudohypertension, inappropriate blood pressure measurement and control as well as the white coat effect, suspicion of resistant hypertension requires an analysis of drugs which the hypertensive patient is treated with. According to one definition – ineffective treatment with 3 or more antihypertensive drugs including diuretics makes it possible to diagnose resistant hypertension. A multidrug therapy including angiotensin – converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, long-acting calcium channel blockers and mineralocorticoid receptor antagonists has been demonstrated to be effective in resistant hypertension treatment. Nevertheless, optional, innovative therapies, e.g. a renal denervation or baroreflex activation, may create a novel pathway of blood pressure lowering procedures. The right diagnosis of this disease needs to eliminate the secondary causes of resistant hypertension e.g. obstructive sleep apnea, atherosclerosis and renal or hormonal disorders. This paper briefly summarizes the identification of the causes of resistant hypertension and therapeutic strategies, which may contribute to the proper diagnosis and an improvement of the long term management of resistant hypertension (**Adv Clin Exp Med 2016, 25, 1, 173–183**).

**Key words:** diagnosis, management, resistant hypertension.

The epidemiological trends of the past few years have indicated an approximately 30% increase in the frequency of hypertension diagnosis. Despite this significant incidence and prevalence in the general population, in a large proportion of patients, it is possible to achieve optimal control of blood pressure, only if the criteria for the proper selection of antihypertensive treatment (in accordance to guidelines) are met, including optimal compliance and elimination of pseudo resistance and secondary cases of disease. Nevertheless, one estimation of the efficacy of treatment is not encouraging and indicates that approximately 9–18% of patients meet the criteria of diagnosis of resistant hypertension (RH) [1].

## Definition

Resistant hypertension is diagnosed when, despite treatment with at least three antihypertensive agents (including a diuretic) from different classes in correct combination and at the highest

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tolerated doses, the target blood pressure level is not achieved [2] – < 140/90 mm Hg for the general population and < 140/85 mm Hg for patients with diabetes and chronic kidney disease.

This definition also includes patients in whom effective blood pressure control requires the use of at least four drugs [2]. It is very important to rule out the causes of pseudo-resistance to treatment, which usually include an improper technique of blood pressure measurement, non-adherence of the patient, especially regarding therapeutic recommendations, and finally the white coat effect [2].

## Epidemiology

Considering the epidemiological data, the efficacy of antihypertensive treatment is quite variable. In the NHANES study, target blood pressure (BP) values, were achieved in only 53% of the patients treated with antihypertensive drugs [3]. An even lower percentage of BP target levels, i.e. < 130/80 mm Hg, was observed in patients with diabetes [3] and chronic kidney disease [4]. A large study based on the Spanish Ambulatory Pressure Registry covered about 68,000 patients treated for hypertension, 12% of whom were diagnosed with resistant hypertension (RH). Ambulatory blood pressure measurement (ABPM) confirmed true resistance to treatment in 62.5% of the patients, and in the remaining 37.5%, the ineffectiveness of the therapy was due to the white coat effect [5].

Analysis of ALLHAT study results has shown that 47% of the patients were resistant to treatment during the first-year follow-up, and at the end of the study, 27% of the patients were taking at least three antihypertensive drugs [6].

Data from the Polish national survey NATPOL 2011 is worth mentioning in this context. It has been shown that the incidence of hypertension in the adult Polish population amounts to 32%, i.e. about 10.5 million people [7]. Although the detection of hypertension has not improved significantly and amounts to about 70% (compared to the results of the previous NATPOL-PLUS study from 2002), significant progress can be observed in the proportion of patients successfully treated with antihypertensive drugs, i.e. 26% in the present study vs. 14% of women and 10% of men in the NATPOL-PLUS 2002 study [7].

## Causes of Resistant Hypertension

Identification of resistant hypertension as a specific category is important, as the RH subpopulation experiences a significantly higher incidence and greater severity of organ damage than patients with pharmacologically-controlled HTN. An extremely important question to consider in this aspect is whether or not there are any patients in whom pharmacological BP normalization is impossible, and whether or not the major cause for the observed resistance is an inappropriate pharmacotherapy alone or sub-optimal patient-doctor cooperation.

In most cases, persistently elevated BP is due to chronic systolic hypertension. There is increasing evidence that resistant hypertension is not a rare occurrence in the population with good access to specialized medical care [8].

Considering the multitude of potential mechanisms responsible for therapeutically resistant hypertension, it is necessary to identify the reasons for losing control over BP and to introduce corrective measures. Reducing morbidity and mortality in this group often requires aggressive therapy.

Resistant hypertension should be considered in three overlapping dimensions [9]:

– resistant physician,
– resistant patient,
– resistant hypertension itself – provided the two previous reasons are excluded.

The reasons for the lack of patient-doctor cooperation (resistant patient) are complex and significantly affect BP control. They include such factors as poor medication adherence resulting, for example, from the side effects of antihypertensive drugs, an incomprehensible dosing regimen, the absence of a subjective feeling of illness or excessive cost of the treatment. Nevertheless, a patient's non-adherence to hypertensive therapy can be easily and routinely detected by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis of antihypertensive medications or their metabolites, which was revealed by Tomaszewski et al. [10]. Therefore, the physician's role in patient education seems invaluable [9].

The most common causes of resistant hypertension on the doctor's side involve:

1. Inappropriate blood pressure measurement.
2. Pseudo-resistant hypertension.
3. The white coat effect.
4. Incorrect treatment decisions (inappropriate drug selection, inadequate dosage, the use of combination therapy without understanding the mechanisms triggering high blood pressure development, inefficient use of diuretic therapy).
5. Doctor's inertia in achieving target BP values [9].

Approximately one-third of primary care practitioners do not implement antihypertensive therapy in patients with DBP ≥ 90–100 mm Hg,

and even more do not do this in patients with SBP = 140–160 mm Hg. The authors of several other studies found that most doctors do not treat isolated systolic hypertension or do not try to optimize control over it [9]. The problem of the physician's therapeutic inertia is not only an unjustified delay in the onset of treatment or its intensification. It might also be due to unreasonable skepticism to the guidelines, distrust of treatment goals and lack of time to provide the patient with detailed therapeutic and lifestyle recommendations. In some cases, the doctor's inertia should be considered as a lack of assertiveness, when a patient adapted to high BP refuses complete treatment or to take many medications in order to manage an asymptomatic condition. Furthermore, in the vast majority of cases, general practitioners/family physicians attempt to reduce the doses, or to mitigate the drug regimen even, without verifying the BP measurements in patients who complain about the putatively too low BP values in measurements acquired at home.

Resistant hypertension itself, the causes of which are shown in Table 1, may only be diagnosed after having excluded all the above-mentioned factors [11].

# Pathogenesis of Resistant Hypertension

## Hyperaldosteronism

Identifying aldosterone as an important factor inducing drug resistance was a milestone in the understanding of RH pathogenesis and treatment. These mechanisms are complex and involve much

**Table 1.** Causes of resistant hypertension [10]

| | |
|---|---|
| Hypervolemia | excessive sodium intake,<br>impaired kidney function:<br>defective pressure natriuresis<br>a) chronic kidney disease<br>b) renal artery stenosis (increased renin, angiotensin, aldosterone levels with sodium retention)<br>heart failure (aggravate sodium retention),<br>drugs cause sodium retention (mineralocorticoid receptor agonist, estrogens, nonsteroidal anti-inflammatory drugs),<br>fluid retention caused by vasodilators dilate arterioles and stimulate RAAS (minoxidil, hydralazine, alpha blockers),<br>ineffective use of diuretics |
| Activity of neuronal sympathetic system | chronic stress<br>chronic pain<br>hypertension provoked by fear, hyperventilation, paroxysm of panic fear (vasoconstriction) |
| Drugs | non-steroidal anti-inflammatory drugs NSAIDs (inhibition of renal prostaglandin production, decrease renal blood flow, retain sodium),<br>glucocorticosteroids,<br>licorice (suppress the metabolism of cortisol by beta hydroxysteroid dehydrogenase and stimulate mineralocorticoid receptor),<br>erythopoetin stimulating agents (increase vascular production of vasoconstrictors e.g. thromboxane),<br>cyclosporine/tacrolimus (enhance sympathetic nervous system activity, renal vasoconstriction, sodium and water retention),<br>antidepressants (monoaminooxidase inhibitors MAO-I),<br>sympathicomimetics (nasal decongestants),<br>oral contraceptives with estrogen,<br>anti-VEGF (VEGF stimulate nitric oxide production and vasodilatation),<br>cocaine, amphetamine |
| Undiagnosed secondary hypertension | kidney diseases (sodium retention, decrease in nitric oxide production which causes vasoconstriction),<br>renal artery stenosis (due to atherosclerosis or fibromuscular dysplasia which reduce renal perfusion pressure and stimulate renin, angiotensin, aldosterone release and vasoconstriction),<br>obstructive sleep apnoea (more reactive oxygen species which reduces nitric oxide bioavailability,<br>endocrinological disorders (primary hyperaldosteronism, hypo/hyperthyroidism, hyperparathyroidism, pheochromocytoma, acromegaly, congenital adrenal hyperplasia, carcinoid tumor |

more than the hypervolemia-inducing aldosterone effect on sodium reabsorption.

The results of several recent studies have conclusively confirmed the importance of the direct vasoconstrictive effect of aldosterone through the vessel wall myocytes and disintegration of its homeostasis conditioning proper tension. Therefore, blocking aldosterone activity seems to be a potentially effective way to combat resistant hypertension.

The importance of primary aldosteronism (PA) as a cause of hypertension implies the need for more sensitive diagnostic instruments than the evaluation of plasma renin activity (PRA) and aldosterone levels. Determination of ARR (aldosterone/PRA) enables the identification of more PA patients, even without a laboratory diagnosis of hypokalemia. The effective elimination of factors leading to obtaining false-negative ARR results is crucial [12].

False-negative ARR results might be caused by using:

– ACEI,

– Diuretics, which elevate renin synthesis.

False positive ARR results might be caused by using:

– HRT/oral contraceptives, which increase the hepatic synthesis of angiotensinogen and suppression of renin synthesis,

– Beta-blockers, which suppress renin synthesis.

Is slight aldosteronism enough to disturb sodium-potassium homeostasis, and is that why low doses of spironolactone restore it? Considering the spironolactone pharmacodynamics only in terms of antagonizing the effects of aldosterone and other mineralocorticoids seems to be an oversimplification. Aldosterone plays a key role in RH pathogenesis – but also by means of other non-renal mechanisms, where the intensity of its action does not depend on its absolute amount alone. Blocking aldosterone hormone activity requires quantitatively about 1000-fold higher doses of spironolactone by weight than the amount of aldosterone secreted per day. Therefore, that does not explain the effects obtained with low doses of spironolactone, i.e. 25 mg, which may inhibit relatively small amounts of aldosterone. Aldosterone-induced myocardial fibrosis and hypertrophy may also involve vessels, and the beneficial effect of spironolactone may, as in the case of heart failure, extend far beyond its diuretic action, including a regression of their unfavorable remodeling.

According to estimated figures, the prevalence of primary aldosteronism in the RH population is about 20% [2]. However, blocked and low renin levels may occur in up to 75% of RH patients, indicating the crucial role of RAAS and aldosterone excess in cases other than primary aldosteronism as well [13]. The data regarding the prevalence of PA was obtained in Greek studies, which included a large group of patients with resistant hypertension (true resistance was confirmed in 1616 of 2032 patients) [14]. Twenty one percent of patients with elevated levels of plasma aldosterone and aldosterone-renin ratio (ARR) were subject to biochemical tests confirming PA diagnosis (the saline loading test and fludrocortisone test); primary aldosteronism was diagnosed in 11.3% of cases [14]. According to M.C. Acelajado and D.A. Colhoun, patients diagnosed with primary aldosteronism are at a higher risk of cardiovascular complications (in the form of cerebrovascular accidents, myocardial infarction or dysrhythmia) compared to hypertensive patients without PA [15].

Moreover, supplementation of antihypertensive combination therapy with a mineralocorticoid receptor antagonist significantly improves the effectiveness of the treatment, irrespective of the biochemical criteria for PA diagnosis [15].

A prospective study involving 175 patients with resistant hypertension (documented by ABPM), in which the patients received 25–100 mg/d of spironolactone, showed that after about 7 months of this therapy, the mean drop of systolic blood pressure (SBP) was 16 mm Hg, and the mean drop of diastolic blood pressure (DBP) was 9 mm Hg. These values were confirmed by ambulatory blood pressure measurement (ABPM). The doctor's office measurements also revealed better blood pressure control, with a mean improvement of 14 mm Hg for SBP and 7 mm Hg for DBP. In control ABPM, target BP values were achieved in 48% of patients. The results mentioned above show that the addition of a mineralocorticoid receptor antagonist, as a fourth or fifth medication to the antihypertensive regimen in RH patients, results in improved BP control [16].

Further evidence of effective BP optimization brought about by adding an aldosterone receptor antagonist to the combination therapy was provided by the ASCOT-BPLA study, where the addition of spironolactone at a dose of 25 to 50 mg/d as a fourth antihypertensive drug (according to the study protocol, one group of patients received amlodipine and perindopril, the other received atenolol with bendroflumethiazide, and the third drug, used in the case of lack of therapeutic effects, was doxazosin) reduced SBP by 21.9 mm Hg and DBP by 9.5 mm Hg [17]. Other important evidence for the efficacy of spironolactone in lowering systolic BP in patients with resistant hypertension has been provided in the first randomized multicenter trial with the aldosterone receptor antagonist ASPIRANT. The addition of 25 mg of spironolactone significantly reduced

ambulatory daytime and nighttime SBP [18]. Similarly to spironolactone studies, the work published by Krum et al. demonstrated significant BP improvement after supplementing the antihypertensive regimen with eplerenone, a selective aldosterone receptor antagonist, in patients in whom monotherapy blocking the RAAS did not ensure optimum BP control. An antihypertensive regiment based on the angiotensin II converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARBs) was supplemented with 50 or 100 mg of eplerenone. After 8 weeks of the combination therapy, a reduction in blood pressure was noticed: for ACE-I plus eplerenone regimen – SBP 13.4 ± 1.35 mm Hg, DBP 9.9 ± 0.88 mm Hg and for ARB plus eplerenone – SBP 16.0 ± 1.37 mm Hg, DBP 12.7 ± 0.81 mm Hg [19].

## Obstructive Sleep Apnea

According to the literature, about 50–60% of patients with obstructive sleep apnoea syndrome (clinically expressed as apnoea/hypopnea index AHI) suffer from hypertension. The pathogenesis of hypertension in patients with obstructive sleep apnoea (OSA) seems to be multifactorial. Possible explanations involve increased tension of the sympathetic nervous system, leading to elevated blood pressure (BP) as a result of higher cardiac output and vascular resistance and fluid retention secondary to tissue hypoxia and the effects of an increased aldosterone level [20]. Interesting results were obtained by Gonzaga et al., who investigated the prevalence of primary aldosteronism and obstructive sleep apnoea in patients with resistant hypertension. OSA was found in 84% of PA patients and in 74% of individuals with normal aldosterone levels [21]. The study by Pedrosa et al. assessing the most common secondary causes of RH development, included 120 patients with resistant hypertension. The results were as follows: obstructive sleep apnoea (AHI above 15 events/h) was the most common cause of RH – it was found in 64% of patients, PA constituted 5.6% of the causes; the other reasons were renal artery stenosis 2.4%, renal parenchymal diseases 1.6%, oral contraceptives 1.6% and thyroid dysfunction 0.8% [22]. The relationship between OSA and resistant hypertension is further confirmed by studies in which the use of specific OSA therapy, i.e. a CPAP (continuous positive airway pressure) device, reduced blood pressure. A study by Lozano et al. compared the efficacy of drug therapy alone in RH patients with concomitant OSA and drug therapy supported by OSA specific treatment, i.e. CPAP. Control ABPM revealed that patients treated with CPAP achieved better BP control (SBP reduction of 9.7 mm Hg and DBP of about 7.0 mm Hg) [23]. The correlation between hypertension and obstructive sleep apnea should especially be considered when in ABPM nocturnal increases of BP or an absence of BP reduction is present, however Kasiakogias et al., in a 3-year follow-up study, have shown no difference in BP or drug usage in patients with OSA who either continued or discontinued treatment with positive airway pressure therapy [24]. In recent years, four meta-analyses have also shown that the effect of continuous, positive airway pressure therapy on ambulatory BP is very small (1–2 mm Hg reduction) [25].

## The Role of Kidneys and Sympathetic Nervous System in Resistant Hypertension Development

According to current knowledge, the role of the sympathetic nervous system seems to be one of the key pathomechanisms in resistant hypertension development [26]. Coexistence and correlation between obstructive sleep apnoea syndrome, abdominal obesity and elevated aldosterone levels in patients with resistant hypertension require further studies, but it seems the main common factor for these conditions is the increased activity of the sympathetic nervous system [26].

Another important pathomechanism paving the way for resistant hypertension development is adrenergic hyperstimulation of the kidneys. There are many kidney-derived mechanisms favoring RH development, such as impaired pressure natriuresis (as a consequence of chronic kidney diseases – parenchymal and involving renal arteries [27]) which, under physiological conditions, is responsible for renal sodium excretion. Other causes include: local disturbance of nitric oxide synthesis, adverse effects of drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs), but also selective inhibitors of cyclooxygenase-2 (COX-2), glucocorticoids and cyclosporine, then non-renal causes of sodium retention, including hyperaldosteronism, obstructive sleep apnoea, increased activity of the sympathetic nervous system and the RAAS, vasodilators (hydralazine, minoxidil), excessive salt consumption and finally inefficient use of diuretics [27].

## Secondary Basis of Resistant Hypertension

Secondary causes are responsible for 5–10% of RH cases. Their incidence increases with age, particularly in relation to hypertension secondary to

atherosclerotic renal artery stenosis. Some of the more common causes of secondary RH are renal pathologies (parenchymal diseases, vascular hypertension), PA, OSA, and rarer causes include Cushing syndrome/disease, pheochromocytoma, thyroid gland dysfunction (hyper- and hypothyroidism), hyperparathyroidism, coarctation of the aorta or intracranial tumors [2].

## Diagnostics of Resistant Hypertension

Ambulatory blood pressure measurement (ABPM) is more indicative of cardiovascular events than BP measurement at the doctor's office. Prospective cohort studies have shown that even when BP measurements taken in a clinic are in the normal range, but 24-h ABPM reveals elevated BP, the risk of cardiovascular events is significantly higher than in patients with normal results of both measurements. In the RH population, ABPM is also more effective in assessing circadian BP profile changes in response to drugs and physical activity than incidental/irregular measurements [28].

In one study, ABPM has enabled the detection of white coat hypertension in 44% of 286 investigated patients with suspected RH. Individuals from the "true RH" group experienced much more common organ complications (nephropathy, left ventricular hypertrophy) and a significantly smaller BP reduction at night in comparison with the group with white coat hypertension diagnosis [29]. This study confirmed that: 1. Twenty-five percent of patients with suspected RH had good BP control in ABPM; 2. For one third of the people with RH initially diagnosed at the doctor's office, the BP values collected later on by means of ABPM were normal = white coat effect; 3. ABPM can be considered an optimal initial method verifying RH diagnosis.

In which situations should ABPM be performed as a test of differentiating RH from white coat hypertension?

– large differences between the measurements taken at the doctor's office and at home,
– normal blood pressure in self-measurements,
– resistant hypertension without organ damage.

British guidelines concerning hypertension management by the National Institute of Health and Clinical Excellence (NICE) in the UK 2011 emphasize the importance of ambulatory blood pressure measurement (ABPM) in all patients and, in order to confirm the diagnosis, they recommend this test in those individuals in whom clinical measurements show BP 140/90 mm Hg [30]. The main advantage of this method is that it provides a wide range of measurements performed in the "natural" patient's environment, which represents a more reliable assessment and may reveal patients with normal daytime office measurements and coexisting target organ damage. Moreover ABPM helps in classifying the hypertension pattern (dipper, non-dipper, reverse dipper), which is impossible during home or office measurements. That classification gives an opportunity to arrange chronotherapy and distinguish patients at a higher cardiovascular risk. [31]. Nonetheless, the poor quality of raw data acquired in a common practice, the set up of cut-off points for both, the normal range of blood pressure and for the load of hypertension hinder the physician from appropriately interpreting the results. Hence, much more effort should be made in focusing on the quality of the data, equipment and measurement techniques in order to prevent misdiagnosis of the blood pressure control.

Another important element is so-called pseudo-hypertension – observed more frequently in the elderly, in whom vessel wall calcification makes artery compression with the cuff impossible, and the measurement results seem to indicate severe HTN, but no organ damage is observed. Implementation of intensive treatment triggers symptoms of organ hypoperfusion without a decrease in BP. Patients with pseudo-hypertension often have aortic wall calcifications described on the chest X-ray. The pseudo-hypertension problem may be to some extent solved by employing the Osler maneuver – when the pulse can be felt on the radial artery despite filling the cuff above the SBP value – or using a Doppler probe for BP measurement. Finally, the ultimate verification method is an intra-arterial BP measurement.

A comparison of patients meeting the RH criteria (isolated RH in at-home measurements and chronic RH) vs. well-controlled HTN + white coat HTN revealed that RH patients: are older, more often suffer from coexisting ischemic heart disease and chronic renal failure, take more medications (more often at least 4 and significantly less often 3 or less) compared to the well, and have higher SBP and DBP values – both when measured at the doctor's office and at home.

In the group of patients taking at least 3 antihypertensive prescription drugs, approximately 66% of RH cases were confirmed based on at-home measurements. People with RH diagnosis based on at-home measurements require more aggressive therapy. Agarwal et al. presented a meta-analysis of 37 randomized controlled trials (RCTs) comparing the degree of BP control improvement, based solely on clinical BP measurements versus home measurements. The results clearly showed the advantage of home BP measurements, which

contributed to better BP control and were much more effective in eliminating the doctors' therapeutic inertia [32].

According to the recommendations of the American Heart Association from 2008, diagnosis of a patient with RH should first exclude the reasons of pseudo-resistance, identify the factors contributing to RH development, including the secondary etiology, and finally assess hypertension-induced organ damage (Fig. 1) [2].

## Treatment of Resistant Hypertension

Treatment of RH is difficult and often requires the implementation of expensive diagnostic procedures to identify its secondary causes and, as far as possible, an effective use of polypharmacy. The therapy should essentially be aimed at three objectives:

– identification and elimination of the causes (if reversible),

– diagnosis and appropriate treatment of RH secondary etiology,

– selection of effective treatment [2].

Health-promoting lifestyle modification is a component of non-pharmacological treatment, and is an extremely important aspect of RH management. Patients should always be recommended to modify their lifestyle by losing weight, intensifying physical activity and introducing a low-fat diet (Dietary Approaches to Stop Hypertension-DASH) [2]. Reducing salt intake, preferably down to 100 mmol of sodium per day, is another important recommendation. A study published by Graudal et al. compared the effects of a low and high sodium diet. In the group of individuals on a sodium-controlled diet, a drop in BP (by 3% in hypertensive patients) was accompanied by increased levels of renin, aldosterone, noradrenaline, adrenaline, cholesterol by 2.5% and triglyceride by 7% [33].

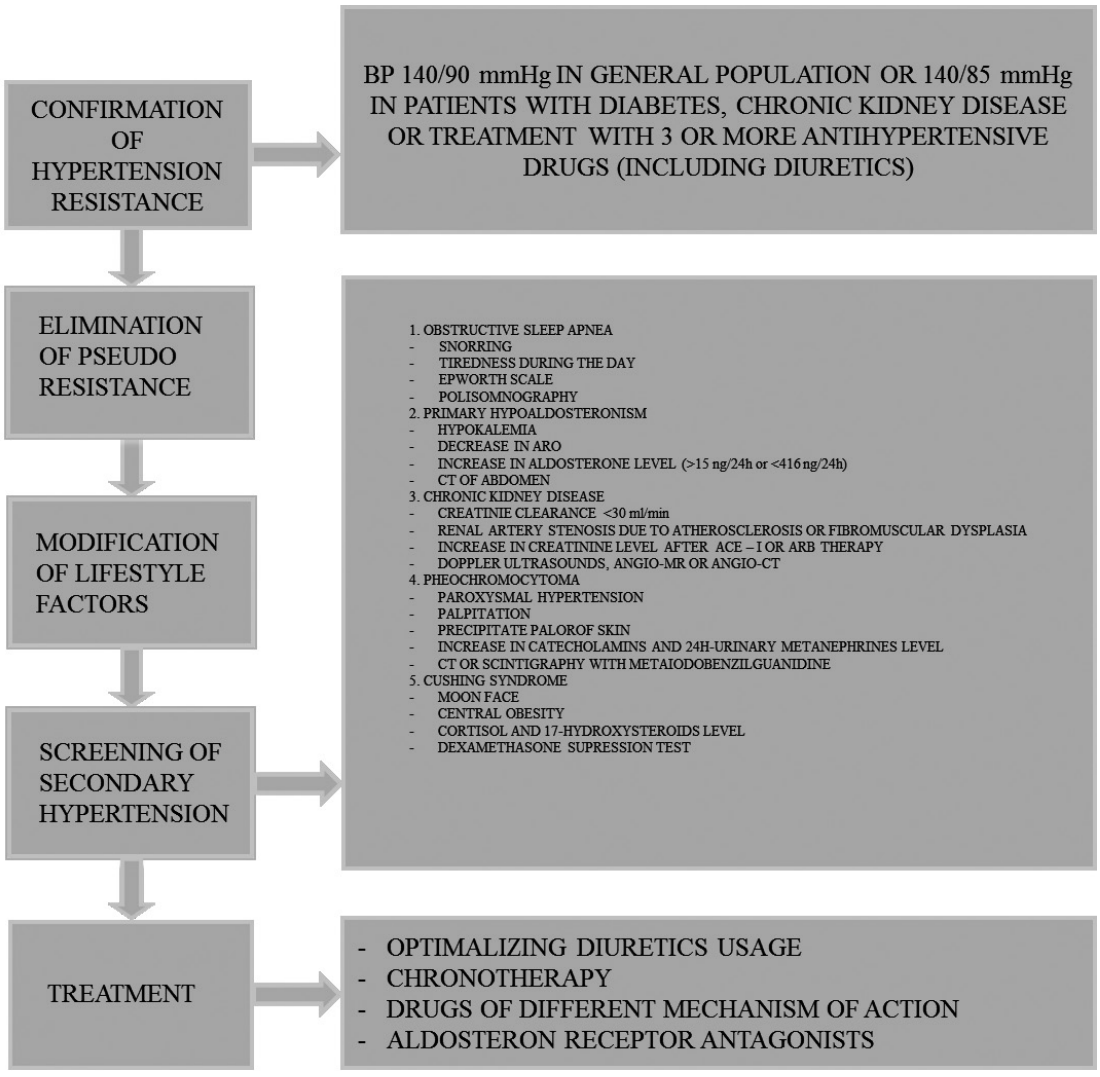


**Fig. 1.** Algorithm of diagnosing resistant hypertension [10]

A drug regimen should be based on combination therapy, taking into account the basic mechanisms conditioning arterial hypertension development, such as sodium metabolism/volemia, renin–angiotensin–aldosterone system (RAAS) and increased tension of the sympathetic nervous system [34]. Most clinical trials involved dual therapy, with particular emphasis on diuretic treatment [2]. Therapy based on the combination of a diuretic (thiazide diuretic for the first-line treatment and a loop diuretic in the case of impaired renal function with creatinine clearance < 30 mL/min) and drugs affecting RAAS seems to be well justified [2]. The ACCOMPLISH study evaluated a combination of ACE-I and a calcium channel blocker (CCB). Fewer cardiovascular events were reported as compared to diuretic plus CCB therapy [35]. However, it requires further and long-term studies, and that is the reason why the combination of ARB or ACE-I with a diuretic or CCB seems favorable from the pathomechanical point of view. As recommended by the American Heart Association guidelines from 2008, adopted by the Polish Society of Hypertension, three-drug therapy with ACE-I or ARB, a calcium channel blocker and a thiazide-like diuretic is effective and well tolerated [2]. The use of the β-blocker is particularly recommended in patients with concomitant ischemic heart disease or congestive heart failure [2]. If no BP targets are achieved, it is recommended to supplement the polytherapy with a drug from the mineralocorticoid receptor antagonist group. Moreover, bearing in mind the increased risk of hyperkalemia resulting from polypharmacy, close monitoring of the serum potassium level is essential [2]. Despite their high antihypertensive effectiveness, older drug classes, such as centrally acting alpha-agonist drugs (clonidine) and direct vasodilators (hydralazine, minoxidil), serve as secondary medications due to their severe side effects [2].

The NICE [30] recommends the following algorithm of antihypertensive treatment: first-line therapy for patients up to 55 involving ACE-I or ARB, and CCB in elderly patients (or a thiazide-like diuretic in the case of poor tolerance). If BP optimization is not achieved, combination therapy comprising CCB and ACE-I or ARB is recommended; and at the third stage, a thiazide-like diuretic is added to this regimen. If the target BP values are still not achieved, RH is diagnosed; and in normokalemic patients, the polytherapy is supplemented with a fourth drug, spironolactone; and if the serum potassium level > 4.5 mmol/L, a diuretic dose is increased. The fifth drug in this therapy is an α or β-blocker [30].

# Surgical Treatment of Resistant Hypertension

## Renal Denervation

Since in some patients, the use of maximal doses of antihypertensive drugs and exclusion of the secondary aetiology of hypertension did not result in reaching target BP values, research on improving the renal denervation method initiated in the 1960s was started. Denervation treatment was based on a correlation between the kidney-related effects of sympathetic nervous system activity and the pathophysiology of hypertension. Considering changes in the renin level and sodium excretion, induced by a slight growth in sympathetic nervous system activity (long before a clinically noticeable reduction in renal blood flow and glomerular filtration rate), the researchers began studying a non-selective sympathectomy. Despite alleviating the primary disease, it had numerous side effects, including orthostatic tachycardia, intestinal disorders and sexual dysfunction. Innovative denervation methods involve selective percutaneous ablation of kidney afferent and efferent fibers *via* femoral artery access.

In a study described by Krum et al., the selective ablation resulted in a statistically significant reduction of blood pressure by 14/10, 21/10, 22/11, 24/11 and 27/17 mm Hg, occurring 1, 3, 6 and 9 months and one year after the procedure, respectively. The antihypertensive effect was durable, and no regeneration of previously denervated fibers was observed [36]. Encouraged by the results of their research, Esler et al. tested the method next year in the Symplicity-HTN-2 study, involving a larger group of patients with resistant hypertension. In this study, patients were randomly assigned to a control group continuing the current antihypertensive regimen, and the treatment group which underwent ablation. Six months after the procedure, a significant decrease in blood pressure measured at the doctor's office was reported in the study group (from 178/97 mm Hg to 143/85 mm Hg), whereas no reduction was found in the control group [37]. There were also no significant side effects of the procedure, except for an aneurysm at the site of injection and the renal artery dissection, which should be associated with the procedure methodology.

Even more interesting results were reported by Witkowski et al., who performed renal denervation [37] in 10 patients with confirmed RH and coexisting obstructive sleep apnoea syndrome. They obtained not only a reduction in SBP and DBP by 34/13 mm Hg after 6 months of treatment, but also AHI minimization [38]. However,

another trial, SIMPLICITY HTN 3, has deadened initial enthusiasm of renal denervation's effectiveness [39]. In view of this trial, renal denervation by ablation has fallen short of its secondary efficacy goals, and failed to reach its primary efficacy endpoint. SIMPLICITY HTN 3 showed that renal denevation seems to have a non-favorable impact on morbidity-mortality and cannot be a promising method for the treatment of hypertension resistant to a three-drug regimen [39].

## Electrical Stimulation of the Carotid Sinus Baroreceptors

In view of the increasing number of patients diagnosed with resistant hypertension and technological progress, studies on baroreflex stimulation of the carotid sinus, started in the 1960s, have been resumed. Devices implanted in the carotid sinus area strengthen the impulse from baroreceptor afferent fibers to the center of cardiovascular control in the brain, thus supporting blood pressure reduction. In addition, constant baroreceptor activity diminishes the amount of secreted norepinephrine and weakens sympathetic nervous system activity [38].

In 2003, 11 patients without hypertension, who underwent elective carotid endarterectomy, were enrolled in the BRASS (Baroreflex Activation System Study), involving short-time (transient) stimulation of carotid sinus baroreceptors. A decline in SBP values from 144 mm Hg to 131 mm Hg was observed, and the results were apparently correlated with stimulation intensity [40].

A multicenter prospective study, DEBuT-HT (Device-Based Therapy in Hypertension Trial), evaluated the safety and efficacy of baroreflex activation in 45 patients. The study group consisted of patients over 21, whose blood pressure was > 160/90 mm Hg despite treatment with at least three antihypertensive drugs, including a diuretic. The study excluded patients with clinically significant orthostatic hypotension, cardiac arrhythmias, clinically significant valvular dysfunction, carotid artery stenosis exceeding 50% and hypertension caused by potentially removable factors. The study results showed a statistically significant decrease in blood pressure by 21/12 mm Hg after a three-month follow-up in the study group and a mean improvement by 33/22 mm Hg after a two-year follow-up [41].

Another randomized and double-blinded Rheos Pivotal study included 267 patients with resistant hypertension (defined as mean arterial blood pressure from five measurements above 160/80 mm Hg, SBP in ABPM ≥ 135 mm Hg, despite triple regimen). The patients had a device stimulating the carotid sinus implanted. It was activated one month after the implantation in the first group and 6 months after the procedure in the other group. The study did not meet the endpoints for acute responders or procedural safety. However, target systolic blood pressure values of < 140 mm Hg were achieved in 42% of patients in group A versus 24% of patients in group B, which was statistically significant [42].

New methods of hypertension treatment may provide effective solutions for patients not responding to standard antihypertensive therapy and qualifying into the RH group, which is at an increased risk of cerebrovascular accidents, myocardial infarction, heart failure and chronic kidney diseases. The elevated risk in these patients is the result of chronic, poorly-controlled hypertension, leading to organ damage in the form of left ventricular hypertrophy, chronic kidney disease and retinopathy.

# Conclusions

An exact estimation of RH prevalence is not easy (partly due to an inaccurate definition of the problem in scientific research) but it is necessary, as it shows an upward trend and is becoming an increasingly important clinical problem. The increased risk of cardiovascular complications in this group of patients requires a proper choice of correct antihypertensive therapy, taking into account the main pathomechanisms determining resistant hypertension development [6]. Further studies evaluating the relationship between obstructive sleep apnoea and increased aldosterone levels and RH development seem essential, and prospective research to evaluate the long-term effects of renal denervation and baroreceptor stimulation is also necessary.

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