An update of resistant hypertension: A stepwise approach

Athanasios J. Manolis
MD, PhD, FESC, FAHA, FACC

ABSTRACT

Hypertension (HTN) is the number one risk factor for cardiovascular events and is the leading cause of death worldwide. However the awareness treatment and control of blood pressure (BP) continues to be low worldwide despite the continuous effort for improvement. A particularly severe form of HTN is resistant hypertension (RH). In the ESH guidelines HTN was defined as resistant when despite life style changes and treatment with more than three drugs in maximum tolerated doses (thiazide/thiazide like diuretics, an RAS blocker and a calcium channel blocker), BP continues to be >140/90 mm Hg. However its important to exclude low adherence, secondary HTN with clinic but also with out-of-office blood pressure and 24h BP, in order to exclude pseudo-resistant HTN.
The prevalence of RH ranges from 5%-30%, on the basis of the definition used. However the true prevalence of RH after applying a strict definition and having excluded pseudo-resistant HTN is less than 10% and close to 5% in treated patients. The pathophysiology of true RH involves neurohormonal activation.
RH increases the risk of cardiovascular morbidity and mortality and renal outcomes. Epidemiological studies are necessary to more precisely define the frequency of RH and better assess this problem in the general population.

Key-words: *resistant hypertension, precisely*

Diagnosis

The diagnosis should rule-out pseudo-resistance HTN. Pseudoresistance is suboptimal BP control secondary to medication nonadherence, white-coat effect, or poor measurement technique. The exclusion of pseudo-hypertension is of paramount importance for the establishment of an accurate diagnosis. BP is often measured inaccurately; wrong-sized cuffs, measurement of BP only once, cuff placement over the patient's clothes, and wrong position of the patient are common mistakes performed in everyday clinical practice. Apparent treatment-resistant HTN is the term used in epidemiological studies for cases in which patients meet the criteria for RH but have unverified adherence or medication dosing or have not ruled out the white-coat effect. Under-treatment is also a common cause of pseudo-resistant hypertension, and studies indicate that a lack of BP control is often attributable to the absence of treatment intensification. There are some important questions to answer in this field. Is the patient taking the medication? Are the measurements accurate? What is the patients BP out of the office?

Risk factors

Lifestyle factors such as excessive alcohol (three or more drinks per day), sodium intake that exceeds 10 g per day and several drugs and substances may increase BP levels and contribute to the presence of RH. Non-steroidal anti-inflammatory drugs (NSAIDs) represent probably the most common agents in terms of worsening BP control. The use of NSAIDs not only increases BP levels but also can blunt the effect of various antihypertensive drugs such as diuretics and RAS blockers. The hypertensive effect of NSAIDs is more pronounced in pa-

Director B' Cardiology Department, Piraeus, Greece METROPOLITAN Hospital, Piraeus, Greece, Adj. Professor of Hypertension, Boston University, Boston, USA, Advisory Board Member, European Society of Hypertension

tients with chronic kidney disease. Other substances that can increase BP levels are decongestants and stimulant agents used for weight loss and also contraceptives, cyclosporine, erythropoietin, and cortisone that increase BP levels mainly through fluid retention.

Secondary HTN

Patients with resistant hypertension should be evaluated for secondary hypertension, such as chronic kidney disease, primary aldosteronism, obstructive sleep apnea, renovascular hypertension, catecholamine secreting tumors, Cushing syndrome, since recognition and directed therapy may improve blood pressure control. Kidney disease should be assessed in patients with an elevated serum creatinine or abnormal urinalysis. Primary aldosteronism is more common than previously thought and often goes undiagnosed, with a prevalence ranging from 8% to 30% in various hypertensives. Obstructive sleep apnea is very common in patients with resistant hypertension. Treating obstructive sleep apnea with continuous positive airway pressure (CPAP) in patients with RH has been shown to decrease 24-hour ambulatory blood pressure. Obesity and obstructive sleep apnea are both risk factors for RH.

Treatment

Blood pressure targets should be individualized based on patient characteristics, medication side effects, patient tolerance, and preferences. In patients with RH like in general population BP should be reduced below 140/90 mmHg and below 130/80 mmHg if well tolerated. According to recent 2023 ESH HTN guidelines effective treatment of true resistant hypertension should combine (i) lifestyle changes (particularly reduction of sodium and alcohol intake, implementation of regular physical activity and weight loss in overweight or obese patients), (ii) discontinuation of interfering substances, (iii) rationalization of current treatment and (iv) the sequential addition of antihypertensive drugs to the existing triple therapy. It is important to start first with nonpharmacological treatment that will support pharmacological therapy. It is well known that a healthy lifestyle is a very important factor affecting BP values. Patients should therefore, first of all, limit their dietary salt supply to 4-6 g/day and start physical activity. The best form of sport that lowers both SBP and DBP is regular aerobic exercise, including walking or running on a treadmill. Another element affecting the reduction in pressure values is, of course, the weight loss.

Pharmacological treatment consists of a group of ≥3 hypotensive drugs. The classic regimen consists of the use of a RAS blocker, long-acting calcium channel blocker (most commonly amlodipine), and long-acting thiazide/or thiazide like diuretic.

In patients with preserved glomerular filtration rate, the preferred first-line diuretic is either chlorthalidone or indapamide because of their longer half-life and more potent antihypertensive effect compared with hydrochlorothiazide. Loop diuretics are preferred in patients with an estimated glomerular filtration rate less than 30 mL/min and Torsemide can be proffered because of once a day dose. If blood pressure is still not controlled on maximally tolerated therapy with these 3 agents, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) should be the fourth-line agent. The addition of other agents should be based on individual factors. Vasodilating beta-blockers (labetalol, carvedilol, nebivolol, bisoprolol) may be the preferred fifth-line agent unless there are special conditions. Other choices include clonidine, a centrally acting alpha-2 agonist. The PATHWAY-2 trial demonstrated that spironolactone was superior in BP compared with bisoprolol (a beta-blocker), doxazosin (an alpha-blocker), or placebo as add-on therapy in patients with resistant hypertension on 3 blood pressure medications. However the trials PATHWAY-2 and ReHOT were short-term efficacy studies showing the effect on BP-lowering after 12 weeks of treatment and both studies included a relatively small number of patients, with low control rate at the end of the study. Side effects of spironolactone include hyperkalemia and gynecomastia, and the drug should be used with caution in chronic kidney disease. If gynecomastia becomes intolerable, eplerenone should be the choice. However in many countries, eplerenone is only approved in patients with HF, and eplerenone and spironolactone are not approved for use in hypertension. In a survey in the USA only 9% of patients with RH were treated with an MRA, and only 30% of patients were prescribed spironolactone at enrolment in the RADIANCE TRIO trial in patients with resistant RH. New more selective nonsteroidal MRAs such as finerenone, could be might alternative to spironolactone for patients RH. Spironolactone should be used with caution in patients with reduced eGFR and baseline potassium

levels >4.5 mmol/l. Direct vasodilators, such as hydralazine or minoxidil, should be used in combination with diuretics and b-blockers because they may cause severe fluid retention and reflex sympathetic activation with tachycardia. In other comorbidities such as patients with OSA, continuous CPAP may be of moderate benefit, especially when this condition is severe (AHI >30 events/h). In obese patients, GLP1 receptor agonists can reduce body weight, modestly lower BP and improve CV prognosis in patients with type 2 diabetes or with established CVD. Bariatric surgery can lower BP, CV risk factors and risk of CV events in severely obese patients and may, reduce the burden of antihypertensive medication when these patients have resistant hypertension. In patients eligible for treatment with SGLT2is, their use may add a moderate BP-lowering effect to the background of the antihypertensive therapy RH.

Non Pharmacologic Treatment

Non Pharmacologic treatment includes mainly devices such as renal denervation, and carotid baroreceptor stimulation.

Renal denervation (RDN): is a minimally invasive, investigational procedure and the mechanism includes the interruption of the renal sympathetic activity by destroying sympathetic nerves localized close to the renal arteries. According to 2023 ESH hypertension guidelines RDN can be considered as an additional treatment option in patients with RH if eGFR is >40 ml/min/1.73 m^2 (II B). It is important to confirm RH and to exclude secondary causes of hypertension before the procedure. Early trials on RDN are focused on severe hypertension, with SBP over 160 mmHg. In the SYMPLICITY HTN-2 trial, they found that RDN is safe and provides a lasting reduction in BP to 1 year. However, the SYMPLICITY HTN-3 trial proved to be a failure. New study, the SPYRAL HTN-OFF MED confirmed the efficacy of RDN in lowering BP in the absence of medications. The SPYRAL HTN-ON MED trial showed remarkably lower values of BP at 6 months in the RDN group. The RADIANCE-HTN TRIO using a newer catheter design showed a decrease of 5.8 mmHg compared with controls, a modest benefit. Baroreflex activation therapy: was initially associated with a high number of adverse incomes, mainly related to periprocedural complications due to the implantation of electrodes around both carotid arteries. However, the procedure has developed and shown promising effects in recent years.

The first study was the DEBuT-HT trial. After 3 months of baroreceptor stimulation, a reduction in SBP of 21 mmHg and DBP of 12 mmHg was achieved. The reduction in BP was even greater after 12 and 24 months of treatment. The Rheos Pivotal Trial, resulted in an average reduction 25 mmHg. Similar outcomes were revealed in the Barostim neo trial with 26 mmHg reduction.

Conclusions

To properly diagnose RH, BP measurement should be performed meticulously following the recommendations of current guidelines. It is also necessary to exclude factors that may contribute to the misdiagnosis of RH, so-called pseudo-RH.

In the diagnosis of RHT, it is crucial to consider the presence of secondary causes that contribute to its development. Early detection of secondary HT, particularly in younger patients, holds the potential to prevent irreversible structural and functional changes in organs, thus mitigating the risk of organ failure.

The pharmacological treatment of RH is complex. The main groups of drugs are blockers of the RAA system, long-acting calcium channel blockers, and long-acting thiazide diuretics, which are combined in polytherapy. In addition to pharmacological treatments, all patients at every stage of therapy should take care of the principles of a healthy lifestyle, i.e., limit salt intake, increase physical activity, and reduce body fat. Furthermore, the use of autonomic neuromodulation therapies in RH treatment has become very promising recently. Clinical trials on device-based therapies are still ongoing.

CONCLUSIONS

Given the association with multiple comorbidities and the need for multiple and complex drug therapeutic regimens, we recommend to address patients with true resistant hypertension to a hypertension specialist or, if necessary, to a hypertension specialist center. A dedicated tertiary BP clinic can be useful to perform the necessary diagnostic steps, optimize the multidrug treatment regimen, reduce the likelihood of drug-related adverse effects and increase adherence to treatment. Patients should receive a dedicated program of follow-up.

REFERENCES

1. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2023; 41: 1874-2071.
2. Yahr J, Thomas G, Calle J, et al. Resistant hypertension: A stepwise approach. *Clev Cl J Med* 2023; 90; 115-25.
3. Dybiek J, Krzeminska J, Radzioch E, et al. Advances in the pathogenesis and treatment of resistant hypertension *Int J Mol Sci* 2023; 24: 12911.
4. Doumas M, Imprialos K, Kallistratos M, et al. Recent advances in understanding and managing resistant/refractory hypertension. F1000 *Research* 2020; 9: 169.
5. Mancia G, Brunstorm M, Burnier M. Rationale of treatment recommendations in the 2023 ESH hypertension guidelines. *Eur J Intern Med* 2024; 121: 4-8.
6. Carey R, Calhoun D, Bakris G, et al. Resistant hypertension: Detection, evaluation and management: A scientific statement from the American Heart Association. *Hypertension* 2018; 72: e53-e90.
7. Sarafidis P, Bakris G. Resistant hypertension. An overview of evaluation and treatment. *J Am Coll Cardiol* 2008; 52: 1749-57.
8. Kallistratos M, Pavlidis A, Manolis A. Follow-up of patients with resistant hypertension. Researchgate.net/publication 2013 Nov.
9. Manolis A, Kallistratos M, Doumas M, et al. Recent advances in the management of resistant hypertension. F1000 Prime *Reports* 2015; 7: 03.
10. Rimoldi S, Messerli F, Bangalore S, et al. Resistant hypertension: what the cardiologist needs to know. *Eur Heart J* 2015; 36: 2686-95.
11. Schmieder R, Mahfoud F, Mancia G, et al. European Society of Hypertension position paper on Renal denervation. *J Hypertens* 2021; 39: 1733-174112.
12. Swaminathan R, East CA, Feldman D, et al. SCAI position statement on renal denervation for hypertension: patient selection, operator competence, training and techniques, and organizational recommendations. *Journal of the Society for cardiovascular angiopathy & interventions* 2023; 101121.
13. Yaxley J, Thambar S. Resistant hypertension: an approach to management in primary care. *J Family Med Prim Care* 2015; 4: 193-9.
14. Camafort M, Kreutz R, Cho MC. Diagnosis and management of resistant hypertension. *Heart* 2023 Dec 22.