



## PRECISION MEDICINE IN RESISTANT HYPERTENSION – A REVIEW

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### ABSTRACT

Resistant hypertension (RH) is characterized by blood pressure that remains elevated despite the use of three or more antihypertensives at maximum tolerated doses. This review explores the prevalence, pathophysiology, diagnosis, and treatment of RH, with a focus on precision medicine approaches. Pathophysiological mechanisms contributing to RH include primary aldosteronism, renal vascular hypertension, and obstructive sleep apnea. Diagnosis of RH requires careful exclusion of pseudoresistance. Treatment strategies for RH involve the use of first-line antihypertensives, followed by the addition of mineralocorticoid receptor antagonists and other approved drug classes. Precision medicine approaches, including pharmacogenomics, gene therapy, and the use of biomarkers and diagnostic tools, help tailor medications to the right RH patient. Newer treatments, such as endothelin antagonists and aldosterone synthase inhibitors, are being investigated. Device-based therapies such as, renal denervation and baroreflex activation therapy, may be considered for patients with persistent RH despite optimal medical therapy. Lifestyle modifications, such as the DASH diet and regular exercise, are essential components of RH management. The application of artificial intelligence and digital health technologies may further enhance the diagnosis and treatment of RH. Future directions include the development of novel pharmacologic agents, non-invasive neuromodulation techniques, and joint efforts by public and private institutions to validate biomarkers and optimize treatment strategies.

### INTRODUCTION

#### Definition of RH

Resistant hypertension (RH) is defined as above-goal elevated blood pressure (BP) in a patient even after the concurrent use of 3 antihypertensive drug classes (long-acting calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin

receptor blocker ,a diuretic) at maximum or maximally tolerated daily doses.

Resistant hypertension, is a good illustration of situation in which inadequately chosen medications can contribute to ongoing problems, risks, and frustrations. RH also includes patients whose BP achieves target values with  $\geq 4$  antihypertensive medications.



They are more likely to have medication adverse effects, a secondary cause of hypertension, increased risk for target organ damage compared with hypertensive patients without drug resistance.

### Diagnosis of RH

These patients are taking  $\geq 3$  anti-hypertensive drugs. Thus, non-adherence in taking prescribed anti-hypertensive medications, errors in BP measurement and the white coat effect must be excluded before RH is diagnosed, as they are reclassified as pseudoresistance. Overestimation of the prevalence of “true” RH may occur when one fails to identify inadequate adherence.

### Prevalence of RH

Prospective Observational Study consisting of 100 people taken in Department of General Medicine, Hypertension OPD, Medical OPD, Medical Wards Govt. The Kasturibai Gandhi Memorial Hospital, Chennai, including Hypertensive patients aged 40 to 70 years from July 2018 to **January 2019 reported the following findings:**

The prevalence of RH in this study population was reported to be 18%. The limited data gathered from studies conducted in neighboring Southeast Asian countries show that physicians can expect to encounter RH one in every ten hypertensive patients on treatment.

A study on hypertensive patients reported that the prevalence of RH increased with age, especially in females compared to males, implying that sex and age may be used to predict the development of RH.

Increased use of non-narcotic analgesics, including NSAIDs, aspirin, and acetaminophen, contributes to negative BP control. Hence they must be avoided or

withdrawn in resistant hypertensive patients.

Chronic kidney disease and advanced retinopathy are more common in individuals with resistant hypertension than in those with non-resistant or uncontrolled hypertension. Patients with resistant hypertension had significantly higher waist circumference, albuminuria, and serum creatinine levels and lower glomerular filtration rate.

Studies have consistently indicated that hypertension and hypercholesterolemia frequently coexist, causing what is known as dyslipidemic hypertension.

### Pathophysiology of RH

Resistant hypertension doesn't represent a single pathologic entity. Primary Aldosteronism is common in 20-23% of RH cases. It increases risks of atrial fibrillation, stroke, heart disease, vascular stiffness, and tissue fibrosis. Aldosterone's elevated levels worsen BP even within normal ranges. Spironolactone (25 mg) reduces BP in RH independent of aldosterone levels. Aldosterone causes endothelial swelling, sodium retention, cytoskeletal changes, and reduced nitric oxide levels, promoting vasoconstriction.

Reduced local nitric oxide production causes vasoconstriction of adjacent vascular smooth muscle cells. MR activation in vascular smooth muscle enhances angiotensin II-induced vasoconstriction. In the brain, MR increases sympathetic activity. Low-renin causes involving the distal nephron's handling of sodium, either through dysfunction of the mineralocorticoid receptor (MR) or direct tubular pathology, are another secondary cause.



Other Causes are Renal Vascular Hypertension, which occurs mainly due to atherosclerosis, and Obstructive Sleep Apnea (OSA), which is present in approximately 71% of RH patients versus 38% of controls.

### Treatment Of Resistant hypertensive patients:

Drug classes used to treat resistant hypertension are as follows:

1. First line: ARB, ACE-I , CCBs and Diuretics
2. Fourth line: Mineralocorticoid receptor antagonist (SPIRONOLACTONE or EPLERENONE)
3. Additional approved classes to consider: Beta blockers, Central alpha agonist
4. Hydralazine
5. Minoxidil

Due to anti-androgenic actions of SPIRONOLACTONE, MRA EPLERENONE is often preferred in male patients as it is associated with lower rates of impotence and gynecomastia.

In patients with reduced renal function or underlying CKD, the risk of hyperkalemia may favor the use of non-steroidal MRAs over steroidal MRAs.

The 2023 European Society of Hypertension (ESH) guidelines recommend that the fourth drug should be chosen based on the estimated glomerular filtration rate (eGFR) i.e. SPIRONOLACTONE in patients with eGFR >330 mL/min and CHLORTHALIDONE in those with eGFR <30 mL/min.

It has been found that MRAs reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF). They are recommended in patients diagnosed with resistant hypertension and secondary hyperaldosteronism.

If blood pressure remains uncontrolled despite the use of four drugs, a  $\beta$  blocker,  $\alpha$  blocker,  $\alpha$  agonist such as CLONIDINE, vasodilator such as HYDRALAZINE (combined with a  $\beta$  blocker), or MINOXIDIL may be added.

The ESH/European Society of Cardiology (ESC) guidelines no longer recommend MINOXIDIL due to side effects such as, heart rate elevation and fluid retention during its usage.

SGLT-2 inhibitors have not been studied in patients with resistant hypertension. They do have a modest reduction in BP of approximately 4/2 mm Hg. However, they may be particularly important in resistant hypertension as they lead to reductions in cardiovascular outcomes, heart failure, and the progression of CKD.

ACE inhibitors can cause cough, angioedema, and hyperkalemia; ARBs can cause hyperkalemia and CCBs use may lead to peripheral edema, flushing, tachycardia, dizziness, and cardiac depression. Beta-blockers can cause drowsiness, sleep disturbances, depression, visual hallucinations, erectile dysfunction, and peripheral vascular side effects.

Poor adherence to prescribed treatments, lack of follow-up to the hospital, clinician and health care system barriers, adverse drug effects, polypharmacy, drug costs, long duration of treatment, and lack of communication from doctors pose as treatment barriers. Medical comorbidities, psychological difficulties, and social



disadvantages such as poverty in the patient can hinder the attainment of BP control. Suboptimal adherence to prescribed antihypertensive therapy is a also major contributor.

### **PRECISION RESISTANT HYPERTENSION**

Precision hypertension is the “approach to hypertension prevention and treatment that considers the unique genes and environment of each hypertensive patient” Personalized medicine uses diagnostic tools based on a patient’s distinctive molecular or risk profile to optimize disease management and its outcomes. Precision medicine enhances prevention and treatment by integrating data from multiple sources.

In precision hypertension, prevention and treatment are tailored to an individual’s genetic and environmental exposures. Differences in blood pressure and organ damage arise from both environmental factors and genetic susceptibility. These variations also affect patient responses to treatments aimed at lowering BP and preventing organ damage.

### **GENOMICS AND GENE THERAPY**

Pharmacogenomics in hypertension specifically focuses on the variations in DNA and RNA characteristics related to individual drug responses and may suggest tailored antihypertensive therapeutic options to reduce side effects and healthcare costs.

Through a “genotype-guided” approach, the response of a hypertensive patient to a selected class of medication may be predicted according to the dose prescribed. Due to genomic and lifestyle variations, individuals show different responses to the same drug dosage.

The Genome-Wide Association Study (GWAS), which identifies disease-associated single-nucleotide polymorphisms (SNPs) is popular.

In hypertension research, GWAS studies have discovered approximately 63 loci influencing blood pressure, although these variants are responsible for less than 1% of the variation in blood pressure in the general population. GWASs have identified approximately 1500 SNPs with weak effects on BP. These findings indicate that the majority of human hypertension is multigene based.

A previous GWAS study identified a single SNP in the upstream region of the Uromodulin gene (UMOD) which is associated with blood pressure regulation and hypertension. The UMOD gene may interact with the co-transporter 2 (NKCC2) channel causing modulation in reabsorption of filtered Na<sup>+</sup>. Thus, in patients carrying this mutation, FUROSEMIDE could be the first-line therapeutic choice, as it is an inhibitor of NKCC2.

The genetic polymorphism rs4149601G>A of NEDD4L has been associated with reduced ENaC expression, sodium retention and hypertension with lower plasma renin activity. Patients carrying this mutation could better respond to thiazide diuretics.

In the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study only HYDROCHLORTHIAZIDE showed a greater blood pressure lowering effect in patients with GG alleles. In the Nordic Diltiazem (NORDIL) study, carriers of the G allele exhibited better outcomes in response to the thiazide diuretic/β-blocker combination treatment than patients with AA genotype.



According to the International Verapamil SR Trandolapril Study (INVEST), patients who carried the G allele when not treated with a thiazide diuretic, showed cardiovascular risk.

Another GWAS study involving over 60,000 participants identified a polymorphism in ADRB gene. This gene encodes the  $\beta$ -1 adrenergic receptor for catecholamines, and the Arg389 and Ser49/Arg389 haplotypes have been associated with a greater response to  $\beta$ -blockers. In the INVEST study, patients with these haplotypes presented increased cardiovascular risk on VERAPAMIL therapy alone, which was offset by using  $\beta$ -blockers.

The transcriptome, proteome, and metabolome profiles are more precise indicators of real-time phenotypes than genomics alone.

It has been shown that the atenolol-induced changes in metabolism are dependent on race and genotype thus causing differential responses to beta blockers.

An alternative approach to precision medicine in HTN is the use of a panel of genetic markers associated with HTN to generate a Genetic Risk Score (GRS) or Polygenic Risk Score (PRS). This is then used to predict an individual's risk of developing HTN and possibly its cardiovascular complications.

Genetic risk scores and quantitative risk measurements derived from the summation of multiple risk associated SNPs have been proposed to identify susceptible individuals before they develop high BP.

**Gene therapies:** Gene therapies include replacing a disease-causing gene with a healthy gene, inactivating a disease-causing

gene that is not functioning properly, or introducing a new or modified gene into the body to help treat a disease.

**RNAi:** RNAi is a natural process by which RNA molecules suppress gene expression by binding to mRNA. RNAi is performed using siRNAs and miRNAs. ZILEBESIRAN is a siRNA therapeutic that specifically targets AGT (angiotensinogen) synthesis in the liver. RNAi takes days or weeks to show its effects. Thus, it is unsuitable for cases that require a rapid decrease in blood pressure.

The full safety profile, interaction with other medications, and cost-effectiveness of siRNA compared with other drugs still need to be determined.

**Antisense oligonucleotides:** They are an alternative to siRNAs. The antisense oligonucleotides IONIS-AGT-LRx targets AGT mRNA in the liver

**Gene editing:** This is a process that can add, delete, or replace DNA at specific locations in the genome. The most cited is Crispr-Cas9.

This method is ideal for treating monogenic hypertension, such as Liddle syndrome, Gordon syndrome, apparent mineralocorticoid excess, glucocorticoid-remediable aldosteronism which can be permanently eradicated by germline editing.

## NEWER TREATMENT FOR RESISTANT HTN

Endothelin antagonists, aldosterone synthase inhibitors, novel nsMRAs, inhibitors of angiotensinogen production by the liver with small interfering RNA (siRNA), atrial natriuretic peptides and aminopeptidase A inhibitors are newer drugs for this treatment.



In precision treatment, patients with CKD showed a greater response to drugs. FINERENONE is the best-studied nsMRA; however, it is a weak antihypertensive agent. BAXDROSTAT, LORUNDROSTAT, and DEXFADROSTAT are highly selective inhibitors of aldosterone synthase. LORUNDROSTAT effectively lowered blood pressure in a small RCT in patients with uncontrolled hypertension.

RAS blockers attenuate the potassium depletion induced by thiazide diuretics, thereby minimizing the occurrence of hypokalemia

**Patients with diabetic kidney disease:** ESAXERENONE and OCEDURENONE provide more effective treatment of resistant hypertension.

**Angiotensinogen synthesis inhibitors:** These are antisense oligonucleotides that inhibit RNA translation and siRNAs. Circulating angiotensinogen levels decreased proportionally due to ZILEBESIRAN. The coadministration of the ARB VALSARTAN with the neutral endopeptidase (NEPRILYSIN) inhibitor SACUBITRIL was a powerful antihypertensive in preclinical studies. Angiotension receptor blocker (ARB) OLMESARTAN and a Calcium Channel Blocker (CCB) AZELNIDIPINE was effective in reducing systolic and diastolic blood pressure in patients with resistant hypertension both in office and at home.

Drugs that may interfere with the treatment of resistant hypertension include NSAIDs, Sympathomimetics, Nasal decongestants, Caffeine, Cocaine, etc. They must be avoided.

## BIOMARKERS AND DIAGNOSTIC TOOLS

Biomarkers are key in detection and diagnosis of disease, risk assessment and prognosis, and prediction of responses to therapeutic or preventative interventions in precision medicine.

The Genetics of Hypertension Associated Treatment (GenHAT) study was used for biomarker discovery and validation of drug-by-genotype interactions reported from smaller, less representative cohorts.

Identifying functional genetic and epigenetic markers is important for developing a new category of mechanism-based genetic biomarkers to manage hypertension from an individualized perspective.

An ideal biomarker with a high predictive accuracy for the response to antihypertensive therapies is still unavailable.

Arterial stiffness and peripheral arteriolar resistance can be increased by arteriosclerosis, elevated sympathetic system activity, the renin-angiotensin system, and increased body fluid volume, which increases blood pressure. It can be estimated by measuring the carotid-femoral pulse wave velocity (PWV) or analyzing blood pressure pulses.

The PWV (applanation tonometry) measures blood pressure waves. Peripheral photoplethysmographic (PPG) pulse blood flow to a specific tissue can be measured using laser Doppler (in the microcirculation) or Doppler ultrasound (in a large artery). Heart rate variability can be measured using either ECG or PPG.

The PPG-based technique can provide accurate SBP measurement required for effective precision hypertension management.



The two available techniques for BP measurement are manual-auscultatory sphygmomanometry and oscillometric BP.

The accuracy of oscillometric BP can be increased by multiple measurements and 24h ambulatory BP monitoring (ABPM). Both ABPM and multiple BP measurements at home (HBPM) are considered more accurate than single office measurements.

Strategies to prevent worsening or causing HTN are early treatment in high-risk individuals and preventing comorbidities (e.g., vascular stiffening, renal dysfunction). Improving lifestyle and sleep in high-risk individuals.

### DEVICES BASED THERAPIES

If medical therapy is ineffective, device-based interventions may ultimately be an option for adjunctive treatment.

Minimally invasive denervation can be achieved via catheter-based application of radiofrequency, ultrasound, or injection of neurotoxic agent.

During the pre-2000s–2009 Percutaneous renal sympathetic denervation showed initial promise. A 2009 study using radiofrequency ablation showed a 22/11 mmHg BP drop at 6 months.

Symplicity HTN Trials were conducted where HTN-2 (Open-label) showed a 33/11 mmHg greater BP reduction vs. standard care and HTN-3 (Blinded, Sham-Controlled) showed no significant difference in BP.

The SPYRAL Program HTN-OFF MED Trial included 331 patients not on BP meds. This showed a 3.9 mmHg greater 24-hr systolic BP reduction with denervation. HTN-ON MED Extensions study showed patients on 1–3 BP medications had no

significant difference in 24-hr BP, but the sham group used more medications and had higher office BP

Safety outcomes indicated a low incidence of procedure-related and clinical adverse events with RDN.

Global expert consensus supports renal denervation as adjunct therapy in patients with resistant hypertension and those unable to tolerate or adhere to multiple BP medication

Ultrasound-based denervation uses ultrasound energy via a water-filled balloon to create circumferential ablation. Possibly due to deeper nerve ablation the Ultrasound-based denervation showed greater BP reduction than RF in the main artery only (–13.2 vs. –6.5 mmHg).

Carotid baroreceptor activation therapy involves the use of an implanted pulse generator connected to leads placed. ESH/ESC guidelines no longer recommend baroreflex stimulation. This is a more invasive procedure than RDN that leaves the patient with internally implanted hardware. This carotid sinus stimulation leads to reduced sympathetic nervous system activity and enhanced vagal activity.

The central arteriovenous anastomosis (ROX coupler device, ReCor endovascular ultrasonic renal denervation device and median nerve stimulation) uses an electroacupuncture technique to reduce sympathetic outflow.

Atrioventricular interval modulation therapy involves programming a sequence of variably timed short and longer atrioventricular intervals to reduce blood pressure mostly targeted to hypertensive



people implanted with cardiac pacemakers each year.

### AI AND PRECISION MEDICINE

AI algorithms are now being used in hypertension diagnosis and management. AI algorithms are being used to reevaluate previous clinical trials to assess mistakes and improve clinical trials in the future.

Geisinger Health in Pennsylvania AI chatbot provides patients with the results of their exome sequencing. Smartwatches have Food and Drug Administration approval to detect atrial fibrillation and irregular heart rhythm. Another AI algorithm utilizes omics data to generate a risk score for an individual's potential development of hypertension.

A study designed to test 5 AI algorithms found that their predictive power was no different to that of traditional regression-based statistical modeling.

### LIFESYCLE MODIFICATIONS

According to the TRIUMPH trial, lifestyle modifications, including weight loss, physical activity, and dietary changes, were associated with a significant reduction in blood pressure among patients with resistant hypertension.

**Diet:** The Dietary Approaches to Stop Hypertension (DASH) is a dietary intervention that has been shown to be effective in reducing blood pressure in patients with resistant hypertension which includes consumption of fruits, vegetables, whole grains, and low-fat dairy products while limiting the intake of processed foods, saturated fats, and added sugars.

An estimated 1-g (43.5-mmol) reduction in daily sodium intake produces a 2.1- and 1.2-mmHg decreases in SBP among

hypertensive and normotensive patients, respectively.

AHA recommends an ideal daily sodium intake of <65 mmol/d (1.5 g/d) and to reduce daily sodium intake to <100 mmol/d (2.3 g/d) and to consider more stringent restrictions to <65 mmol/d (1.5 g/d) on a case-by-case basis.

Mediterranean-style diet, which emphasizes the consumption of fruits, vegetables, whole grains, fish, and healthy fats, has been found to be effective in reducing blood pressure in patients with resistant hypertension.

**Exercise:** Exercise can lead to reductions in both systolic and diastolic blood pressure in patients with resistant hypertension.

Dynamic resistance exercise was also shown to reduce BP by 1.8/3.2 mmHg among hypertensive patients.

According to AHA,  $\geq 150$  min/wk (in 3–5 sessions of 30–40 minutes) of moderate to intense aerobic activity, opting 2 to 3 sessions of light resistance training per week for better control.

### LIMITATIONS

Limitations in using genomics for precision medicine is that they typically only analyze a small fraction of the genome and gene-gene interactions are neglected.

Genomic information alone is not usually adequate to predict disease onset, environment and other factors are expected to play a critical role in the pathophysiological process.

It remains a challenge to identify which genetic marker best suits the pharmacogenetic approach in HTN of those under-investigated populations.

The current GWASs are heavily skewed toward White people also they are unable to



fully explain the genetic risk of common diseases and identifying rare genetic variants

It is difficult to identify true causal associations due to the fact that many SNPs either intergenic or located in genes may have no direct biological relevance to disease.

Identifying the intermediate and sub-intermediate phenotype of HTN has not been systematically documented in many low- and middle-income countries. Such populations are also affected by HTN where awareness of genetic tests is not practical to afford genetic testing. The prevalence of the intermediate and sub-intermediate phenotype of HTN remains unclear.

### **COST EFFECTIVENESS IN RESISTANT HYPERTENSION**

Studies suggest that interventions like renal denervation may be cost-effective for individuals with high baseline cardiovascular risk, but not necessarily for all patients with resistant hypertension. RDN cost-effectiveness is sensitive to factors like patient risk and device costs.

Poor adherence to prescribed medications is a major factor contributing to the challenges in managing resistant hypertension and significantly impacts cost-effectiveness

### **FUTURE DIRECTIONS**

More research must take place on novel pharmacologic agents or combinations of existing drugs to improve blood pressure control.

Use of non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDC) could be more

applied in today's treatment. They act by selectively modulating the autonomic nervous system to regulate and reduce blood pressure. They are minimally invasive techniques and offer a more cost-effective and safer option compared to other invasive interventions available today since it does not require any medication or surgery.

The use of machine learning and artificial intelligence may also offer new opportunities for improving the diagnosis and management of resistant hypertension.

Another potential application of precision medicine in resistant hypertension is the use of digital health technologies to monitor blood pressure and other physiological parameters. Wearable devices and mobile applications could be used to collect data on blood pressure, heart rate, physical activity.

Public and private institutions collaboration may be required to validate the impact of biomarkers on clinical outcomes and clinical decision making, evaluation of efficacy, cost-effectiveness, and safety outcomes, optimization of medication dosing to minimize adverse effects and maximize therapeutic benefits, and identification of high priority areas. This might enable safe, efficient and adherent therapy.

Greater training in contemporary “-omics” technologies for biomedical researchers and physicians and other stakeholders including patients, legislators, healthcare agencies, and consumers.

There is a critical need for development and dissemination of analytical methods tailored for large numbers of variables and



validation of their ability to predict therapeutic response and preventive lifestyle modifications.

## CONCLUSION

Resistant hypertension (RH) is elevated blood pressure (BP) in a patient despite 3 antihypertensive drug classes at maximum or maximally tolerated daily doses with increased risk of target organ damage. Gene therapy, gene editing, pharmacogenomics and use of biomarkers in resistant hypertension has been used to tailor treatment for individuals unresponsive to standard therapy. However, limitations in using genomics across diverse populations, high costs, non-adherence, and health system barriers continue to restrict widespread implementation. Future research should focus on refining precision approaches, validating biomarkers, ensuring cost-effectiveness, and developing non-invasive, scalable treatments. A multidisciplinary, data-driven strategy involving genomics, digital health, and patient-centered care will be key to improving outcomes in resistant hypertension.

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