Επίκαιρο Άρθρο

Innovative approaches for managing resistant hypertension in 2025

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ABSTRACT

The prevalence of true resistant hypertension (RHTN) is about 5% of the total hypertensive population and a careful diagnostic approach emphasizing detailed history and clinical assessment represents the cornerstone for the proper evaluation of individuals with RHTN. For the treatment measures, the three pillars for the management of hypertension should be considered: (i) the endorsement of appropriate lifestyle measures, (ii) the rationalization, simplification and/or up-titration of prescribed pharmacological therapy, and (iii) the consideration of interventional neuromodulation therapeutic choices; namely the implementation of sympathetic renal denervation that has established beneficial impact, proven safety profile, and has been officially introduced and upgraded in recent European Hypertension Guidelines. In the era of new emerging and promising pharmacological choices and implementation of neuromodulation interventional therapies, the fight against RHTN and towards adequate BP control will be significantly reinforced.

Key-words: difficult-to-control hypertension, novel pharmacological therapies, renal denervation, resistant hypertension, sympathetic neuromodulation

INTRODUCTION

According to the most recent 2023 European Society of Hypertension (ESH) guidelines for the management of arterial hypertension, the definition criteria for true resistant hypertension (RHTN) are summarized below [1]:

- Office systolic blood pressure (BP) ≥140 mmHg or office diastolic BP ≥90 mmHg
- Maximum recommended and tolerated dosages of a three-drug combination including a RAAS blocker, a CCB, and a diuretic
- Uncontrolled out-of-office BP
- Exclusion of secondary and pseudo-resistant hypertension cases (e.g., due to poor medication adherence)

Interestingly, since RHTN regards treated hypertensives, it has been argued that the target BP values for the definition of RHTN should correspond to treatment targets (i.e., office BP <130/80 mmHg) and not to hypertension diagnosis thresholds (i.e., office BP <140/90 mmHg)[1].

PATHOPHYSIOLOGY

The pathophysiology of true RHTN involves multiple neurohumoral mechanisms and a complex interplay between them including increased levels of vasoregulatory hormones such as aldosterone, endothelin-1 and vasopressin and increased sympathetic activity[1]. These factors contribute to sodium and fluid retention, further activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, increase in peripheral vascular resistance and arterial stiffness leading to impaired vascular function[1]. These mechanisms lead to hypertension mediated target organ and cardiorenal damage[1,2]. In this respect, individuals with RHTN are at higher CVD risk and present higher rates of adverse cardiovascular outcomes[2] (Figure 1).

EPIDEMIOLOGY

The prevalence of apparent and true RHTN is difficult to be precisely determined since it is influenced

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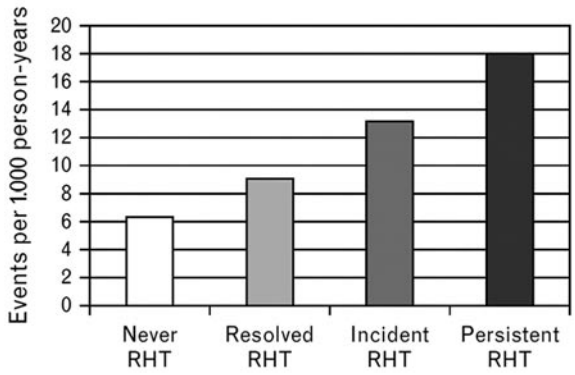

Figure 1. *Incidence rates of cardiovascular events among individuals with RHTN. Reproduced from reference [2].*

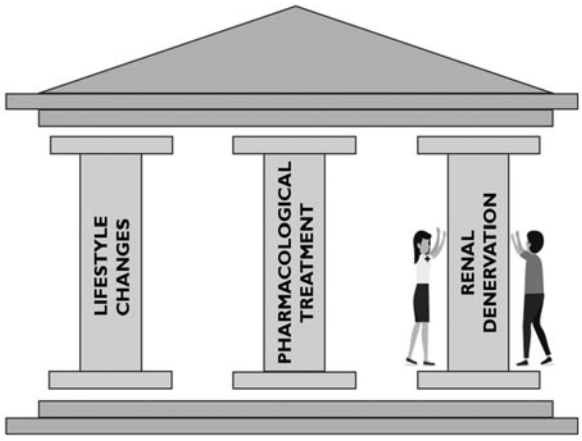

Figure 2. *The three pillars for the management of hypertension. The important role of a shared decision-making process between the patient and the treating physician is highlighted for renal denervation.*

by a number of factors[1]. Firstly, the clinical setting, with RHTN prevalence being significantly different in general population, in high CVD risk populations [e.g., chronic kidney disease (CKD)], in populations assessed in specialized and dedicated hypertension centers, or in populations participating in clinical trials[1]. Additionally, pseudo-resistant causes are not homogeneously considered in various studies and registries. Lastly, the use of treatment targets vs hypertension diagnosis thresholds for the definition of RHTN in some studies represents another source of heterogeneity[1]. The prevalence of RHTN becomes obviously higher when treatment targets (office BP <130/80 instead of 140/90 mmHg) are used, and lower when individuals with normal out-of-office BP are excluded[1]. Taking the above into consideration, a reasonable estimate of apparent and true RHTN is up to 10%-20% and 5% of the overall hypertensive population, respectively[1]. Risk factors for RHTN are demographic characteristics and clinical factors such as obesity, excessive alcohol consumption, increased sodium intake, older age, male sex, Black-African origin, low income, mental health conditions (e.g., depression), high BP values at diagnosis, high CVD risk or established CVD[1].

MANAGEMENT

The three pillars for the management of hypertension are shown in Figure 2. The initial step is the endorsement of appropriate lifestyle measures including dietary interventions, weight loss, salt restriction, smoking cessation, reduction of alcohol intake, and implementation of regular physical activity[1,3]. Accordingly, pharmacological measures include rationalization and simplification of current treatment and/or addition of antihypertensive regimens. Finally, device-based neuromodulation treatment with sympathetic renal denervation (RDN) has been officially introduced and upgraded in recent guidelines and is another arrow to our quiver for the management of hypertension[1,4].

Pharmacological treatment

Before considering the fourth antihypertensive drug, re-evaluation of the prescribed therapy should be performed[1]. Replacing current drugs with a simpler treatment plan to improve adherence is feasible using tailored drug options preferably in the form of single pill combinations where possible[1]. If the estimated glomerular filtration rate (eGFR) is ≥30 ml/min/1.73m^2, then intensification of thiazide diuretic therapy may be effective, e.g., switch to a more potent agent such as chlorthalidone[1]. If eGFR is <30 ml/min/1.73m^2, switch to a more proper diuretic may be necessary, e.g., to a loop instead of a thiazide diuretic[1].

According to the most recent ESH guidelines, if BP remains uncontrolled despite the intake of appropriate dosages of three antihypertensive regimens, then addition of a fourth drug or interventional neuromodulation through RDN should be considered after thorough discussion with the patient in the context of a shared decision-making process (Figure 3). In case that additional pharmacotherapy is selected, the fourth drug can be any regimen. Evidence from the PATHWAY-2 study indicated that spironolactone, a mineralocorticoid receptor antagonist (MRA), may be the most appropriate next step[5], considering the eGFR and potassium levels[1]. A point of novelty compared to

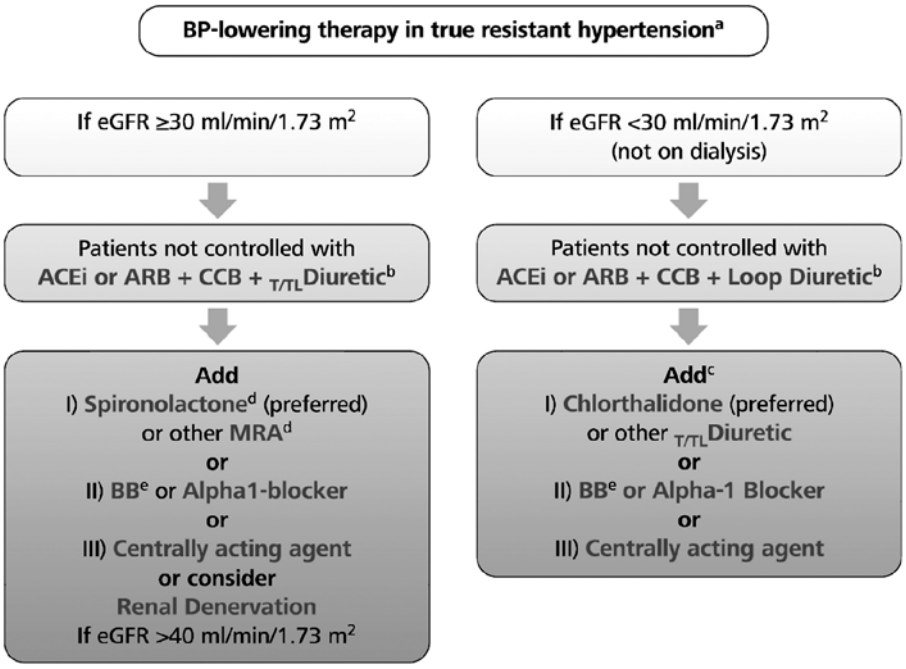

Figure 3. *Approach to treatment after confirmation of true resistant hypertension. Therapeutic choices include addition of a pharmacological regimen or interventional neuromodulation through renal denervation after discussion with the patient on an individualized basis. Reproduced from reference [1].*

previous guidelines is the recommendation for addition of chlorthalidone on top of loop diuretics in patients with eGFR<30 ml/min/1.73m^2 based on the findings of the CLICK study including patients with CKD and uncontrolled hypertension[6]. Spironolactone may not be well tolerated by all patients due to its antiandrogenic adverse effects and eplerenone, another MRA with less interference with progesterone or androgen receptors, although less potent, can be alternatively used. When MRAs are contraindicated or not tolerated, other drug choices are alpha-1 blockers (e.g., doxazosin), beta-blockers (e.g., bisoprolol) and centrally acting agents (e.g., clonidine)[1,5,7]. Other drug classes such as non-steroidal MRAs (e.g., finerenone), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and sacubitril/valsartan are not specifically indicated for hypertension; however, may exhibit mild BP lowering effects and may be useful in patients with specific indications[1].

After years of experience with traditional antihypertensive medications, we are glad to live in the era of emerging new pharmacological options. These novel drugs may completely change and update the management plan of hypertension and will probably play a significant role especially in the RHTN management approach.

The dual endothelin receptor antagonist aprocitentan has been shown to offer BP lowering effects in individuals with RHTN and its wide use is awaited in the future[1,8]. This agent targets the endothelin pathway, a pathway known to be implicated in the pathogenesis of hypertension, which has not been therapeutically targeted until now[9,10]. This pathway is activated especially in individuals with RHTN and consists of a vasocontriction peptide, endothelin-1 (ET-1), and two endothelin receptors (ETAR and ETBR). Non-selective blockade of these receptors has been found to offer significant antihypertensive benefits mainly through vascular smooth cell relaxation and subsequent vasodilation[9,10]. Aprocitentan has been studied in the PRECISION phase 3 trial including 730 individuals with RHTN and has demonstrated a significant and sustained antihypertensive effect (follow-up up to 48 weeks) of about 5 mmHg (placebo corrected) assessed with both office and ambulatory BP measurements[8]. Aprocitentan was overall well tolerated, presenting an expected dose-dependent mild-to-moderate oedema and fluid retention, highlighting the need for careful use in high-risk patients including those with diabetes, CKD, and heart failure.

The selective aldosterone synthase inhibitor baxdrostat has also been shown to effectively lower BP

in individuals with RHTN and further phase 3 data are soon awaited[1,11]. Therapies targeting the RAAS have played a crucial role for the management of hypertension and as discussed above, the most efficient fourth drug for individuals with RHTN is a MRA directly targeting and inhibiting the effects of aldosterone[1]. In this line, an alternative approach targeting a higher level of the cascade and aiming a more intense aldosterone inhibition would be reasonable[11]. Baxdrostat is a highly potent and selective aldosterone synthase inhibitor; thus, reduces the production of aldosterone resulting in decrease of plasma aldosterone and inhibition of sodium and water reabsorption[11]. Baxdrostat has been studied mainly in the context of phase 1 and 2 trials including RHTN patients[11]. Phase 1 trials confirmed the selectivity of baxdrostat that did not affect cortisol levels; while the first phase 2 trial conducted to assess its dose-dependent antihypertensive effects was early terminated due to significant BP lowering in the active drug arm (placebo corrected decrease of about 10 mmHg)[11].

Zilbesiran represents another approach to RAAS inhibition and introduces a novel group of subcutaneously administered pharmacological regimens in the field of hypertension[12,13]. Zilbesiran is a small interfering RNA (siRNA) therapeutic agent that binds with high affinity to receptors found in hepatic cells causing significant reduction in hepatic angiotensinogen mRNA, and further inhibition in the production of angiotensinogen[12,13]. Angiotensinogen is the predominant precursor for angiotensin peptides and in this context plays a key role in the regulation of BP levels[12,13]. Zilbesiran has been evaluated in one phase 1[12] and one phase 2 trial[13], both conducted in hypertensive individuals in general and not exclusively in patients with RHTN. In the first trial, 107 patients were included and a dose-dependent reduction in serum angiotensinogen and ambulatory BP was observed with a single zilbesiran injection during a follow-up period of up to 24 weeks[12]. In the phase 2 trial, data from 377 patients were analyzed and indicated a significant BP lowering effect (placebo corrected decrease of about 15 mmHg) with different doses at various injection intervals[13].

Other novel drug agents, treatment targets and approaches including gut microbiota interventions, or even vaccines are under intense research[9,10]. Fascinating advancements regarding the pharmacological treatment of hypertension in general and especially RHTN are awaited in the future.

Renal denervation

Device-based hypertension therapy targeting the autonomic nervous system has been an interesting field of research[14]. In both animal preclinical models and human studies overactivation of the sympathetic nervous system (SNS), including the renal sympathetic nerves (both the afferent and the efferent component), has been shown to play a key role in BP modulation, hypertension, and hypertension-mediated organ damage[15]. Accumulating evidence regarding the efficacy and safety of RDN has been translated to formal recommendations in recent guidelines supporting the use of RDN in selected cases; thus, rendering RDN the third pillar for the management of hypertension[1,4] (Figure 2). Various technologies have been investigated and developed for the denervation of renal arteries, with the most significant being the: (i) radiofrequency (RF), (ii) ultrasound (US), and (iii) chemical alcohol-mediated approaches (Figure 4).

The "Second-generation randomized sham-controlled trials" used updated catheter technologies and recruited either treatment naïve or treated participants (including RHTN), demonstrating significant BP reductions with RDN[16]. Outcome trials for RDN are not expected in the near future; however, using BP reduction as a surrogate marker for CVD events reduction is not an unusual or unrealistic approach[17]. Furthermore, RDN has been shown to be associated with regression of left ventricular mass index providing additional information regarding its clinical efficacy[18]. Notably, RDN is a method with proven safety in terms of renal function deterioration and development of new renal artery stenosis[1,16].

Efficacy and safety of RDN especially in individuals with RHTN have been shown for extended follow-up periods of up to 10 years[19], with the respective long-term Greek results being currently under preparation. Except for the established efficacy and safety, RDN is accompanied by significant advantages including the "always-on" phenomenon, the relatively simple interventional procedure, and the potential beneficial pleiotropic effects in different clinical entities and comorbidities (e.g., atrial fibrillation and obstructive sleep apnea)[16].

The implementation of RDN has been upgraded in the 2023 ESH hypertension guidelines and is recommended as a treatment option in individuals with uncontrolled BP despite pharmacological treatment, especially in patients with true RHTN, and

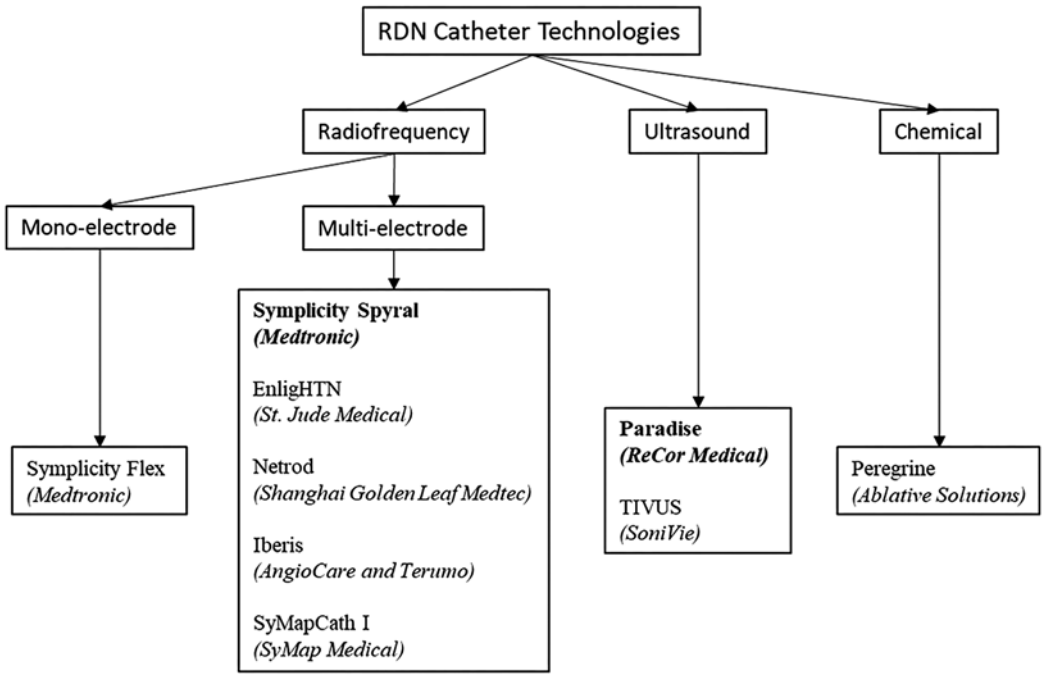

Figure 4. *Renal denervation catheter systems. In bold the FDA approved systems.*

2023 European Society of Hypertension Guidelines

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73m² who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with true resistant hypertension if eGFR is >40 ml/min/1.73m².	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
RDN should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

2024 European Society of Cardiology Guidelines

Recommendations	Class[a]	Level[b]
To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for resistant hypertension patients who have BP that is uncontrolled despite a three BP-lowering drug combination (including a thiazide or thiazide-like diuretic), and who express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590]	IIb	B
To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for patients with both increased CVD risk and uncontrolled hypertension on fewer than three drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590]	IIb	A

Figure 5. *Recommendations of recent guidelines regarding the implementation of renal denervation for the management of hypertension. Reproduced from references [1,4].*

eGFR >40 ml/min/1.73m^2 (Figure 5)[1]. Lower eGFR values represented an exclusion criterion from major RDN trials; however, initial observational data are in favor of potentially significant benefit in CKD patients, which remains to be investigated and validated by future research. Similarly, the recent 2024 European Society of Cardiology (ESC) guidelines have also introduced RDN for patients with RHTN but also for those at high CVD risk and uncontrolled hypertension on fewer than three drugs (Figure 5). All guidelines highlight the need for RDN to be performed in experienced specialized centers and in the context of a shared decision-making process after objective and complete patient's information[1,4,16].

CONCLUSION

True RHTN is a condition encountered in up to 5% of the total hypertensive population and represents hypertension cases with complex background pathophysiological mechanisms, demanding meticulous

assessment by hypertension experts. In the light of new promising pharmacological options and interventional neuromodulation therapies with established clinical value, we hope and expect that in the future the term RHTN will be abandoned and for the remaining very few cases the term "difficult-to-control hypertension" will be more appropriate.

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