

# The expert position of the Polish Cardiac Society, the Polish Society of Hypertension, and the Polish Society of Nephrology on renal denervation

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## ABSTRACT

Renal denervation is an innovative method of treating hypertension (HT), used in clinical practice for about a decade. The pathophysiological basis of this method derives from the role of efferent and afferent fibers of the sympathetic nervous system, entering and leaving the kidneys, in the development of HT, especially treatment-resistant HT. Initial clinical trials have suggested the high efficacy of denervation in the treatment of patients with resistant HT. However, the results of the Symplicity HTN-3 trial, which introduced a sham procedure as a control, undermined these hopes, although this trial was criticized for its methodology. Recent research, using latest-generation catheters and more stringent protocols, confirms a significant reduction in blood pressure in patients after this procedure. Renal denervation should be considered in patients with HT (after excluding all hormonal causes and ischemic etiology) that is resistant to pharmacological treatment. Pseudo resistance, e.g., caused by so-called white-coat HT, should be ruled out. Every patient should complete 24 hours ambulatory blood pressure monitoring. Lack of cooperation between the patient and the physician, irregular use of antihypertensive medications, and non-compliance with other therapeutic recommendations should also be excluded. However, the condition for the success of renal denervation is the precise determination of patient eligibility and the performance of the procedure in specialized centers with appropriate experience.

**Key words:** hypertension, pharmacotherapy, renal denervation, surgical treatment, treatment

## INTRODUCTION

Renal denervation (RDN) is an innovative treatment for hypertension (HT) that is resistant to pharmacological therapy, which has been used in clinical practice for about 10 years. RDN involves ablation of the fibers of the sympathetic nervous system surrounding the wall of the renal arteries by means of an appropriate intravascularly placed catheter. Ablation of the fibers entering the kidneys (the efferent fibers) causes inhibition of renin production, and increased natriuresis and blood flow through the kidneys. Concurrent ablation of the sympathetic nervous system fibers exiting the kidney (the so-called afferent fibers) leads to a decrease in the activity of the central sympathetic system [1]. These pathophysiological factors justified the conduct of clinical trials, which initially showed great efficacy of this method in patients with resistant HT.

However, the Symplicity HTN-3 trial, in which the effect of RDN was compared with the effect of a sham procedure for the first time, did not show the benefits of RDN [2]. In recent years, however, enormous progress has been made both in the methods and design of catheters used for RDN. In addition to traditional methods using radio frequency current for RDN, ultrasound waves or the administration of alcohol to the wall of the renal artery are also currently used during denervation procedures. The tips of the catheters used for RDN have also changed significantly, making the efficacy of these procedures much greater [3]. Trials using new RDN methods involving a control group subjected to a sham RDN procedure and appropriately conducted meta-analyses have shown high efficacy of this treatment method in patients with resistant HT [4, 5].

Taking into account the above factors, experts representing the Polish Hypertension Society (PTNT, *Polskie Towarzystwo Nadciśnienia Tętniczego*), the Polish Cardiac Society (PTK, *Polskie Towarzystwo Kardiologiczne*), and the Polish Society of Nephrology (PTN, *Polskie Towarzystwo Nefrologiczne*) have issued this document, which is intended to present the most up-to-date and at the same time practical guidelines for RDN procedures.

## DEFINITIONS, EPIDEMIOLOGY, AND CLINICAL CONSEQUENCES OF RESISTANT HYPERTENSION

According to the 2023 definition of the European Society of Hypertension (ESH), resistant HT is diagnosed when systolic and diastolic blood pressure values are  $\geq 140$  mm Hg and  $\geq 90$  mm Hg, respectively, despite the use of 3 antihypertensive medications used hitherto at the maximum recommended and tolerated doses — renin–angiotensin–aldosterone (RAA) inhibitor (angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist), a calcium channel blocker, and a thiazide-like/thiazide diuretic. It should be pointed out that the latest guidelines of the European Society of Cardiology (ESC) from 2024 and the PTNT/PTK guidelines from 2024 or KDIGO (Kidney

Disease: Improving Global Outcomes) define the same characteristics for resistant HT [6–9].

There is a consensus that uncontrolled blood pressure control should be confirmed by ambulatory blood pressure monitoring (ABPM), and it is necessary to exclude the causes of pseudoresistance (especially patient non-adherence and non-compliance). Performing ABPM in a patient with resistant HT allows us not only to determine the true nature of HT but also allows for the assessment of the blood pressure profile, taking into account the night hours. It has been shown that the absence of a nighttime dip in blood pressure may be characteristic of patients with concomitant obstructive sleep apnea (OSA), chronic kidney disease (CKD) or an undiagnosed secondary form of HT. At the same time, it was noted that in the absence of ABPM, home blood pressure monitoring (HBPM) is recommended, to confirm true resistant HT [6, 7].

It is also recommended that patients with secondary HT be identified as shown in clinical trials conducted, especially over the last decade, indicate a high incidence of resistant HT in patients with the most common forms of secondary HT (primary hyperaldosteronism and renovascular HT) as a result of atherosclerotic or dysplastic stenosis of the renal artery [10].

It should be emphasized that the prevalence of true resistant HT in the general population with treated HT is difficult to estimate and is subject to many factors in the diagnosis of treatment resistance, e.g., the studied population, the reference level of the centers, the groups of antihypertensive medications used, and the blood pressure target adopted. Despite significant differences in individual studies, the actual prevalence of true resistant HT in the general population treated for HT does not exceed 5%, while pseudoresistance affects up to 10%–20% of patients. This means that in the Polish population treated for HT, true resistant HT may occur in several tens of thousands of people [6, 10–12].

Clinical trials to date indicate that patients with true resistant HT are characterized by a more pronounced development of early and late organ complications vs. patients with effectively treated HT. In addition, the conducted clinical trials have provided important evidence suggesting that patients with resistant HT have a significantly higher risk of cardiovascular episodes vs. persons with successfully treated HT [6, 10–12].

Resistant HT is especially highly prevalent in patients with CKS, reaching in some studies 40%. Moreover, in CKD patients resistant HT is a marker of high cardiovascular and renal risk that significantly accelerates the CKD progression [9, 13].

It is also pointed out that the pathogenesis of resistant HT is complex, which is discussed in detail in the next subsection. From a clinical point of view, demographic risk factors for the development of resistant HT include, among others, male gender, black ethnicity, older age, obesity, excessive alcohol consumption, high sodium

intake, depression, and advanced atherosclerotic process and hypertensive organ damage [6, 10–12].

According to guidelines, including PTNT/PTK (2024), the general principles for the treatment of resistant HT should include non-pharmacological methods and anti-hypertensive treatment. The principles of diagnosis and treatment of resistant HT are discussed later in this position statement [6, 10–12].

## **PATHOPHYSIOLOGICAL FOUNDATIONS OF TRUE RESISTANT HYPERTENSION**

Understanding the pathophysiological mechanisms of true resistant HT is crucial for its effective treatment and prevention of cardiovascular events. The pathophysiology of this condition includes a variety of often intersecting mechanisms that lead to treatment resistance. One of the key roles is played by the sympathetic system.

### ***Vascular remodeling***

In patients with resistant HT, structural changes in blood vessels are observed, such as hypertrophy of the arterial muscle membrane, thickening of the vessel walls, and increased vessel stiffness [14]. These changes lead to an increase in peripheral resistance and make it difficult to achieve blood pressure control. In many cases, vascular remodeling results from chronic exposure to high blood pressure in patients with undiagnosed or ineffectively treated HT.

### ***Excessive sodium and water retention***

Excessive sodium and fluid retention leads to an increase in intravascular volume, which in turn raises blood pressure, especially at night. Hypervolemia is frequently found in CKD patients, especially in more advanced stages of this disease may result from impaired renal function, and inadequate diuretic treatment [15].

### ***Activation of the renin–angiotensin–aldosterone system***

Both angiotensin II and aldosterone have a direct effect on vascular smooth muscle cells and intensify the fibrosis process, which leads to vascular stiffness and increased peripheral resistance [16].

### ***Endothelin***

Endothelin plays an important role in the pathophysiology of resistant HT, especially associated with CKD. By binding to type A and type B endothelin receptors, it increases peripheral resistance and enhances vascular remodeling [17].

### ***Obesity, metabolic syndrome, and sleep apnea***

Obesity is associated with increased activity of the sympathetic system and the RAA system, and increased sodium and water retention. Metabolic syndrome, characterized by insulin resistance, also contributes to an increase in blood pressure through various mechanisms, including

endothelial dysfunction and inflammation. The overlap of these mechanisms is particularly important in patients with sleep apnea syndrome, who are characterized by frequent occurrence of pharmacotherapy-resistant HT [18, 19].

### ***The role of the sympathetic system***

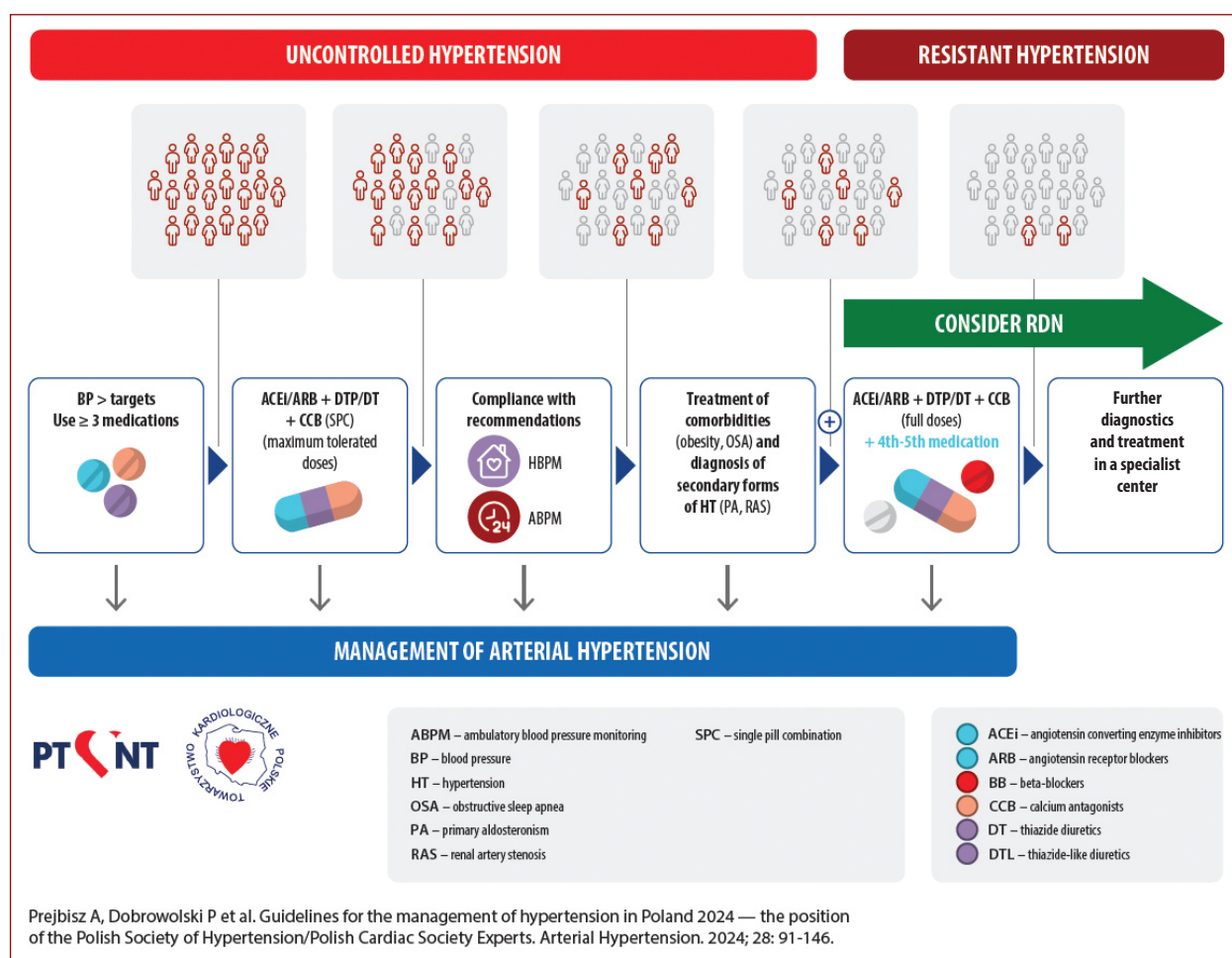
The sympathetic system is of fundamental importance in the pathophysiology of true resistant HT [1, 20]. In patients with resistant HT, increased sympathetic activity is observed by microneurography [21]. Excessive sympathetic activation affects many mechanisms that promote resistance to HT treatment [22]. Increased release of norepinephrine leads to an increase in heart rate and narrowing of blood vessels. These effects synergistically increase blood pressure. The sympathetic system has a direct effect on kidney function by increasing renin release and sodium and water retention. Norepinephrine released by sympathetic nerves stimulates beta-adrenergic receptors in the renal paraglomerular apparatus, leading to increased renin secretion. In addition, increased renal sympathetic activity leads to reduced renal blood flow and increased sodium retention. Activation of the sympathetic system leads to an increase in vascular stiffness, which is the result of both the direct action of catecholamines on the vascular walls and the indirect effects resulting from excessive activation of the RAA system.

Despite recognition of the key role of the sympathetic system in the pathophysiology of resistant HT, current pharmacological treatment does not completely target hyperactivity of this system [23]. Beta-blockers, which inhibit the cardiac effects of norepinephrine, are not always effective in reducing sympathetic activity at the peripheral and renal levels. Angiotensin-converting enzyme inhibitors and angiotensin II receptor type 1 antagonists inhibit the RAA system, but their effect on the sympathetic system is limited. In conclusion, the pathophysiology of true resistant HT is complex and largely related to excessive sympathetic system activity. Current pharmacological treatments are not always able to effectively reduce this activity.

## **CURRENT ALGORITHM FOR THE MANAGEMENT OF RESISTANT HYPERTENSION**

The first step in the event of resistant HT, i.e., failure to achieve the target blood pressure in a patient receiving 3 antihypertensive medications (including a diuretic) in full doses, is to **exclude pseudo-resistant HT**, including the following:

- white-coat HT (with the help of HBPM and/or ABPM);
- errors in blood pressure measurement (e.g., incorrect adjustment of the cuff size with respect to the circumference of the arm, an unvalidated device, and/or errors in the technique of measuring blood pressure by the patient during HBPM);
- failure to comply with treatment recommendations (non-compliance and nonadherence). Improvement of



**Figure 1.** Management of a patient with uncontrolled and resistant hypertension — Polish Society of Hypertension/Polish Cardiac Society Position 2024, modified — proposal for positioning the renal denervation site in the management of a patient with uncontrolled and resistant hypertension [8]

adherence can be achieved by using single pill combinations, hence their prominence in current Polish and international recommendations (Figure 1) [6–8, 24, 25].

Subsequently, **all medications and other substances taken by the patient** that may cause an increase in blood pressure, e.g., non-steroidal anti-inflammatory drugs, corticosteroids, pseudoephedrine (including nasal preparations), oral contraception, theophylline, licorice, stimulants and dietary supplements, and erythropoiesis-stimulating factors in CKD patients should be systematically reviewed. Also, there is a need to review adherence and compliance in terms of lifestyle modifications, especially lack of weight reduction (obesity), insufficient physical activity, excessive alcohol drinking and excessive salt consumption, and smoking [6–8, 24, 25].

Another element in the diagnosis of resistant HT is **screening for secondary forms of HT**, especially the following [6–8, 24, 25]:

- OSA (characteristic clinical symptoms, non-dipper or reverse dipper profile in ABPM, and arrhythmias and/or

conduction disorders exacerbating during sleep; diagnostics using questionnaires and polysomnography);

- CKD (assessment of renal function by serum creatinine, estimated glomerular filtration rate [eGFR], and urinary albumin to creatinine ratio [UACR]);
- renal artery stenosis (especially in patients with sudden deterioration of renal function, generalized atherosclerosis, or in the case of suspected fibromuscular dysplasia, especially in young women; first-choice examination: Doppler ultrasound of the renal arteries);
- primary hyperaldosteronism (hypokalemia spontaneous or caused by diuretics, weakening of muscle strength; first-choice examination: aldosterone–renin index);
- pheochromocytoma (sudden increases in blood pressure in combination with general symptoms, i.e., palpitations, headache, increased sweating, pale skin; first-choice examination: blood and/or urine methoxycatecholamine).

At the same time, an attempt should be made to modify the existing antihypertensive treatment by using

**a triple single pill combination** (angiotensin-converting enzyme inhibitor or angiotensin II receptor type 1 antagonist in combination with a calcium antagonist and a thiazide-like/thiazide diuretic) in full doses, which leads to improved blood pressure control in many patients [6–8, 24, 25]. Thiazide or thiazide-like diuretics are recommended if the eGFR is  $>30$  ml/min/1.73 m<sup>2</sup>. Chlorthalidone (at a dose of 12.5–25 mg/day) can be used together with or without a loop diuretic when the eGFR is  $<30$  ml/min/1.73 m<sup>2</sup> [6].

If the target blood pressure values are not achieved, spironolactone, an aldosterone antagonist, should be used as the fourth medication in antihypertensive therapy [8, 24, 25]. In the randomized PATHWAY-2 trial, in patients with resistant HT, the addition of spironolactone resulted in a significantly greater reduction in blood pressure than the addition of doxazosin or bisoprolol [26]. Spironolactone should be used with caution in patients with eGFR below 45 ml/min/1.73 m<sup>2</sup> and/or plasma potassium above 4.5 mmol/l spironolactone due to the risk of hyperkalemia and/or renal impairment. In the case of spironolactone intolerance, eplerenone is a potential alternative [27]. Due to high risk of hyperkalemia, treatment with mineralocorticoid receptor antagonists should be accompanied by careful monitoring of serum potassium concentration. The approval of an aldosterone synthesis inhibitor — baxdrostat — is expected soon. In recent years, two potassium-binding agents registered for chronic use in patients with hyperkalemia were implemented i.e. calcium patiomer, and sodium zirconium cyclosilicate. Patiomer is an unabsorbable organic polymer containing the calcium–sorbitol complex, and sodium zirconium cyclosilicate has a crystalline structure and is also not absorbed from the digestive tract. This medication works by selectively capturing potassium in the gastrointestinal tract. Both above mentioned drugs are highly effective in chronic hyperkalemia treatment and are well tolerated. Use of these drugs allows continuation of RAA system inhibitors therapy despite of hyperkalemia.

In the next steps of pharmacotherapy in patients with resistant HT, **an increase in the number of antihypertensive medications to 5–7** should be considered, using the following [6–8, 24, 25]:

- loop diuretic (preferably torasemide) added to a thiazide/thiazide-like diuretic — especially in patients with CKD (especially with eGFR below 30 ml/min/1.73 m<sup>2</sup>) or with symptoms of sodium and water retention;
- $\beta$ -blocker (preferably bisoprolol) — in patients with indications for  $\beta$ -blocker, this class of medications is included earlier [27, 28];
- $\alpha$ -blocker (preferably doxazosin XL) [26];
- a centrally acting medication (preferably clonidine) [29];
- a direct vasodilator (dihydralazine) [6–8, 24, 25].

## RENAL DENERVATION: MODE OF ACTION, TECHNIQUES, AND TECHNOLOGIES

It is important to emphasize that renal artery denervation does not replace pharmacotherapy, therefore, the neph-

rologist modifies therapy, monitors electrolyte balance, monitors renal function, and assesses long-term hemodynamic outcomes.

### Mode of action

The kidneys are innervated by two types of sympathetic system fibers: efferent fibers, which run from the central nervous system to the kidneys, and afferent fibers, which originate in the kidneys and conduct impulses to the central nervous system. Both types of fibers run along the renal arteries within their adventitia. Stimulation of efferent fibers results in vasoconstriction of renal vessels and, consequently, a decrease in renal flow and decreased glomerular filtration, increased secretion of renin and norepinephrine, and increased reabsorption of sodium ions in the renal tubules. All of this can lead to the development of HT. Experimental studies have also shown that stimulation of renal afferent fibers by affecting centers in the posterior hypothalamus causes increased activity of the central sympathetic system. Renal fibers of the sympathetic nervous system therefore have a significant impact on the participation of the kidneys in the pathophysiology of HT. The RDN method operates by downregulating the activity of sympathetic nerve fibers (both afferent and efferent) running along the wall of the renal artery. This is done using various methods, such as radio frequency current, ultrasonic waves, or intramural alcohol application (chemical denervation) [30].

### Overview of available technologies and description of the procedure

Currently, two devices for RDN are more widely used in Poland (Tables 1 and 2). Both technologies require femoral access; optimally, the puncture of the common femoral artery should be performed under local anesthesia and ultrasound visualization. Prior to performing the denervation, renal artery arteriography should be performed, and 200 micrograms of nitroglycerin should be administered intraarterially to reduce the risk of significant arterial spasm.

The Symplicity Spyral catheter (Medtronic, Minneapolis, MN, US) is a 4 Fr, 4-electrode catheter, which is inserted into the arterial lumen by the over-the-wire method using a 0.014-inch guidewire. The required diameter of the vascular sheath is 6 Fr. When the guidewire is removed, the catheter takes the shape of a helix, matched to the shape of the renal artery. The catheter allows 4 electrodes to be supplied with energy at the same time, which allows 4 quadrants of the arteries to be denervated at the same time or individual electrodes to be switched off if necessary. The catheter is suitable for arteries with a diameter of 3 to 8 millimeters; therefore, this catheter allows denervation to be performed within the peripheral branches, located distal to the bifurcation of the renal artery trunk. During the procedure, the catheter is connected to a radio frequency generator, which constantly controls the temperature inside the artery by emitting a current according to a built-in

**Table 1.** RDN systems available

| System                   | Manufacturer                 | Denervation method  | CE mark |
|--------------------------|------------------------------|---------------------|---------|
| <b>Symplixity Flex</b>   | Medtronic                    | RF ablation         | Yes     |
| <b>Symplixity Spyral</b> | Medtronic                    | RF ablation         | Yes     |
| ReDY                     | Renal DYNAMICS               | RF ablation         | Yes     |
| Iberis                   | Terumo                       | RF ablation         | Yes     |
| Renlane                  | Cordis Corporation           | RF ablation         | Yes     |
| EnligHTN                 | St Jude Medical (Abbott)     | RF ablation         | Yes     |
| ThermoCOOL               | Biosense Webster Diamond Bar | RF ablation         | Yes     |
| Vessix                   | Boston Scientific Natick     | RF ablation         | Yes     |
| <b>PARADISE</b>          | ReCor Medical                | Ultrasound ablation | Yes     |

Systems with a rich evidence base are marked with bold

Abbreviations: RF, radiofrequency

**Table 2.** Comparison of the Simplicity Spyral RF and Paradise US systems for renal artery denervation. Based on [32]

|                                 | Simplicity Spyral RF                                                                                                              | Paradise US                                                                                                                                                                                                                                                      |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anatomical eligibility criteria | Treatment of all reachable renal arteries with a diameter of 3–8 mm                                                               | Treatment of reachable main renal arteries with a diameter of 3–8 mm                                                                                                                                                                                             |
| Access                          | Femoral access (6 Fr)                                                                                                             | Femoral access (7 Fr)                                                                                                                                                                                                                                            |
| Delivery                        | Possibility of using high support guidewires or supportive guidewires in cases of tortuous anatomy                                | Possibility of using secondary guides or guidewires in cases of tortuous anatomy                                                                                                                                                                                 |
| Ablation sites                  | Main renal artery and its branches                                                                                                | Main renal artery, 2–3 ablations per artery. Catheter size and ablation site selection can be pre-performed using computed tomography/magnetic resonance angiography, and final positioning can be performed during the procedure under ultrasound visualization |
| Contact with the artery wall    | Ensuring proper contact of the RF electrodes with the vessel wall. Ensure power delivery (duration at least 45 s, optimally 60 s) | Full closure of the renal artery lumen before balloon inflation                                                                                                                                                                                                  |
| Duration                        | Simultaneous ablation at 4 points (duration at least 45 s, optimally 60 s)                                                        | 7 s for ablation                                                                                                                                                                                                                                                 |

algorithm. The application duration is 60 seconds. After the procedure, 200 micrograms of nitroglycerin should be administered intraarterially again, and a follow-up arteriography should be performed to assess possible intraoperative complications [31].

The second system, Paradise (Recor, Palo Alto, CA, US), involves of a balloon catheter, inside which there is a piezoelectric transducer converting the energy emitted by the generator into an ultrasonic wave. The required diameter of the vascular sheath is 7 Fr. The catheter is available in different sizes; the choice of catheter depends on the diameter of the renal artery. It is possible to perform ablation in arteries with a diameter of 3.5 to 8 mm. After inserting the balloon over the 0.014-inch guidewire and placing it in the lumen of the renal artery trunk, 2–3 seven-second ablations are performed, covering the entire circumference of the artery at the same time. Ablation is not performed in the peripheral branches of the artery. During the application, the balloon catheter is automatically rinsed with saline solution to avoid excessive temperature rise within the lumen of the renal artery [31].

Due to the pain associated with RDN, the procedure is performed under shallow analgosedation. Analgesics (fentanyl, morphine) and hypnotics (e.g., midazolam) are administered. The procedure is performed on full anticoagulation with unfractionated heparin, with a target APTT of >250 seconds.

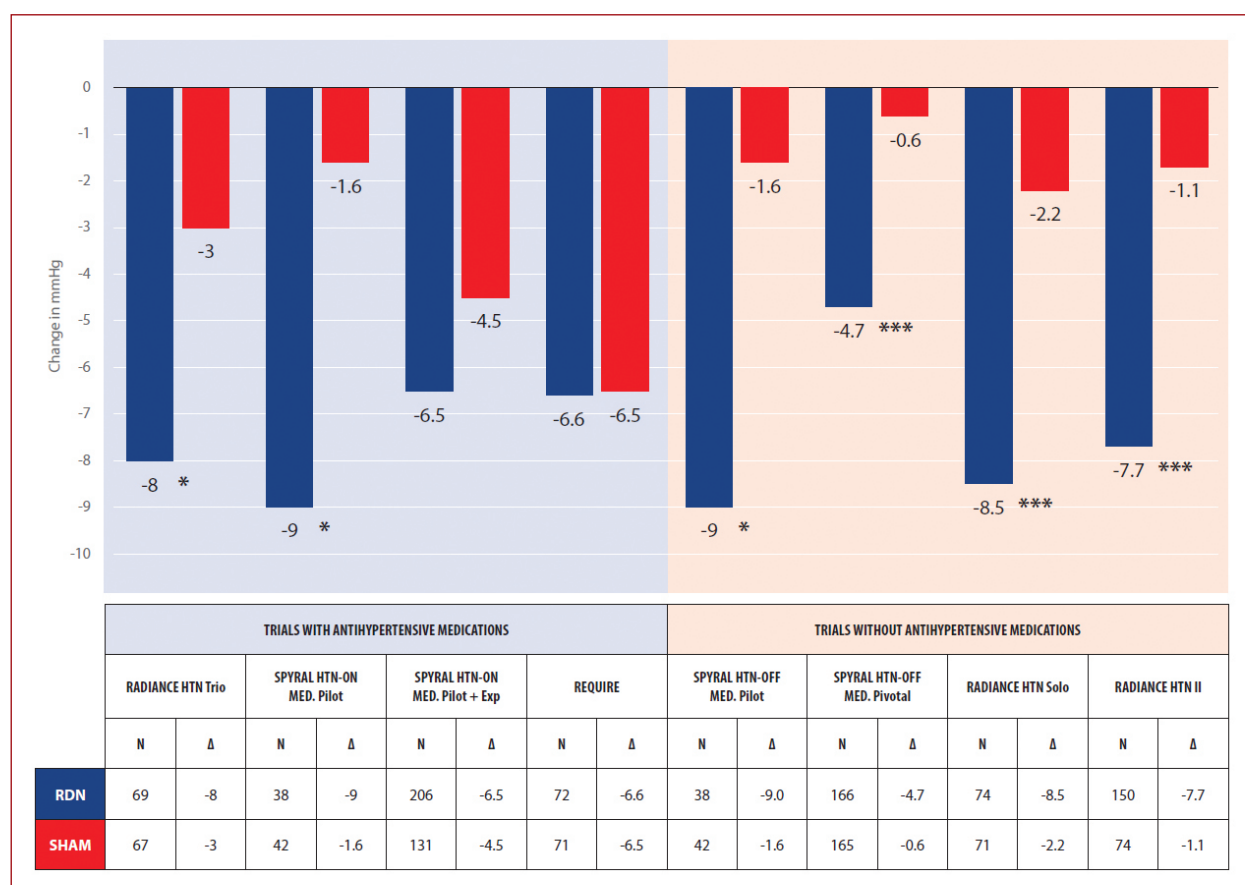
**Table 3.** Patient preparation for the renal denervation procedure. Based on [32]

|                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adequate hydration according to the procedure for contrast agent                                                                                                                                                                     |
| Administration of unfractionated heparin during the procedure (100 IU/kg to achieve activated clotting time >250 s)                                                                                                                  |
| Perioperative administration of a loading dose of aspirin, followed by aspirin 75–100 mg daily for 1 month following the procedure                                                                                                   |
| Patients using oral anticoagulants are managed according to the Canadian Cardiovascular Society guidelines for endovascular interventions                                                                                            |
| Analgesia and sedation according to the anesthesia procedure with monitored anesthesia care: low-dose opioids (e.g., morphine 1–3 mg or fentanyl 1–2 µg/kg intravenously) and benzodiazepines (e.g., midazolam 2–3 mg intravenously) |
| Intraoperative vital signs monitoring                                                                                                                                                                                                |
| Medications used in the management of adverse events must be available at the catheterization laboratory (e.g., flumazenil, naloxone)                                                                                                |
| Intravenous blood pressure medications (e.g., nitroprusside, urapidil, nitroglycerin, phentolamine)                                                                                                                                  |

A comparison of both systems and patient preparation are presented in Tables 1–3.

### EFFICACY, SAFETY, AND COST-EFFECTIVENESS OF RENAL DENERVATION — SUMMARY OF CLINICAL TRIAL RESULTS

The efficacy of RDN as a form of HT therapy has been intensively studied. The results of trials on the first generation of devices used for RDN procedures were inconclusive, and their reliability was limited by significant methodological problems, the key ones being suboptimal selection of pa-



**Figure 2.** Change in systolic pressure measured by ambulatory blood pressure monitoring [34–41]

The asterisks indicate statistical significance: \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . In the SPYRAL trials: HTN-ON Pilot, HTN-ON Pilot + Ext., HTN-OFF Pilot, HTN-OFF Pivotal, and REQUIRE, 24-h ambulatory blood pressure monitoring measurement was the primary endpoint

Abbreviation: RDN, renal denervation

tients (the eligibility criterion was based mainly on systolic blood pressure), frequent changes in pharmacological treatment during the trials (lack of standardization), insufficient experience of the operators, and lack of adequate blinding of patients and the staff evaluating the results, as well as the lack of use of sham treatment in the early period of the trials [32, 33]. Consequently, the results of these early trials did not provide conclusive evidence of the effectiveness of RDN, prompting scientific societies around the world to be very cautious in their recommendations in this regard.

In 2017, several trials began on second-generation devices used for RDN procedures, while introducing significant changes in the design and conduct of clinical trials. These changes enabled, among other things, better patient selection, the use of more accurate blood pressure monitoring methods (including assessment of blood pressure changes in ABPM as the primary endpoint), laboratory monitoring of adherence, and a sham procedure in the control group. The trials used modern systems based on radio wave or ultrasound technology [32, 33].

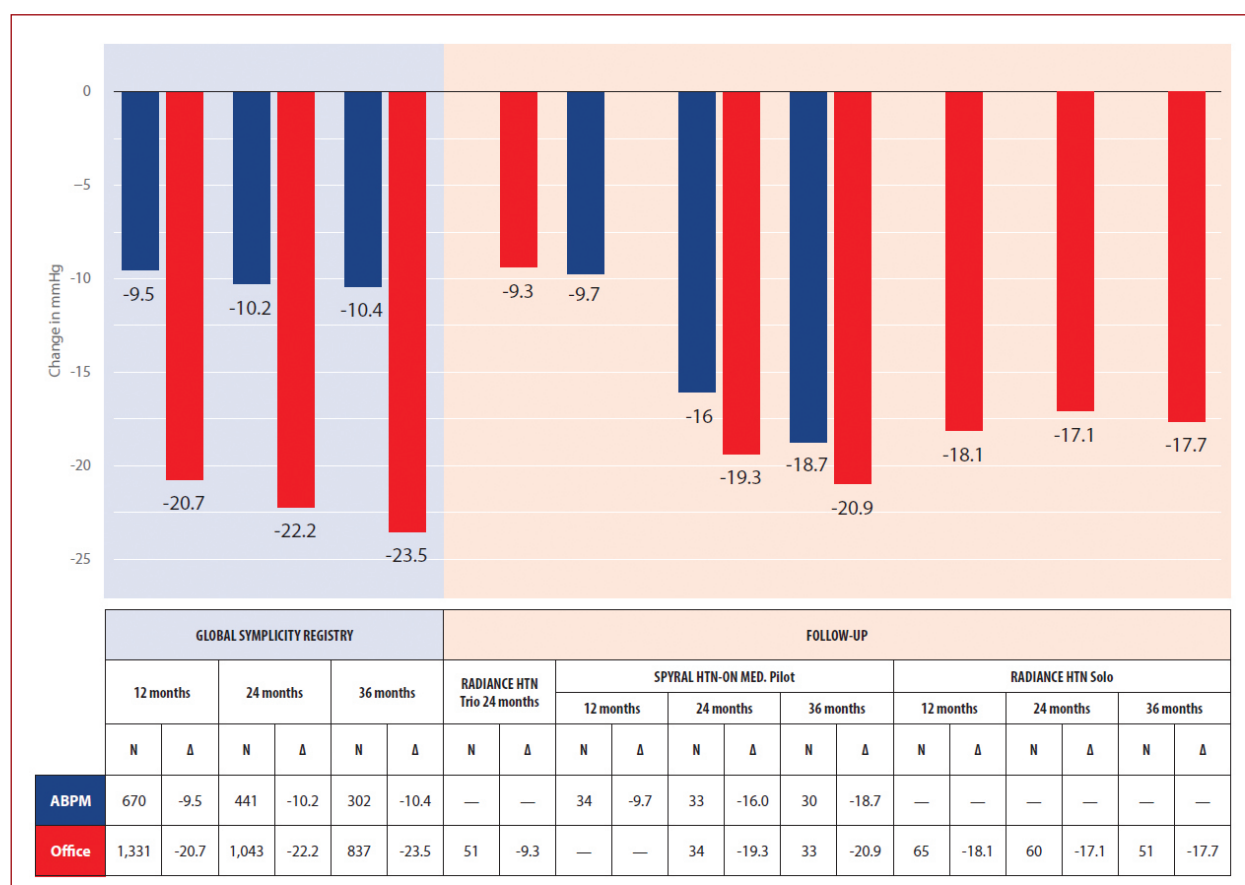
The results of these trials confirmed that RDN is effective in lowering blood pressure in patients taking antihypertensive medications and in those who are not

using pharmacological treatment. With a few exceptions, all randomized controlled trials showed statistically significant and clinically significant reductions in blood pressure in the RDN group compared to the sham control group (Figure 3) and confirmed the favorable safety profile of this method [34–41].

Compared to the groups subjected to the sham procedure, the mean reduction in blood pressure in ABPM was significantly greater in the RDN group, ranging from  $-4.7$  to  $-9.0$  mm Hg for systolic blood pressure and  $-3.7$  to  $-6.0$  mm Hg for diastolic blood pressure (Figure 3) [34–41].

Two trials, RADIANCE-HTN TRIO and DENERHTN, showed that the reduction in blood pressure following RDN was maintained regardless of adherence and compliance, which allows us to define the effect of RDN as “always-on”, constant — regardless of pharmacokinetics, adherence, compliance, and dosing regimen [34, 42].

The results of the trials for the second-generation RDN also showed a significant reduction in nighttime blood pressure [34–37, 39, 43], which is an important goal in reducing cardiovascular risk [44–48]. In a detailed *post hoc* analysis of the SPYRAL HTN-ON MED trial, it was observed that the morning increase in blood pressure was smaller in the group that underwent RDN, which can be explained



**Figure 3.** Change in systolic pressure vs. baseline in patients with resistant hypertension undergoing renal denervation measured by ambulatory blood pressure monitoring (ABPM) and in the doctor's office — >12 months follow-up results [5, 55, 57, 58]

by a decrease in sympathetic activity [49]. Blood pressure measured in the doctor's office also decreased. In patients undergoing RDN, a reduction in systolic pressure in the range of  $-9.0$  to  $-11$  mm Hg [34–39, 41] and diastolic pressure by approximately  $-5$  mm Hg [34, 36–39, 41] was observed. The observed changes were statistically significant vs. the sham procedure.

It is worth noting that the effectiveness of RDN is not uniform in all patients. A significant reduction in systolic blood pressure measured in the office or during ABPM of at least 5 mm Hg was observed in 60%–70% of patients at 2–6 months follow-up. Additionally, approximately 20% of patients undergoing RDN achieve target blood pressure in HBPM or ABPM, which is also more than twice the percentage vs. the sham procedure group [39, 43, 50]. It is worth noting that these results were achieved with fewer medications taken in the RDN group [39].

A meta-analysis of 9 randomized, sham-controlled (i.e., dummy procedures) trials involving 1643 patients found that after an average of 5 months of follow-up, RDN was associated with a significant reduction in 24-hour blood pressure: systolic ( $-4.2$  mm Hg; 95% confidence interval [CI],  $-5.4$  to  $-3.0$ ;  $P < 0.00001$ ), diastolic ( $-2.4$  mm Hg; 95% CI,  $-3.4$  to  $-1.6$ ) and daytime blood pressure in ABPM (systolic:  $-5.1$  mm Hg; 95% CI,  $-6.8$  to  $-3.5$ ; diastolic:  $-2.9$  mm Hg; 95% CI,  $-3.9$  to  $-1.9$ ). Similarly, office blood pressure

was reduced in the RDN group (systolic:  $-5.5$  mm Hg; 95% CI,  $-7.1$  to  $-3.8$ ; diastolic:  $-3.2$  mm Hg; 95% CI,  $-4.2$  to  $-2.1$ ) vs. the placebo group [51].

Based on the currently available data, no significant differences in the efficacy of blood pressure reduction between radiofrequency RDN and ultrasound RDN were found [3, 52].

At the same time, a meta-analysis of 12 trials involving 433 patients found that RDN may also contribute to improving heart structure and function in patients with resistant HT. Following RDN, a reduction in left ventricular mass index of  $13.1$  g/m<sup>2</sup> (95% CI,  $-18.4$  to  $-7.8$ ;  $P < 0.00001$ ), a decrease in left ventricular posterior wall thickness by  $0.6$  mm (95% CI,  $-0.9$  to  $-0.3$ ;  $P < 0.00001$ ), and a decrease in ventricular septum thickness by  $0.8$  mm (95% CI,  $-1.1$  to  $-0.5$ ;  $P < 0.00001$ ) were observed. In addition, there was an increase in left ventricular ejection fraction of  $1.8\%$  (95% CI,  $0.7$ – $2.9$ ;  $P = 0.001$ ). Nevertheless, there were no statistically significant changes in the internal diameter of the left ventricle during diastole (95% CI,  $-1.40$  to  $0.24$ ;  $P = 0.17$ ) or in diastolic function (E/A ratio) (95% CI,  $-0.04$  to  $0.14$ ;  $P = 0.28$ ) [53].

The long-term efficacy of RDN is assessed as part of the Global Symplicity Registry (GSR), which aims to follow patients undergoing this procedure long term. This registry, which includes 196 sites, represents the largest prospective

**Table 4.** Complications and adverse events (%) in sham-controlled clinical trials and in the Global Symplicity Registry

|                                  | Clinical trials [4]                         | Global Symplicity Registry [5] |
|----------------------------------|---------------------------------------------|--------------------------------|
| Population                       | Meta-analysis of 15 RCTs, n = 1723 patients | n = 1749 patients              |
| Follow-up                        | Up to 6 months                              | 36 months                      |
| Death                            | 0.23%                                       | 5.7%                           |
| Death from cardiovascular causes | NR                                          | 2.9%                           |
| Myocardial infarction            | 0.78%                                       | 2.5%                           |
| Stroke                           | 0.67%                                       | 4.5%                           |
| End-stage renal failure          | 0                                           | 1.8%                           |
| Hypertensive crisis              | 1.75%                                       | 3.1%                           |
| Renal artery stenosis >70%       | 0.25%                                       | 0.3%                           |

Abbreviations: NR, not reported; RCT, randomized controlled trial

observational trial to monitor the safety and efficacy of RDN in real-world clinical settings in patients with resistant HT. So far, more than 3000 patients have been enrolled, of whom 2652 are under a 3-year follow-up.

The results presented in the GSR trials indicate that RDN allows for a permanent and significant reduction of both office and ABPM blood pressure (**Figure 3**). At 12 months, patients with resistant HT undergoing RDN experienced significant reductions in systolic blood pressure in both in-office measurements (–20.7 mm Hg vs. baseline) and ABPM (–9.5 mm Hg vs. baseline). Office and ABPM blood pressures remained reduced at a similar level also in long-term follow-up (up to 36 months), with a tendency for a slight deepening of the effect over time [5]. The magnitude of the observed effect allows the estimation that, in the population, 45 major cardiovascular events are prevented per 1000 treated over a 3-year follow-up period. In addition, based on these data, it is estimated that the number of patients who need to be treated to avoid one major cardiovascular event is 22 in the population with resistant HT, which is primarily due to a significant reduction of the risk of ischemic stroke [54].

Similar results were observed in the SPYRAL HTN-ON MED and RADIANCE-HTN SOLO trials, which confirm that the effectiveness of RDN in blood pressure lowering is maintained for at least 3 years (**Figure 3**) [55–58]. However, it should be noted that the long-term effect of RDN may depend on various factors, such as changes in pharmacotherapy, adherence and compliance in terms of lifestyle recommendations, especially in terms of salt intake, the process of aging, and the development of cardiovascular or kidney diseases.

The safety of RDN is a key aspect of assessing its clinical feasibility. Trials published so far show that RDN is a relatively safe procedure, with a percentage of perioperative complications below 5%. Local complications, such as pseudoaneurysms, arteriovenous fistulas, or retroperitoneal bleeding, can occur at femoral access sites. These are like those observed in cardiovascular interventions and are usually treated conservatively. A meta-analysis of 50 published RDN trials confirmed the safety of this procedure. Among 5769 patients (follow-up period of 10 249 patient-years),

only 26 (0.45%) experienced renal artery stenosis or dissection. The median time from RDN to any renal intervention was 5.5 months (range: 0–33 months); 79% of all events occurred within a year of the procedure [59].

Similar observations were collected during clinical trials. A meta-analysis of 15 randomized controlled trials involving 2581 patients (RDN, 1723; sham, 858) found that no serious procedural complications were reported in any of these trials, and adverse events are extremely rare (**Table 4**) [4]. Safety data from the largest database, the GSR registry, also showed a very low incidence of perioperative complications and adverse events during the three-year follow-up [5].

Economic analyses confirm that RDN is a highly cost-effective treatment of resistant HT, regardless of the method used (radiofrequency or ultrasound). Based on the latest clinical data and estimates indicating that RDN can significantly reduce the number of serious clinical events in patients with uncontrolled HT, it has been shown that the more time elapses after surgery, the greater the savings resulting from this procedure [60, 61].

## EFFICACY OF RENAL DENERVATION IN SPECIAL POPULATIONS

### *Obstructive sleep apnea (OSA)*

A meta-analysis of trials on the effect of RDN on patients with OSA showed a significant reduction in systolic and diastolic blood pressure in daytime ABPM. This effect persisted for at least 6 months following RDN, and no serious complications were reported in patients with OSA. The meta-analysis included 5 trials involving 434 patients, and its results are consistent with the results of the parent trial and with data from the GSR, which confirm the effectiveness of RDN in lowering blood pressure in this group of patients [62, 63].

Although the meta-analysis did not confirm a significant effect of RDN on the apnea-hypopnea index [63], other isolated trials suggest that RDN may benefit glycemic control in patients with resistant HT and OSA [64]. Therefore, RDN is a potentially useful therapeutic option for patients with severe OSA and metabolic disorders.

### **Chronic kidney disease**

In advanced stages of CKD and in dialysis patients, HT is often refractory and difficult to control pharmacologically. Importantly, even in the end-stage stage, the kidneys can be a source of pathological afferent sympathetic activation — the risk of arrhythmia and sudden death is very high. HT affects also most recipients after kidney transplantation. Causes include calcineurin inhibitor toxicity, graft artery stenosis, and persistent sympathetic activation of the native kidneys.

A review of 11 trials involving 226 patients with CKD and resistant HT who underwent RDN showed its significant clinical benefits. A meta-analysis proved stabilization of serum creatinine and eGFR and a significant reduction in ABPM and office blood pressure for 6 to 24 months following the procedure. The procedure was also associated with a minimal risk of complications [65]. The most recent analysis of 3-year GRS data, including 475 patients with CKD (baseline eGFR <60 ml/min/1.73 m<sup>2</sup> but ≥15 ml/min/1.73 m<sup>2</sup>) and 1505 patients without CKD (baseline eGFR ≥60 ml/min/1.73 m<sup>2</sup>), showed similar reductions in blood pressure in both groups, both in office measurements and in ABPM, regardless of kidney function. No differences in the RDN safety profile were found between groups [66]. Moreover, in another meta-analysis included 238 patients from 11 single-center, non-randomized, uncontrolled studies it was documented that UACR was reduced at 3 months and 6 months after RDN [67]. A small, randomized trial involving kidney transplant recipients also confirmed the effectiveness and safety of the intervention in this population [68]. The results suggest that patients with CKD may be an ideal group for RDN, although data for populations with baseline eGFR <45 ml/min/1.73 m<sup>2</sup> remain limited. It should be emphasized that RDN in CKD patients does not replace nephroprotective pharmacotherapy, therefore the role of the nephrologist is extremely important, whose tasks include modifying the pharmacotherapy, monitoring electrolyte balance and renal function.

Resistant HT is often a multifactorial disease associated with CKD. Renal artery denervation may become an element of combined therapy in interventional nephrology, particularly in high-risk cardiovascular populations, where controlling sympathetic activation may be more important than reducing blood pressure alone.

### **Dialysis patients**

Pilot trials have shown that RDN can effectively lower blood pressure in patients treated with renal replacement therapy in whom pharmacological treatment is ineffective. In the largest controlled trial, which included 12 patients treated with renal replacement therapy and undergoing the procedure, RDN resulted in a significant reduction in office systolic blood pressure, which was maintained for 12 months. In the control group, subjected to pharmaco-

logical treatment only, no changes in blood pressure were observed [69].

### **Atrial fibrillation**

A review with a meta-analysis of six trials on the use of RDN in combination with pulmonary vein isolation for the treatment of paroxysmal and/or persistent atrial fibrillation in 711 patients with HT and atrial fibrillation showed a significantly reduced risk of atrial fibrillation recurrence was in the RDN and pulmonary vein isolation group vs. the pulmonary vein isolation group, significantly reduced systolic blood pressure at 12 months in the resistant HT group, significant increase in eGFR at 6 months, and low overall incidence of complications in both groups both during the procedures and during the follow-up period [70].

Data from a 3-year follow-up within the GRS confirm the above observations regarding the reduction of systolic blood pressure, both in office measurement and in ABPM [5].

### **Patients with untreated HT**

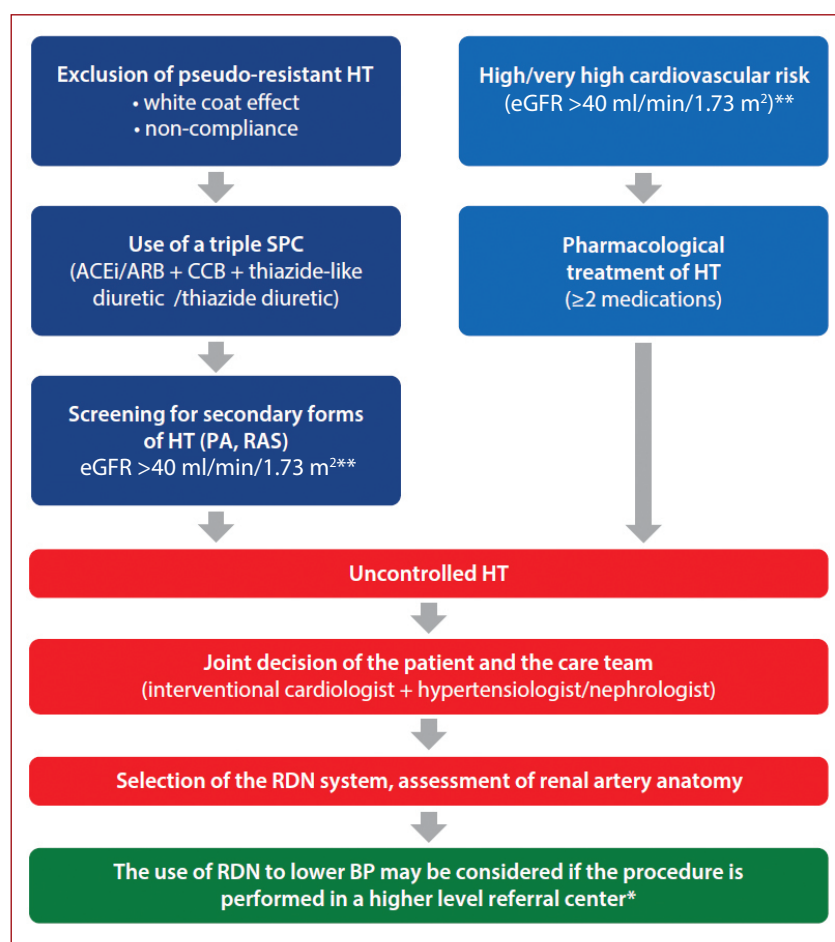
An interesting area of research on the efficacy of RDN is that of patients with HT who are not receiving antihypertensive treatment.

The SPYRAL HTN-OFF MED trial, which is a multicenter, international, randomized, single-blind, controlled trial, evaluated the effects of RDN on blood pressure in 80 HT patients not receiving antihypertensive medications. The results showed a significant reduction in both office and ABPM blood pressures (reduction of mean values over a period of 24 hours −5.5/−4.8 mm Hg) in the RDN group vs. the control group at 3 months [41].

The TARGET BP OFF-MED trial analyzed renal denervation using alcohol application to the renal artery wall in 106 HT patients who were not using or had discontinued antihypertensive medications. Although the procedure was safe, there were no significant differences in blood pressure reduction between the RDN and control groups at 8 weeks. In an extended follow-up of 12 months, a lower antihypertensive medication burden was observed in the RDN group vs. the control group, with a mean number of standard daily doses of  $1.5 \pm 1.5$  vs.  $2.3 \pm 1.7$ ;  $P = 0.017$  [71].

The SPYRAL HTN-OFF MED Pivotal Trial confirmed the effectiveness of RDN in reducing blood pressure in HT patients who did not receive antihypertensive therapy. This trial showed a significant reduction in both 24-hour and office systolic blood pressures vs. the sham procedure, with a mean difference between the groups of −3.9 and −6.5 mm Hg, respectively, at 3 months, in the absence of significant safety concerns [37].

Overall, the results of these trials highlight the potential of RDN as a therapeutic option for the treatment of HT at earlier stages of development than resistant HT, or in special groups of patients such as patients who refuse or are intolerant to antihypertensive medications.



**Figure 4.** Eligibility criteria for renal denervation

\*3<sup>rd</sup> reference level centers in the National Cardiology Network (KSK, *Krajowa Sieć Kardiologiczna*). \*\*Lower values — it is necessary to meet the additional conditions described in the text. Based on [7]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HT, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RDN, renal denervation; SPC, single pill combination

## CLINICAL PRACTICE RECOMMENDATIONS

### Eligibility criteria

Proper patient selection for RDN is a key element in the application of this method for treating HT.

- RDN should be considered in patients with HT (after excluding all hormonal causes and ischemic etiology of existing HT, i.e., caused by stenosis of the renal artery/arteries) that is resistant to pharmacological treatment.
- To demonstrate a truly resistant HT, it is necessary to exclude pseudo-resistant
- HT, e.g., caused by the so-called white-coat HT. Every patient with resistant HT should have an ABPM performed, which is the best method of confirming true resistant HT.
- Prior to final diagnosis of true resistant HT, the lack of cooperation between the patient and the physician, and non-regular use of antihypertensive medications and other therapeutic recommendations should also be excluded. However, some authors believe that demonstrating full non-adherence and non-compliance with the recommendations (failure to detect the presence of antihypertensive medications in plasma/urine) may suggest that other methods of HT treatment, such as RDN, could protect the patient from the occurrence of

dangerous complications associated with high blood pressure, and therefore such patients can also be qualified for RDN.

- In exceptional situations, patients with significant intolerance to most antihypertensive medications may also be qualified for RDN.

Currently, there are no clear determinants that allow us to predict which patients will benefit the most from RDN. However, it can be assumed that these will be patients in whom high stiffness of peripheral vessels is not found and patients with increased activity of the sympathetic nervous system. In practice, these parameters can be assessed based on pulse wave velocity, plasma renin activity, heart rate under ambulatory conditions, and high blood pressure variability, especially during nighttime. In recent years, patients with resistant HT and an increased risk of cardiovascular complications have also been increasingly selected for RDN. **Figure 4** presents the eligibility criteria for the procedure.

The recommendations of the current ESH and ESC guidelines are summarized in **Table 5**. In both documents, the level of RDN recommendation was increased from III in the joint document from 2018 to IIb (**Table 5**) [6, 7]. It is also emphasized that although the safety and efficacy of the procedure in lowering blood pressure have been demonstrated, there are no trials evaluating the robust

**Table 5.** Indications for renal denervation according to European Society of Hypertension 2023 and European Society of Cardiology 2024 guidelines [6, 7]

| European Society of Hypertension Guidelines 2023                                                                                                                                                                                                                             | European Society of Cardiology Guidelines 2024                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73 m <sup>2</sup> 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) | To reduce BP, and if performed at a medium-to-high-volume center, 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 (IIb/B) |
| RDN can be considered as an additional treatment option in patients with true resistant hypertension if eGFR is >40 ml/min/1.73 m <sup>2</sup> (II/B)                                                                                                                        | To reduce BP, and if performed at a medium-to-high volume center, catheter-based renal denervation may be considered for patients with both increased CVD risk and uncontrolled hypertension on fewer than 3 drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment (IIb/A)                                                                      |
| 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)                                                                                                                     | Due to a lack of adequately powered outcomes trials demonstrating its safety and CVD benefits, renal denervation is not recommended as a first-line BP-lowering intervention for hypertension (III/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)                                                                                                  | Renal denervation is not recommended for treating hypertension in patients with moderate-to-severely impaired renal function (eGFR <40 ml/min/1.73 m <sup>2</sup> ) or secondary causes of hypertension, until further evidence becomes available (III/C)                                                                                                                                                                          |

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RDN, renal denervation

endpoints that would show a reduction in cardiovascular risk as a result of RDN and long-term observations of the safety of the procedure [7].

The current ESH and ESC guidelines state that patients with impaired renal function (eGFR <40 ml/min/1.73 m<sup>2</sup>) should not be referred for RDN. This condition is not based on demonstrating the lack of efficacy of RDN in this population but is only because all the randomized clinical trials included patients with reduced eGFR. According to the authors of this statement and the authors of the other recent reviews and position paper, eGFR alone should not unequivocally exclude patients from RDN [72, 73]. The authors of this statement suggest that that CKD patients with eGFR <40 ml/min/1.73 m<sup>2</sup> might be referred to RDN after careful analysis by a nephrologist. RDN in CKD patients should be a part of nephroprotective treatment together with pharmacotherapy according to current Polish Society of Nephrology clinical practice statements [74, 75].

Patients with a renal artery diameter less than 3 mm or with significant anatomical abnormalities of the renal arteries should not be referred for RDN. RDN should not be performed in patients with resistant HT and advanced heart valve defects or, for obvious reasons, in pregnant women.

Currently, it is believed that eligibility for RDN should always be determined by two independent specialists, i.e., a hypertensiologist or nephrologist who assesses the patient's condition and an interventional cardiologist with experience in RDN.

### Postoperative patient monitoring and follow-up

In clinical trials, complications of RDN, both in the postoperative period and in longer follow-up, were rare and almost exclusively associated with access site complications [56]. Concerns were raised about the possibility of developing *de novo* renal artery stenosis secondary to artery damage by RDN, as well as deterioration of renal function. The results of randomized trials and clinical registries do not confirm these concerns, but the number of observations does not clearly rule them out [76]. Considering the above, the fol-

lowing assumptions should be made for patient monitoring following RDN [77, 78]:

- immediately after the procedure, monitoring of femoral access;
- immediately after the procedure, the patient should continue his/her current antihypertensive regimen, ambulatory blood pressure should be assessed the one month, 3 and 6 months, and every 6 months thereafter;
- assessment of kidney function and injury at 3 and 6 months after surgery, and every 6 months thereafter, with eGFR and UACR measurements;
- renal arteries Doppler should be performed 6 months after the procedure, and also as indicated (e.g., increase in blood pressure).

In line with current guidelines adopting lower target blood pressure values, a reduction in the intensity of antihypertensive treatment should be considered in cases of documented, preferably out-of-office, sustained blood pressure reduction to values below 120 and 70 mm Hg [8].

It should be emphasized here, that in the qualification process for RDN, an important role is played by the nephrologist, who, in cooperation with other specialists is involved in proper patient's identification and ruling out secondary forms of HT. The nephrologist might assess safety, CKD stage, proteinuria, risk of renal disease progression, initiates anatomical diagnostics of the renal arteries, and interprets the results of computed tomography and magnetic resonance angiography in the clinical context (e.g., the presence of fibromuscular dysplasia).

### Current avenues of research

The future of RDN looks promising, and ongoing research is focused on refining the procedure and understanding its broader implications for the treatment of cardiovascular diseases that go beyond HT, such as heart failure, arrhythmias, and CKD. The ability of RDN to modulate the activity of the sympathetic system provides grounds for considering its use in these conditions. Nevertheless, the field is facing material challenges, including the need for

more rigorous clinical trials that would validate the existing datasets and position RDN as a standard therapeutic option [1, 32, 79, 80].

Future research should also be focused on several critical domains, including the durability of blood pressure reduction, the impact on clinical outcomes (mitigation of cardiovascular risk, including robust endpoints, possible nephroprotective effects in CKD patients), and the potential to de-escalate antihypertensive pharmacotherapy. There is also a growing interest in developing new devices and techniques that could increase the effectiveness of RDN. Experimental studies are also underway on applying denervation to arteries other than the renal ones, which may enhance the effectiveness of HT management. Identifying predictors of treatment effectiveness and understanding patient preferences are developing areas of research that aim to optimize therapy. The methodology of the procedure is also evolving, with a shift towards the distal sections of the renal arteries and greater use of energy, which is aimed at improving treatment outcomes [1, 32, 81–83].

## SUMMARY

Regardless of the pharmacological treatment of resistant HT, RDN remains a very interesting therapeutic option; recently there has been renewed increase in interest in its use in the treatment of resistant HT.

Based on the current literature review and ongoing discussions, it can be concluded that the use of second-generation RDN catheters and correct trial protocols (using the sham denervation procedure) allow for a significant reduction in blood pressure.

The results of recently published trials unequivocally confirm the effectiveness of this method in the treatment of resistant HT. However, it seems that the prerequisite for obtaining favorable RDN results is the correct qualification of patients for this treatment (confirmation of the occurrence of so-called truly resistant HT) and the implementation of this procedure only in centers with appropriate experience (Figure 4).

## Article information

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