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EXPERT OPINION

Renal Denervation in the Treatment of Resistant Hypertension and Difficult-to-Control Hypertension – Consensus Document of the Croatian Hypertension League – Croatian Society of Hypertension, Croatian Cardiac Society, Croatian Endovascular Initiative, Croatian Society for Diabetes and Metabolic Diseases, Croatian Renal Association, and Croatian Society of Family Physicians of the Croatian Medical Association

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On the behalf of Task force for the Resistant Hypertension and Renal Denervation of the Croatian Hypertension League

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Abstract: Renal denervation (RDN) as a method of treating arterial hypertension (AH) was introduced in Croatia in 2012. A multidisciplinary team and a network of hospitals that diagnose and treat patients with severe forms of AH were established, and a very strict diagnostic-treatment algorithm was prepared. At monthly meetings patients with truly resistant hypertension who were candidates for RDN were discussed. According to the 2021 ESH position statement and 2023 ESH guidelines, RDN is considered an alternative and additional, not a competitive method of treating patients with various forms of AH which must be performed by following a structured procedure and the patient's preference should be considered. In view of the changes in the global scientific community, the Croatian Hypertension League brings this consensus document on RDN conducted with radiofrequency-based catheter, the only currently available method in Croatia. In this document, exclusion and inclusion criteria are shown, as well as three groups of patients in whom RDN could be considered. The new diagnostic-treatment algorithm is prepared and follow-up procedure is explained. In Croatia, RDN is reimbursed by the national insurance company, thus pharmacoeconomic analyses is also shown. Criteria required by an individual centre to be approved of RDN are listed, and plans for prospective research on RDN in Croatia, including the Croatian registry for RDN, are discussed.

Keywords: hypertension, renal denervation, catheter- radiofrequency ablation, consensus, Croatia

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Historical Overview of Renal Denervation in Croatia

Renal denervation (RDN) as a method of treating arterial hypertension (AH) was introduced in Croatia in 2012. After the education of interventional cardiologists and radiologists it was carried out in four centres. The Croatian Society for Hypertension developed an education plan on how to select patients suitable for RDN and how to increase awareness of the new treatment option. Wanting to make this method available to patients with AH, negotiations with the Croatian Health Insurance Fund on the payment of RDN costs for patients with resistant AH were successfully completed. The method has been used and by 2017 we had done 55 RDNs. However, after the Symplicity 3 study, the ESH/ESC guidelines recommended that RDN should only be used in clinical studies until new evidence shows that RDN is beneficial and safe. At that moment, faced with three important facts: 1. the guidelines allowed the use RDN only in clinical studies; 2. RDN was reimbursed by the insurance company; 3. many patients could benefit from RDN, we decided to do use RDN only in strictly selected patients included in the monitoring and in the registry of an ESH Excellence Centre and the Referral Centre for Arterial Hypertension of the Ministry of Health of the Republic of Croatia, University Hospital Centre Zagreb. A very strict diagnostic algorithm was prepared (Supplementary Figure 1), and RDN was performed only in one centre by one interventional radiologist. A multidisciplinary team (Supplementary Figure 2), and a network of hospitals that diagnose and treat patients with severe forms of AH were established. At monthly meetings patients who were candidates for RDN not only from the Referral Centre, but also from other centres that were part of the network were discussed. As a confirmation of persistence in taking medication, which was one of the essential conditions that must be met for the patient to be a candidate for RDN at the Referral Centre for Arterial Hypertension of the Ministry of Health of the Republic of Croatia, we introduced a toxicological analysis and determination of the concentrations of antihypertensive drugs in blood and urine. We continued to follow our strict algorithm and by the end of 2022 we did a total of 84 RDNs (Flex 27 Spyral 57 – methods are explained in Supplementary Para Figure 1). In addition, we performed RDN with CO_2 angiography in eleven patients with CKD and/or hypersensitivity to iodine contrast agents (Supplementary Para Figure 2). After the analysis of several large and important studies that unequivocally clearly demonstrated the great benefit and safety of RDN, a new official ESH document was published in 2021 and adopted in the new 2023 ESH guidelines.[1,2] According to these documents, RDN is a treatment option for AH as a complementary method to changing bad lifestyle habits and using antihypertensive drugs. Therefore, RDN is considered an alternative and additional, not a competitive method of treating patients with various forms of AH. RDN should be performed by following a structured procedure and the patient's preference should be considered. In view of the changes in the global scientific community, the Croatian Hypertension League brings this consensus document on RDN conducted with radiofrequency-based catheter, the only currently available method in Croatia.

Epidemiological Data on Arterial Hypertension and Its Association with CV Risk

Even though an ideal study to estimate the prevalence of true resistant AH has not been conducted, data on frequency can be derived from observational and large controlled clinical studies in which research was conducted on large number of subjects.[3,4] It is estimated that the global average prevalence of resistant AH is around 14.7% in treated hypertensive patients, 22.9% in chronic kidney patients and 56% in transplant patients.[3,4] In the EH-UH 1 study conducted in 2005, the prevalence of AH was 37.5% in line with the reports from some Western European countries with poor control of around 20%.[5] According to the preliminary results of the nationwide study on the prevalence, treatment, and control of hypertension (EH-UH 2 study), in Croatia the prevalence of resistant hypertension (uncontrolled hypertensive patients treated with ≥3 antihypertensive drugs) was 29.1%, 14.1% and 11.3% in the group of treated uncontrolled hypertensive patients, in the group of treated hypertensive patients, and in the whole group of hypertensive patients, respectively (Jelaković, 2023 unpublished data). Prevalence of refractory hypertension (controlled hypertensive patients treated with ≥3 antihypertensive drugs) was 36.6%, 18.8% and 15.1% in the group of treated uncontrolled hypertensive patients, in the group of treated hypertensive patients, and in the whole group of hypertensive patients, respectively. Among all the potential causes of unregulated AH, persistence or adherence is a particularly pronounced clinical challenge, which is emphasized in the ESH-ESC guidelines.[5] In Croatia, CV diseases are the main cause of death. In 2020, they were the cause of death in 40% of cases; a total of 22,817 subjects died – 13,106 women and 9711 men.[6]

Renal Denervation

Procedure

RDN is an endovascular transcatheter method of treating AH with the aim of reducing excessive activity of the renal and systemic sympathetic systems. This is achieved by interrupting (damaging) the nerve endings of the sympathetic system in the adventitia of the renal arteries. The only RDN method currently used in Croatia is based on the use of radiofrequency ablation with an electrode located on the top or end of the catheter. It is described in more details in Supplementary Para Figure 1.

Studies and Meta-Analyses

Effect on Office BP and ABPM

In recent years, the results of studies which showed that RDN is effective and safe in humans were discussed in detail, thus in this paper we are not going to repeat all advantages and drawbacks but focus on recent studies which changed the position of RDN in new 2023 ESH guidelines.[2] Aware of the shortcomings of the Symplicity HTN-3 study, which did not demonstrate a significant effect of RDN on lowering BP, Bhatt et al recommended that the second generation of randomized clinical studies should analyze the influence on BP values measured by ABPM.[7] New studies had a similar design as Symplicity HTN-3 study, ie, one part of the patients underwent renal denervation, and one a placebo, ie sham denervation.[8] In studies which used methods of radiofrequency (Spyral catheter) and ultrasound (Paradise system), results showed good tolerability and efficacy.[9–14] In the second generation of studies, in the groups that underwent the sham procedure, small changes were observed in BP values measured in the office and ABPM values from the baseline mean values of −2.3 to - 4.0 mmHg and 0.5 to –3.1 mmHg, respectively.[9–14] These results contrasted with the results of the Symplicity HTN 3 study, in which lower values of systolic BP measured in the office of 11.7 mmHg were obtained in the group in which the placebo procedure was performed.[7] Compared to the group in which the placebo procedure was performed, the decrease in mean BP values in ABPM was significantly higher in the group that underwent RDN, ie, it was −4.7 to −9.0 mmHg for systolic values and −3.7 to −6.0 mmHg for diastolic values.[9–13,15] Furthermore, in the SPYRAL HTN-OFF MED study, after toxicological analysis excluded subjects who were confirmed to be non-adherent to therapy, the decrease in BP values in ABPM in the group in which RDN was performed was even greater.[9] Two studies RADIANCE-HTN TRIO and DENERHTN, showed that the effect of RDN on lowering BP was independent of adherence to or compliance with the therapeutic plan.[13,14] In the DENERHTN study, after six months of follow-up, patients in the group that underwent RDN had 6 mmHg lower daytime BP values (ABPM measurement) compared to the group that received only standard antihypertensive therapy (at least three antihypertensive drugs, including a diuretic).[14] The results of the second-generation studies showed a significant decrease in the value of nocturnal BP, which is particularly important.[16,17] In a specific post hoc analysis, it was observed that morning BP surge is smaller in the group that underwent RDN, which can be explained by the effect on reducing sympathetic activities.[18] A decrease in values was also observed in BP values measured in the office in patients who underwent RDN and ranged from −9.0 to −10.8 mmHg for systolic and about −5 mmHg for diastolic BP.[9–15] The results of a meta-analysis of seven randomized, sham-controlled studies with a total of 1368 patients, of which 782 underwent RDN, showed that in the group in which RDN was performed, there was a significant decrease in the value of the systolic BP (−3.61 mm Hg; 95% CI: −4.89 to –2.33 mm Hg; $P < 0.0001$) and diastolic BP in ABPM (−1.85 mm Hg; 95% CI: −2.78 to −0.92 mm Hg; $P < 0.0001$), but also systolic BP (−5.86 mm Hg; 95% CI: −7.77 to −3.94 mm Hg; $P < 0.0001$) and diastolic BP measured in the office (−3.63 mm Hg; 95% CI: −4.77 to −2.50; $P < 0.0001$).[19] No difference was observed between patients with and without antihypertensive drug therapy.

Effects on Target Organ Damages

A meta-analysis of 17 studies analyzed the impact of RDN on the regression of target organ damage.[19] The results showed that after the RDN, there was a regression of the left ventricular mass index (LVMI) according to echocardiography by 14.17 g/m^2 (95% CI −18.33 to −10.01, $P < 0.001$) and by 4.75 g/m^2 according to magnetic resonance imaging (95% CI −7.83 to −1.67, $P = 0.003$). RDN had a beneficial effect on reducing augmentation Index (AIx) [−7.05 (95% CI −9.12 to - 4.98, $P < 0.001$)] and pulse wave velocity (PWV) [1.54 m/s (95% CI −2.16 to −0.92, $P < 0.001$)]. The positive

effect of RDN on the regression of target organ damage was independent of basal BP values and their reduction after RDN. In a three-year interval in patients without CKD (basal eGFR > 60 mL/min/1.73m^2) the average drop in eGFR was 7.1 mL/min/1.73m^2, while in CKD patients the drop in eGFR was 3.7 mL/min/1.73 m^2. There was no difference in the decrease of systolic BP after RDN in patients with and without CKD, neither after 6 months, nor after three years of follow-up.

Long-Term Effects (Durability)

Data on performed RDN are entered in the Global SYMPLICITY Registry (GSR) with the aim of long-term follow-up of these patients (Figure 1). The registry also represents the largest prospective cohort study, which in 196 centres monitors the safety and effectiveness of the procedure itself in a real environment in patients with resistant AH. To date, more than 2860 patients treated with RDN have been registered in the registry, of which 2500 are in a three-year follow-up, and the plan is to include a total of 5000 of them. In the first 6 months of follow-up, the average drop in systolic BP after RDN in patients included in the registry measured in office or by ABPM was 12.8 mmHg and 7.2 mmHg, respectively. This drop in BP was even more pronounced in patients with resistant AH: 21.7 mmHg and 8.1 mmHg for systolic BP measured in the office and by ABPM, respectively. The antihypertensive effect of RDN on values of systolic BP measured in the office, as well as on those measured by ABPM, was maintained during the entire three-year follow-up period. Similar result was observed in the SPYRAL HTN-ON MED trial and the RADIANCE-HTN SOLO trial indicating that the BP-lowering efficacy of RDN is sustained for at least up to three years. Furthermore, there is a trend for continuous BP reduction over time. However, long-lasting effect of RDN depends on possible changes in drug therapy, adherence to lifestyle interventions particularly salt intake, ageing or development of any kind of cardiovascular or kidney morbidity.[20]

Results from the Croatian RDN Registry

We present the preliminary results of the pilot project of RDN in Croatia, 18 patients with resistant AH who were included according to our algorithm (Supplementary Figure 1) and followed-up for 6 month,[21,22] Jelaković, unpublished

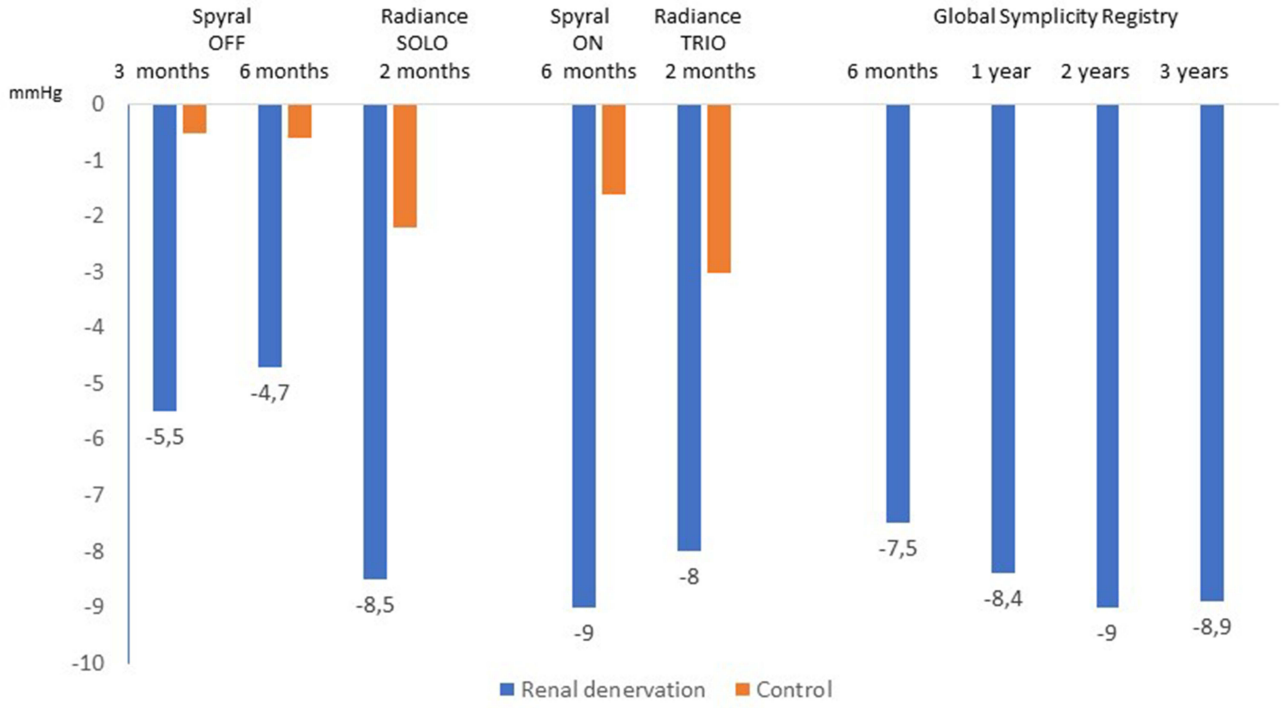

Figure 1 Systolic blood pressure (ABPM) reduction and durability - results obtained in the of sham-controlled studies using new methods and from the Global Symplicity Registry.

data). After 6 months of follow-up, the average BP values were significantly lower, measured in the office, but also by ABPM (Figure 2). At the end of the follow-up period, we observed a significantly higher number of patients who changed the unfavorable nocturnal BP pattern and became dippers. We also observed a strong effect on the morning BP surge, which was 18.2 mmHg lower on average after 6 months (Figure 3). The safety of the effect of RDN on renal function was also monitored, and Figure 4 shows that eGFR was stable during the follow-up period with the positive effect on 24-hour albuminuria.

Complications and Side Effects of Renal Denervation

In a short period of time after the procedure, small irregularities of the wall of the renal artery were observed, which could be attributed to spasm or oedema.[23–25] All those complications are very rare including renal artery iatrogenic dissection.[26] Seven (13%) patients during Symplicity HTN-2 who underwent RDN had transient intraprocedural bradycardia requiring atropine; none had any consequences. According to the data of the GSR on the influence on renal function, for patients in stage 3 of CKD (n = 124), 16 patients progressed to stage 4 of CKD after 16 months. For patients with CKD stage 4 at the beginning, 2 out of 37 patients progressed to CKD stage 5 after six months of follow-up, four patients after 12 months and 2 patients after 24 months. The six-month change in eGFR was numerically higher but did not reach statistical significance in patients with diabetes compared to those without diabetes, and no difference was observed even after 3 years. Based on the three-year data of the GSR, it can be concluded that after RDN, renal patients without CKD had a greater drop in eGFR during the first year after the intervention, the drop in eGFR was similar in patients with and without CKD after 3 years. The incidence of death, CV death (but not non-CV) and all CV and renal events was significantly higher after RDN in patients with CKD than in patients without CKD. However, the question remains whether this is part of basic CKD in situations where BP values are still high despite the lowering of BP after RDN, which represents a significant CV risk. There is no significant difference in deterioration of kidney function in patients with or without CKD.[27] According to the studies published so far, it can be concluded that RDN is a relatively safe procedure, with a rate of periprocedural complications below 5%. Local complications such as pseudoaneurysms, arteriovenous fistulas and retroperitoneal bleeding can occur at the access site of the femoral artery. These complications

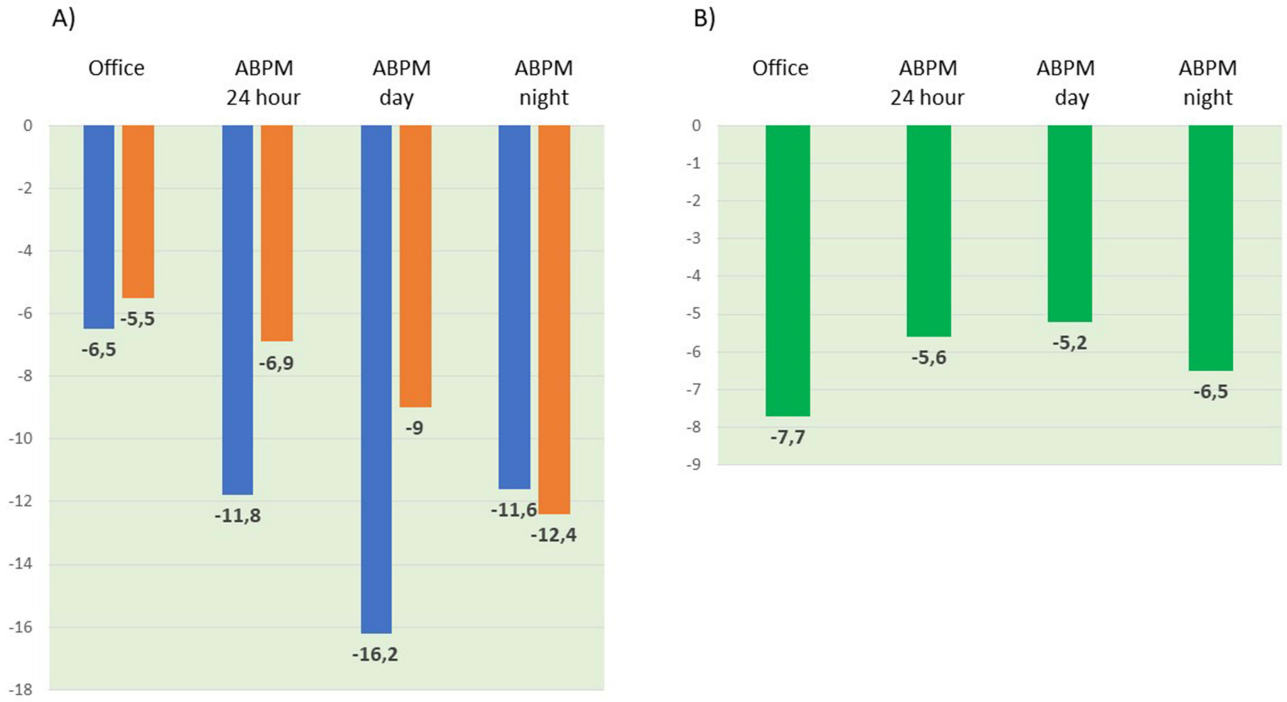

Figure 2 Effect of renal denervation on: (**A**) systolic (blue) and diastolic (red) BP, and (**B**) heart rate after 6 months of follow-up. Data from the Croatian renal denervation registry.

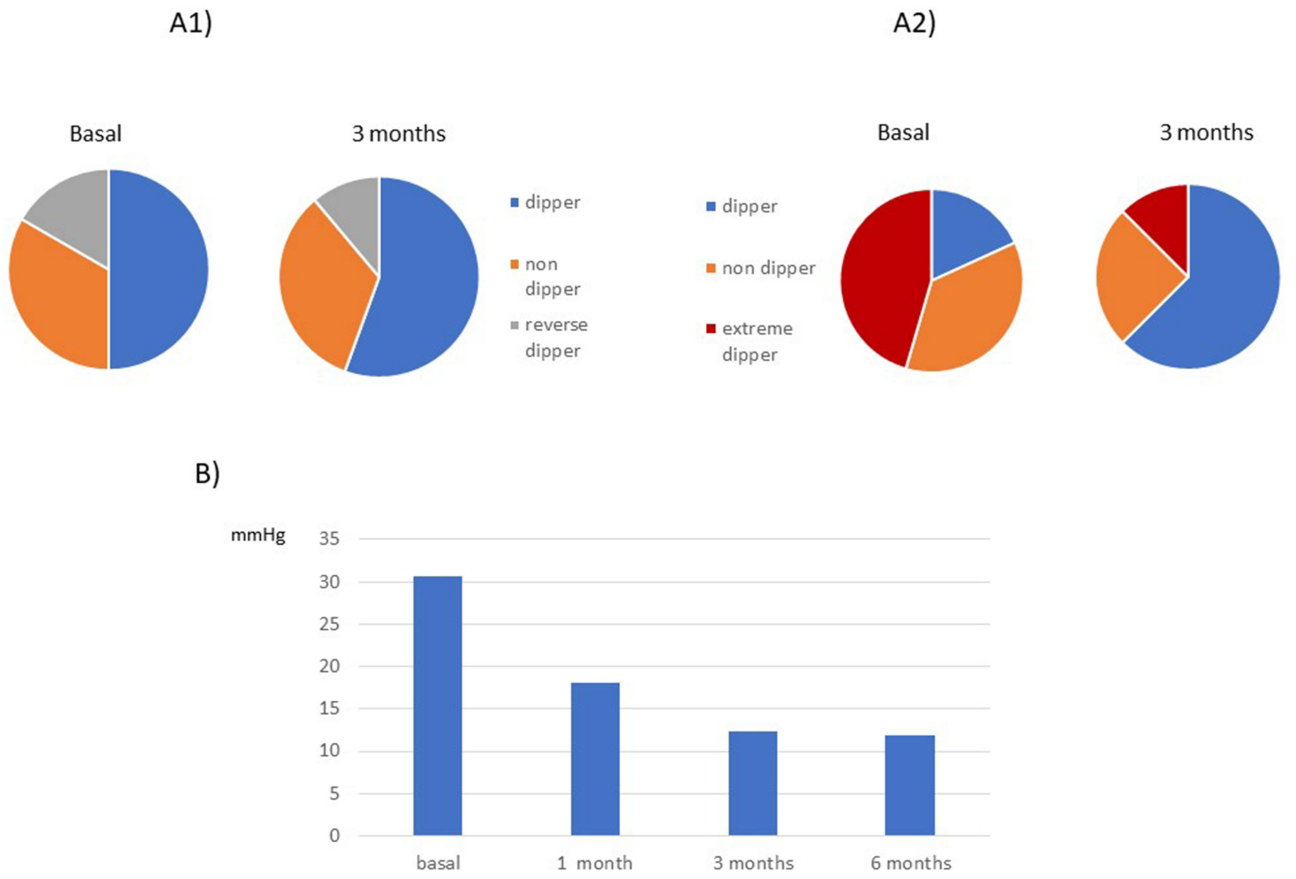

Figure 3 The effect of renal denervation on the nocturnal pattern (systolic blood pressure (**A1**) and diastolic blood pressure (**A2**) and on the morning BP surge (**B**). Data from the Croatian renal denervation registry. Definition of morning BP surge: Sleep-trough morning BP surge is the difference between the mean systolic BP over 2 hours following the awakening and the average of three BP values centered on the lowest nocturnal BP.

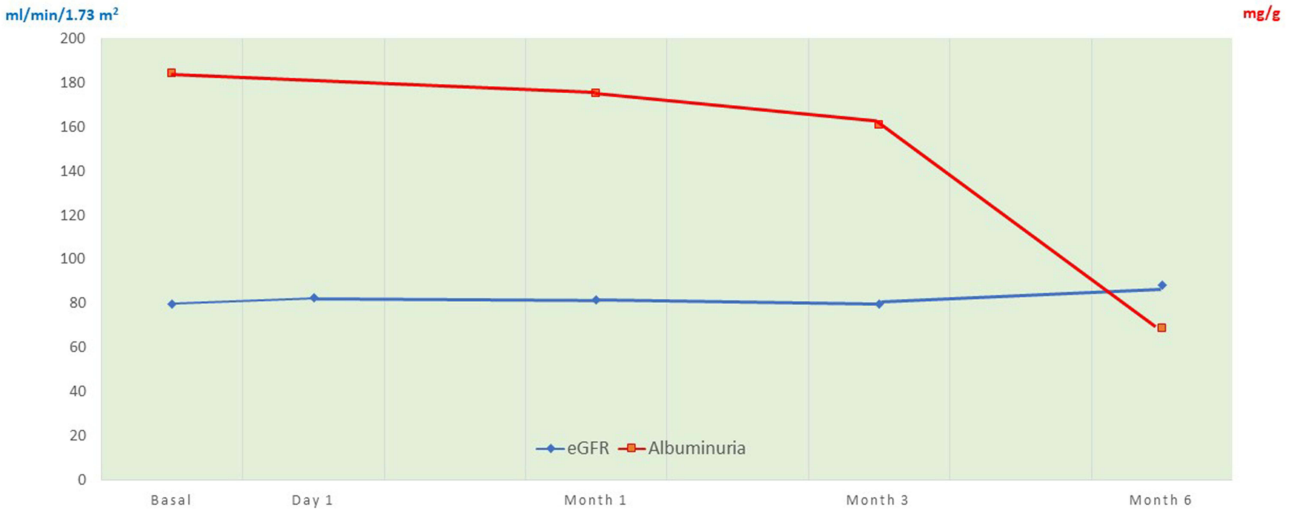

Figure 4 Changes in estimated glomerular filtration rate (eGFR) and albuminuria (24-hour urine) during the six- month follow-up. Data from the Croatian renal denervation registry.

are similar to those in CV interventions and are treated conservatively. A recent meta-analysis of 50 published RDN studies reported the safety of the procedure. Among 5769 subjects out of 10,249 followed-up on for one year, only 26 patients (0.45%) had a renal artery stenosis or dissection. The median time from the RDN procedure to all renal

interventions was 5.5 months (range: 0 to 33 months); 79% of all events occurred within one year of the procedure.[24] Three-year safety data from the largest database, the prospective, open-label GSR, also showed an extremely low incidence of periprocedural complications and adverse events (Table 1).[27]

Renal Denervation and Reinnervation

The morphology and consequences of the short-term and long-term responses of nerves to the application of radiofrequency ablation therapy have not been fully explained. Even though many patients have undergone RDN, there is currently little information on the effectiveness of RDN and the extent of reinnervation. Both afferent and efferent renal nerves are known to contribute to AH. Therefore, it is vital to know whether afferent and efferent renal nerves reinnervate the kidney after radiofrequency RDN. In test animals, many studies have shown that sympathetic efferent renal nerves reinnervate the kidney after surgical denervation. In an extensive study of renal reinnervation after surgical-chemical denervation in rats, the density of immunohistochemical staining for neuropeptide Y, tyrosine hydroxylase, substance P, and calcitonin gene-related peptide was reduced to low levels up to four days after denervation, indicating the efficacy of afferent and efferent nerve denervations, but by 9–12 weeks after denervation both afferent and efferent nerves were reinnervated.[28] An immunohistochemical study by Rousselle et al proved on an animal model that a progressive regenerative response after RDN occurs already after 7 days. The potential of regenerative activity to restore function remains unclear but is likely low given the disrupted architecture of neuromatous tangles at sites of radiofrequency lesions (neuromatous regeneration). Their observations also offer the first recognition of distal nerve atrophy occurring because of successful ablation proximally, visible after 7 and 30 days, and gradually becoming less visible thereafter.[29] Booth et al evaluated the effectiveness of RDN with the Symplicity Flex catheter and the functional and anatomical reinnervation 5.5 and 11 months after denervation in anesthetized sheep.[30] Anatomical and biochemical studies showed that in the first week after catheter-based RDN, renal levels of markers for sympathetic efferent nerves (tissue noradrenaline and immunohistochemistry for tyrosine hydroxylase) and afferent sensory nerves (gene immunohistochemistry for peptides) were significantly reduced for gene-related peptide for calcitonin, but by 11 months after denervation the levels had returned to normal, indicating reinnervation of both sensory afferent nerves and sympathetic efferent nerves.[30] Rippy et al demonstrated that renal nerve damage includes nerve fibrosis, replacement of nerve fascicles by fibrous connective tissue, and thickening of the epineurium and perineurium after 6 months of post-radiofrequency therapy. Renal arteries showed medial and adventitial fibrosis without smooth muscle hyperplasia and inflammatory infiltrates.[31] Mazor et al observed an increase in the average number of total nerves in treated arterial segments 180 days after RDN, suggesting potential plasticity of nerve growth as a compensatory effort for target organ reinnervation.[32] In human studies after kidney transplantation, varying degrees of reinnervation have been observed, probably because the

Table 1 Complications and Side Effects (%) in the Sham-Controlled Trials (Second Generation)

	Studies Spyral HTN-OFF, Spyral HTN-ON, Radiance-HTN SOLO, Radiance-HTN TRIO	**Global Symplicity Registry**
	N = 442	**N= 3000**
Hypertensive crisis/events	0.6	2.6
Stroke/TIA	0.4	3.2
CV death	0.2	2
Newly developed renal artery stenosis	0.2	0.1
Acute myocardial infarction	0.2	
Femoral access site pseudoaneurysm	0.2	
Increase in serum creatinine	0.2	1.5
End-stage-kidney disease		1.6

tissue often arose from failed transplants.[33,34] Even though there is histological evidence of partial reinnervation of human kidney transplants, which begins as early as 28 days after transplantation and ends after 1–2 years, it is proven not to be functional.[35,36] It is currently unknown whether the control of renal vasculature, renin release and sodium excretion in response to changes in renal sympathetic nerve activity is normal in the reinnervated kidney and whether there are changes in the central pathways controlling renal sympathetic nerve activity after RDN. Further preclinical experiments are needed to address these questions if we are to understand the long-term effects of RDN. Further preclinical experiments are needed to address these questions if we are to understand the long-term effects of RDN as suggested in excellent overview by Katsurada and Kairo.[37]

Pharmacoeconomic Analysis

NICE institute, (National Institute of Clinical Excellence, UK - NICE) and other agencies themselves have created models to estimate costs and quality-adjusted life years (QALYs) to establish the cost per QALY or incremental cost effectiveness ratio (incremental cost effectiveness ratio – ICER). The longer time passes, the greater the savings from renal denervation. The response rate to therapy was 93% six months after the RDN procedure, where response was defined as a decrease in BP below 10% (HTN-1). Analyzes of the NICE model showed that RDN is highly cost-effective for the treatment of resistant hypertension. Facts which should be taken into consideration in pharmacoeconomic analyses are shown in Supplementary Box 1.

Cost of Treatment

The analyzes were conducted according to the actual price of drugs, and hospitals charge to the Croatian Health Insurance. This economic model tracks key events in the patient's life cycle within a year, from the introduction of combined therapy to, ideally, maintaining the patient's stable condition. Each therapeutic option and transition state includes all statistically significant parameters that can be quantified and represent direct costs for the Croatian Health Insurance Institute. RDN in the HTN2 study showed cost effectiveness over a longer time horizon, and in this sense, its introduction brings savings to the insurer. To calculate the reference prices of drugs used in Croatian hospitals, the Basic and Supplementary list of drugs, as well as the list of medical and orthopedic aids of the Croatian Health Insurance Institute, were used.

Comorbidity Costs of Hypertension

AH is associated with a significantly increased risk of ischemic heart disease, stroke, and death, and is considered the most significant risk factor in today's world population. Some of the most informative facts are presented in Supplementary Materials.

Cost of Treatment in Croatia

Within the hospital budget, Croatian Health Insurance Institute receives invoices for treatment according to the current hospital system (DTS). The mentioned system implies that certain diagnostic and therapeutic groups are invoiced according to a predetermined amount, regardless of the price of the drugs used during the therapy. This system is adapted to the even distribution of treatment costs between therapeutic protocols that exceed the invoiced amount due to the high price of drugs and those protocols that are significantly lower than the fixed DTS group. In hospitals, the most common DTS coding of events caused by AH is depending on the main diagnosis. So, the main diagnosis is "F67B-Hypertension without CK" in the amount of EUR 597.33 regardless of the funds spent on the drugs themselves, for cerebrovascular events. Here are prices of DTS for comorbidities: B70D-Insult EUR 981.18; F66B; Atherosclerosis of coronary blood vessels without CC EUR 634,18; B69B-TIA and precerebral occlusion without severe CC EUR 741,87; F60B-Circulation disorder with acute myocardial infarction, without invasive diagnostics on the heart, without severe CC EUR 1,160.66; L60C-Kidney failure without severe CK EUR 1.232,46; L70C-Other kidney and urinary system disorders (ischemia, kidney infarction) EUR 921,35. The greatest advantage for the Croatian Health Insurance Institute that will arise from the implementation of this method is based on the reduction of complications, primarily CV and cerebrovascular incidents, which could lead to a reduction in the number of hospitalizations, outpatient care of patients, and consecutively very probably less need for additional diagnostic processing and less frequent visits to specialists.

Patient Selection for Renal Denervation

Algorithm for Setting the Indication

In contrast to the earlier indication of the ESH/ESC guideline that RDN is indicated only in patients with resistant AH, today's recommendations, ie, the indications based on the results of published randomized double-blind studies, are much broader.[2] This is also based on the knowledge that it is important to achieve not only control of BP as early as possible, but also to act on various unfavorable patterns of BP ("always on"). The wish/decision of the patient regarding the method of future treatment is emphasized and considered extremely important. There are several exclusion criteria listed in Box 1. White coat hypertension is listed first, reminding that ABPM is a key diagnostic method in the algorithm for setting the indication for RDN. Next comes pregnancy, and anatomically inadequate renal arteries. Box 2 lists secondary forms of AH in which RDN is not recommended, while in Table 2 shows secondary AH where RDN is possible if it is a resistant or very severe AH. These are obesity, CKD and OSA, conditions with increased sympathetic activity. RDN is possible in patients with primary aldosteronism if surgery is not possible, or if the patient is not prone to surgery, and BP is not controlled with a combination containing mineralocorticoid receptor antagonist. In patients with moderate or severe CKD, including patients with a transplanted kidney and/or in those hypersensitivity to iodine contrast agents CO_2 angiography with or without applied iodine contrast is recommended (Supplementary Para Figure 2). Table 3 presents mandatory and additional tests that should be done before RDN. It is necessary to use validated and recommended devices for ABPM, central aortic pressure and PWV. Additional tests should be done if the centre has such devices and if the physicians are trained to perform these tests precisely and accurately. These are tests that further increase the quality of the examination, contribute to a more precise assessment of the overall CV risk, and are useful for data collection and research. Table 2 presents groups of patients in whom RDN could be considered according to the Consensus of the Croatian Hypertension League. The decision on the method of treatment must be made together with the patient. Patients in group 1 have the same, ie, old indications that were valid before the Symplicity 3 study. New indication is a permanently poor adherence. This is an important

Box 1 Exclusion Criteria for Renal Denervation

Exclusion Criteria
1. White coat hypertension
2. Secondary hypertensions – renovascular atherosclerotic hypertension – primary aldosteronism – hyperthyroidism – hypothyroidism – pheochromocytoma – Morbus Cushing – coarctation of the aorta
3. Pregnancy
4. Anatomically inadequate renal arteries

Box 2 Secondary Hypertension Where Renal Denervation Could Be Considered

Secondary Hypertension where RDN is Possible
1. Obesity
2 Chronic kidney disease* (including haemodialysis patients and kidney transplant patients with resistant AH)
3. Obstructive sleep apnea syndrome (OSA)
4. Primary aldosteronism**

Notes: *RDN to be done with CO_2, or exceptionally with low doses of contrast and then taking care to prevent contrast-induced nephropathy. **In patients in whom surgery is not possible or who is not prone to surgery.

Table 2 Groups of Patients in Whom Renal Denervation Could Be Considered by the Consensus of the Croatian Hypertension League

Group 1 Resistant Hypertension Treated with ACE-i-ARB/CCB/tD in the Optimal dose	Group 2 Uncontrolled Hypertension Treated With ≥ 2 Medicines In The Optimal Dose	Group 3 Special Groups of Patients
Side effects/intolerance of MRA	Side effects to antihypertensive drugs	Chronic kidney disease
Permanently poor adherence (despite education)	Permanently poor adherence (despite education)	Obstructive sleep apnea sy.
Uncontrolled AH	Uncontrolled AH	Atrial fibrillation
	Masked uncontrolled AH	Heart failure
	Non-dipping/rising pattern	Isolated systolic AH (elderly)
	Morning SBP surge (> 50 mmHg)	
	Heart rate (24h) > 74/min	
High/very high CV risk	High/very high CV risk	High/very high CV risk
	HFpEF	
Shared decision making with the patient	Shared decision making with the patient	Shared decision making with the patient

Abbreviations: MRA, mineralocorticoid receptor antagonists; AH, arterial hypertension; SBP, systolic blood pressure; CV, cardiovascular; HFpEF, heart failure with preserve ejection function.

Table 3 Diagnostic Tests Before Renal Denervation

Mandatory Tests Before RDN
Blood group Rh factor
Red blood count
Coagulogram
eGFR
Serum potassium
Plasma renin activity, aldosterone
NT pro BNP
24h urine: sodium, potassium, albumin, creatinine
ABPM*
ECG
Office PWV (Sphygmocor)
Office central aortic pressure*
Additional tests before RDN
ABPM – central aortic pressure and central PWV
CAVI - determination of arterial stiffness independent of BP
ANX - determining the activity of the vegetative nervous system

Note: *Validated devices.
Abbreviations: RDN, renal denervation; eGFR, estimated glomerular filtration rate; ABPM, ambulatory blood pressure monitoring, PWV, pulse wave velocity; CAVI, cardio-ankle vascular index; ANX, sympathetic /parasympathetic activity): The ANSAR ANX 3.0 system.

change compared to earlier attitudes when the patient was required to be cooperative. This shift reflects a different approach and acceptance of the fact that non-adherent patients may also have a very high CV risk. Group 2 is a novelty compared to the earlier recommendations and reflects new evidence from clinical studies which showed that certain patterns of 24-hour BP and increased variability independently increase CV risk, and that RDN has a favorable effect on all components of BP. Patients with HFpEF have additional hardening of the target organs and a higher risk of heart failure progression, and are a group of patients in whom, if BP is not regulated, it is justified to consider RDN. Group 3 includes patients with increased sympathetic activity who can also be discussed as candidates for RDN, especially if there is an associated disease or other damage to the target organs. This group also includes patients with isolated systolic AH. The earlier view was that elderly patients with isolated systolic AH were not candidates for RDN. However, data from the GSR showed that even in this group of patients, there is a significant and permanent lowering of BP. Young patients with isolated systolic AH, in whom the mechanism of AH is completely different, can potentially be candidates, especially if they have elevated central aortic pressure, have tachycardia and/or signs of target organ damage or some other morbidity or metabolic disorder.

Figure 5 shows the diagnostic algorithm. Several elements should be highlighted. CV risk should be assessed using the Systematic Coronary Risk Estimation 2 (SCORE2) and Systematic Coronary Risk Estimation 2-Older Persons (SCORE2-OP) risk algorithms for fatal and non-fatal (myocardial infarction, stroke) CV disease.[35] Apart from the recommendation that mineralocorticoid receptor antagonists must be introduced to patients with resistant AH before considering RDN, if necessary, the introduction of amiloride should also be considered. This is based on the evidence of the PATHWAY-2 study where its effectiveness has been proven.[38] As in all patients with AH, it is also important to continue recommending salt reduction.[2] In our algorithm, a visit to psychologist is important. It helps not only to increase persistence, but also helps the patient to make their own decision for the method of treatment.

Patient Preference

Patients preference should be considered and shared decision about RDN or conservative therapy should be made in every patient. In Japanese study, preference for RDN was expressed by (31.6%).[39] Significant predictors of preference for RDN were younger patient age, male sex, higher home or office systolic BP, poor antihypertensive drug adherence, the

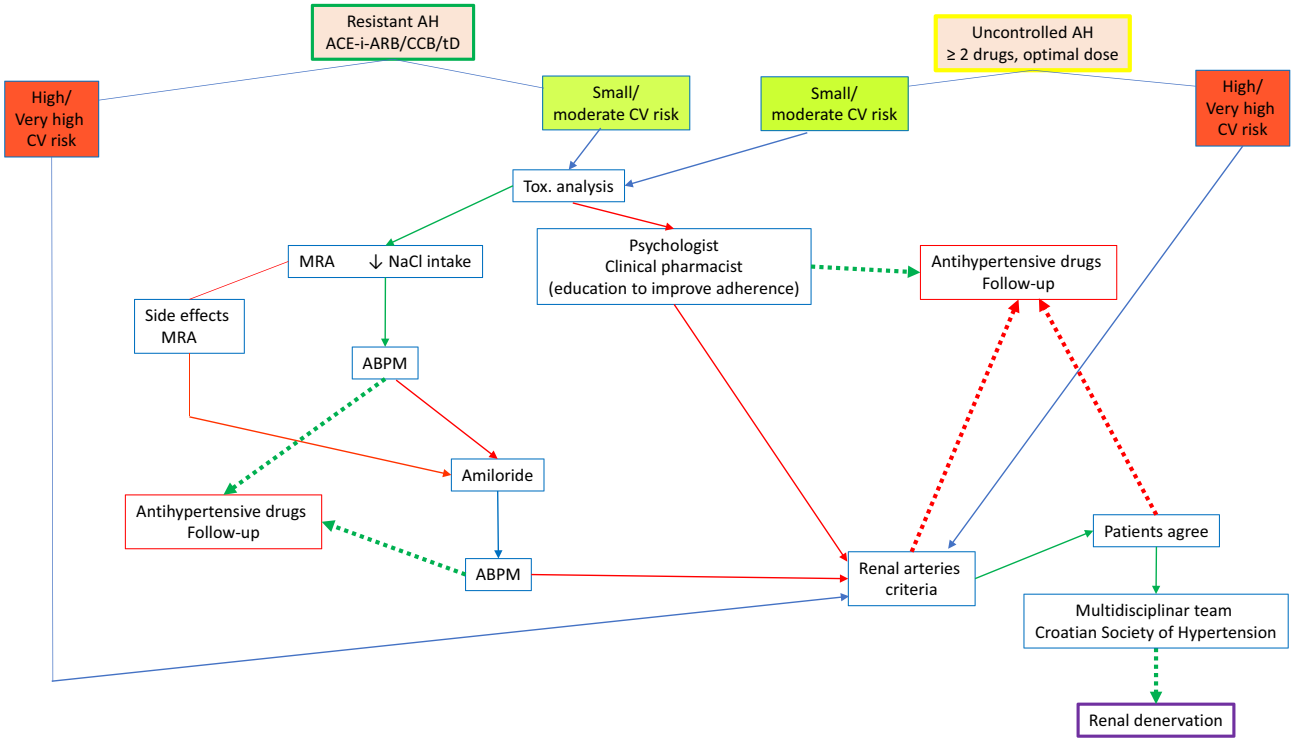

Figure 5 Diagnostic and therapeutic algorithm for setting the indication for renal denervation according the consensus of the Croatian Hypertension League.

presence of heart failure, and the presence of side effects during treatment with antihypertensive drugs.[39] In study conducted in Germany, if not already on medication, 38.2% of patients would prefer RDN, and of those already on drug therapy 28.2% would opt for RDN. Patients who were pro-RDN were younger and more often men.[40] These patients have high expectation of the extent of BP decrease with RDN.

Patient Follow-Up Protocol After Renal Denervation

Measurements and procedures which are recommended before and in the follow-up period after the RDN are presented in Table 4.

Special Populations

Obstructive Sleep Apnoea

Obstructive sleep apnea (OSA) affects 3–7% of the adult population and is associated with an increased risk for CV events.[41] OSA is an independent risk factor for resistant AH, with a prevalence of 65–90%. So far, small observational

Table 4 Tests That Need to Be Done During Patient Follow-Up After Renal Denervation

	−1 Day	+1 Day	+1 Month	+3 Months	+6 Months	+12 Months	+18 Months	+24 Months
Office blood pressure and heart rate (sitting)	+	+	+	+	+	+	+	+
Office blood pressure and heart rate (standing)	+	+	+	+	+	+	+	+
Checking cooperation -medical history	+	+	+	+	+	+	+	+
Checking cooperation -Toxicol. Lab	+		+	+	+	+	+	+
Blood group Rh factor	+							
Red blood cell count	+					+		+
Coagulogram	+							
Serum creatinine (eGFR)	+		+	+	+	+		+
Plasma renin activity, Aldosterone	+					+		+
NT proBNP	+			+	+	+		+
Fasting blood glucose, insulin, HbA1C	+			+		+		+
Uric acid, lipids	+			+		+		+
24h urine: Na, K, albumin, creatinine	+		+		+	+	+	+
ABPM	+	+	+	+	+	+	+	+
ECG	+				+	+		+
PWV	+	+		+	+	+		+
CAP	+	+		+	+	+		+
CAVI	+	+		+	+	+		+
ANX	+	+	+	+	+	+		+
Color Doppler renal arteries					+			+
MRI / CO_2 angiography						+		

Abbreviations: eGFR, estimated glomerular filtration rate; ABPM, ambulatory blood pressure monitoring, PWV, pulse wave velocity; CAP, central aortic pressure; CAVI, cardio-ankle vascular index; ANX, sympathetic/ parasympathetic activity): The ANSAR ANX 3.0 system; MRI, magnetic resonance imaging.

studies have been published that proved that RDN can reduce the severity of OSA syndrome. Symplicity HTN-1, HTN-2, HTN-3 are the most relevant studies regarding the use of RDN therapy. Initial studies showed a significant lowering of BP in patients with resistant AH over a period of three years and an improvement in the severity of the OSA syndrome in patients with resistant AH.[42] In a pooled analysis, RDN was associated with a significant reduction in mean AHI (weighted mean difference −9.61 (95% CI −15.43 to –3.79, P = 0.001)) six months after RDN. One study also reported improvement in oxygen desaturation index and Epworth sleepiness scale scores six months after RDN (97/40). The Symplicity HTN-2 study included 106 patients with resistant AH who were randomly assigned to the RDN-treated group or to the control group. The differences in BP between the groups after six months were 33/11 mm Hg (P < 0.0001), which is the result of a significant lowering of BP in the group treated with RDN (−32/12 mm Hg; P < 0.0001) and without BP changes in the control group. It is important to note that 33% of respondents had diabetes, and 22% of patients had coronary disease. A beneficial effect of RDN on glycaemic control has also been observed.[43] The aforementioned studies showed that RDN can lower BP and improve glycaemic control in patients with resistant AH suffering from sleep-disordered breathing. The above can be understood from the trend of improving the severity of sleep apnoea in patients who underwent RDN. We can conclude that RDN is a potentially useful therapeutic option for patients with resistant AH and severe OSA, especially in those with metabolic dysregulation. More precise randomized controlled clinical trials are needed to confirm these initial data.[43]

Chronic Kidney Disease

AH is often difficult to control with drugs in patients with CKD and the prevalence of resistant AH in these patients is higher than in the general population ranging from 40.4% to 51%.[44] However, the prevalence of true resistant AH in patients with CKD is probably lower, considering the method of measuring BP, as well as the often-present white coat hypertension and low drug adherence in this population. Resistant AH is associated with a significant increase in adverse CV and renal events in the general population and even more so in patients with CKD.[44] Excessive activity of the sympathetic nervous system plays an important role in the pathogenesis of AH in patients with CKD. It is known that efferent renal nerves participate in the regulation of renin secretion, tubular reabsorption of sodium by the kidney and renal hemodynamic.[45] In addition, renal renalase activity and catecholamine clearance are reduced in CKD, with consequent increased exposure of the kidneys to catecholamines.[46] In addition, reduced parasympathetic regulation of sinus node activity and increased sympathetic activity are the cause of autonomic CV dysfunction already in the earliest stages of CKD.[47] There is more and more evidence suggesting that sympathetic overactivity is important in the development and progression of CKD, in the development of AH, and in CV morbidity and death in this population.[48–51]

Renal Denervation in CKD Patients

There is a large concern regarding the safety and efficacy of RDN in patients with eGFR < 45 mL/min/1.73m^2 due to the lack of randomized clinical trials in this group of patients. Nevertheless, preliminary results from small uncontrolled studies have shown that RDN is effective in lowering BP in CKD patients, and there is data that it may even slow the deterioration of renal function regardless of the effect on the BP.[52–55] According to data from the GSR on the effectiveness and safety of RDN in hypertensive patients without and with CKD, this method proved to be effective in lowering BP measured in the office and 24-hour ABPM (systolic BP measured in the office by 11.7 mmHg, 24-hour systolic BP by 9.2 mmHg after 3 years for CKD). This effect is more pronounced in patients without CKD than in those with CKD, although global control of AH was not achieved in most treated patients after three years. Even though patients without CKD had a greater decrease in eGFR during the first year after RDN, there was no significant difference in the decline of eGFR between the two groups after three years of follow-up.[56] The 3-year incidence of CV death (not non-CV) and all CV and renal events was significantly higher after RDN in patients with CKD than in those without CKD, while the incidence of renal artery reintervention due to perforation or dissection and vascular complications was low in both groups without a significant difference in frequency between the studied groups.[57] However, due to the design of the registry and the absence of a sham control group (placebo), it is not possible to assess whether RDN reduces the frequency of CV events in patients with CKD through BP-dependent and BP-independent mechanisms. In

Italian study on the effectiveness and safety of RDN for uncontrolled drug-treated resistant hypertension in a high-risk population with CKD, which included patients with eGFR < 45 mL/min/1.73 m^2 none of the 40 patients had significant complications, nor were there any differences in procedural characteristics.[58] No significant difference in safety and efficacy between the two different types of catheters (unipolar vs tetrapolar) was recorded, which is in accordance with the data from the GSR. In addition, a significant and sustained reduction in 24-hour systolic BP by 9.7 mmHg, 8.4 mmHg and 11.3 mmHg were observed at 3, 6 and 12 months, respectively, after RDN, as well as a significant reduction in systolic BP measured in the office by 13.9 mmHg and 19.7 mmHg after 6 and 12 months of follow-up, respectively. Moreover, the initial heart rate was higher in this group (70.07 ± 11.11 vs 63.3 ± 7.01; p = 0.034) with a significantly lower prevalence of isolated systolic AH (48.3 vs 90%; p = 0.028) and lower E/E' ratio (14.43 ± 3.55 vs 10.54 ± 2.5, p = 0.029). Univariate analysis found that higher 24-hour systolic BP and systolic-diastolic AH are predictors of response to RDN, which is consistent with previous studies.[59] Important new observation is evidence that a lower E/E' ratio was also a predictor of agreement on RDN. Several smaller studies have analyzed whether RDN has a nephroprotective effect. Ott et al showed that albuminuria decreases after RDN in patients with RH and an elevated ratio of albumin to creatinine in the urine.[60] The same group of authors, comparing the annual decline of eGFR three years before RDN and one year after the intervention in 27 uncontrolled treated hypertensive patients with eGFR of 30–59 mL/min/1.73 m2, showed that after the procedure, except for a significant reduction of BP, there was a stabilization of eGFR.[53] Kiuchi et al found similar effects of RDN in 30 patients with mild to moderate CKD and RH.[61] In all months of follow-up after the intervention, there was an increase in eGFR, which remained significant until the end of follow-up at 24 months. Furthermore, Hering et al observed stabilization of eGFR up to 24 months after RDN in 46 patients with stage 3 CKD. Changes in eGFR were not associated with changes in BP, so it seems that the potential nephroprotective effect of RDN occurred regardless of the concomitant decrease in BP.[57] Even though some preliminary results were promising about the beneficial effect of RDN on slowing the progression of renal disease based on the results of a meta-analysis of more than 50 RDN studies that included all types of patients with resistant AH, it was concluded that renal function expressed as a change in eGFR does not change significantly up to 9 months after the intervention.[62] Conversely, in non-randomized studies in which renal function (GFR) was directly measured (mGFR) and not estimated (eGFR), impairment of renal function was observed even 1–2 years after RDN.[56] Therefore, more long-term data with mGFR are needed to conclude on the renal safety of RDN in this population like currently ongoing RDN-CKD Study

Which aimed to demonstrate that RDN effectively reduces 24-h ambulatory BP in 80 patients with CKD stage 3A or 3B.[63]

Renal Denervation in Patients Undergoing Dialysis

Patients in the end stage of CKD (ESKD) on hemodialysis (HD) or on peritoneal dialysis (PD) are a group of patients with a very high prevalence of AH, as much as >80%, of which only 30% are well controlled by a drug therapy.[64,65] It is known that the density of nerves in the inner area of the periadventitial tissue is increased in patients on dialysis and that, regardless of dialysis, hypertensive patients with signs of severe arteriolar damage have a greater number of nerve endings in the adventitia, which may point to the existence of a morphological basis for increased sympathetic activity in these patients and the potential effectiveness of RDN.[66] There is very little data on the effects of RDN on BP reduction in ESKD patients undergoing dialysis for the replacement of their renal function. In one of the first studies on the safety and efficacy of catheter bilateral RDN in dialysis patients from 2013, Schlaich et al showed an effective lowering of BP in 12 patients (average time on dialysis 3.6 ±2.6 years).[67] Compared to the baseline values, systolic BP measured in the office was significantly reduced 3, 6, and 12 months after RDN (by 18 mmHg, 16 mmHg, and 28 mmHg, respectively), while there was no change in BP in three untreated patients for whom intervention was not possible due to atrophic renal arteries, which indicates that atrophic arteries are a limiting factor for the use of RDN in uncontrolled treated hypertensive patients with RH on dialysis. In a prospective pilot study on 6 patients on HD, Ott et al have confirmed that RDN in ESKD patients is associated with a significant lowering of 24-hour systolic and diastolic BP (20 mmHg and 15 mmHg, respectively) 6 months after the procedure without periprocedural complications. In addition, no significant change in hematocrit and ultrafiltration was observed during follow-up, indicating that there was no significant change in volume status and thus the additional effect stated for BP.[68] In the largest to date prospective, randomized study in HD patients, Scalise et al recently reported the effectiveness of catheter-based RDN compared to a drug therapy in 24 patients

with resistant AH to an average of 5.4 antihypertensive drugs, who had been on dialysis for about 6 years. Compared to the group receiving drugs, the RDN group (n = 12) had significant better effect on lowering of office systolic BP 1, 6 and 12 months after RDN, and diastolic BP measured in the office and 24-hour systolic and diastolic BP 6 and 12 months after RDN. There were no changes in the heart rate measured in office and the 24-hour heart rate. No significant periprocedural complications were observed, nor were there any changes in the average number of antihypertensive drugs during follow-up.[69] This study strengthens the evidence for the long-term antihypertensive efficacy of RDN in hemodialysis patients in whom multi-pharmacotherapy fails to control the BP. In addition, this study showed a greater lowering of BP compared to that achieved in previous studies, which the authors explain partly by greater sympathetic activity due to the stage and duration of CKD, but also by the improvement of the method, ie the delivery of a greater number of ablations both on the main and on the more distal segmental branches of the renal arteries, which is in accordance with earlier experimental studies in which a higher efficiency of combined denervation of the main and more distal branches was observed compared to increasing the number of ablations only on the main renal arteries.[70,71]

Renal Denervation in Patients with a Transplanted Kidney

About 70–90% of kidney transplanted patients have AH.[72,73] Sympathetic overactivity resulting from native non-functioning kidneys is an important mechanism of resistant AH in patients after kidney transplantation. Renal and systemic sympathetic hyperactivity contribute to the pathophysiology of the resistant AH. Even though there is histological evidence of partial reinnervation of human kidney transplants, which begins as early as 28 days after transplantation and ends after 1–2 years, it is proven not to be functional.[33–36,36,37] In addition to other factors present in patients with CKD, immunosuppressive therapy with calcineurin inhibitors contributes to vasoconstriction and can increase the activation of the afferent renal sympathetic nervous system in kidney transplant patients.[74,75] Complete RDN can be achieved by bilateral nephrectomy of the native kidneys, which was confirmed in a retrospective study of 32 kidney transplanted patients in whom pre-transplantation bilateral nephrectomy of the native kidneys was performed, after which there was a decrease in systolic BP, number of antihypertensive drugs in therapy, left ventricular mass index and volume of the left atrium, but contrary to expectations, also the worsening of diastolic dysfunction compared to the control group.[76] Even though this method contributes to improving the control of AH, it can be accompanied by various surgical complications, which is why it should be the method of choice for a strictly selected group of patients. There are several reports of improved BP control after catheter based RDN of renal arteries of native non-functioning kidneys in transplant patients with RH and up to 6 months after RDN.[77,78] The case of a patient with refractory AH and transplanted heart and kidney on 6 high-dose antihypertensives was also described.[79] Catheter bilateral RDN of the renal arteries of native kidneys was performed with significantly better control of BP and regression of hypertrophy of the transplanted heart with stable function of the kidney graft one year after RDN.[79] Pietilä-Effati et al described a series of cases on the various effectiveness of RDN in the control of BP in dialysis patients (n = 2 PD and n = 2 HD) with resistant AH and various comorbidities in which a kidney transplantation was performed 6 to 24 months after RDN.[80] There is only one prospective, randomized, clinical single-centre study on 18 transplanted patients with resistant AH lasting 6 months, which studied the feasibility and effectiveness of RDN catheter on the renal arteries of native kidneys in relation to drug therapy.[81] The group of kidney transplant patients who underwent RDN on the renal arteries of the native kidneys had a significant decrease in systolic BP measured in the office and a higher proportion of convertors from reverse dippers and non-dippers to dippers. Even though there was no decrease in 24-hour BP after 6 months (which is consistent with the large randomized Symplicity HTN-3 study), there was a trend of a decrease of nocturnal (not daytime) BP in the RDN group, even though it did not reach statistical significance. There was no difference in the outcomes related to the safety of the method, kidney graft function or renovascular complications between the two groups. Even though statistically insignificant, a decrease in proteinuria and an improvement in spontaneous baroreflex sensitivity were observed as an indirect indicator of a decrease in sympathetic tone.[8,81] Despite encouraging results on the safety of RDN in individual patient reports, one series of patient reports, and the previously described prospective, randomized study on a small number of transplant patients, with a questionable BP-lowering effect, larger, multicentre, randomized, clinical studies are needed (with a sham control group) on the effectiveness and safety of this method in this specific population.

Atrial Fibrillation, Heart Failure and Renal Denervation

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, which had a worldwide prevalence of 0.51% in 2017, which is an increase of 33% from about twenty years ago.[82–84] AH contributes to the onset of AF, and can also affect the duration of AF and be the cause of its recurrence.[84] It has been shown that patients with AH and AF have increased morbidity and death.[83,84] Considering the overlapping mechanism in the occurrence of AF and AH, the idea was put forward that RDN, acting on the autonomic nervous system and reducing sympathetic function, could have a positive effect on reducing the occurrence of AF.[85] It has been clearly proven that the reduction of systolic BP reduces the possibility of repeated episodes of AF, and in 2012, Pokushalov et al conducted a randomized study in patients with refractory, symptomatic AF and resistant AH, in whom pulmonary vein isolation (PVI) was performed on 14 patients, while on 13 patients, in addition to PVI, RDN was also performed.[86,87] The results showed a statistically significant decrease in systolic and diastolic BP in patients who underwent PVI with RDN, while there was no statistical significance for those who had only PVI. In addition, in 69% of patients in whom RDN was performed along with PVI, there were no recurrences of AF episodes during the one-year follow-up period, in contrast to 29% of patients with only PVI performed.[87] In 2022, Nawar et al published a large meta-analysis looking at the effects of RDN in patients with AH treated with PVI. The primary outcome was the frequency of recurrent AF episodes, which were defined as the occurrence of an atrial tachyarrhythmia lasting more than 30 seconds during the follow-up period. In addition to the above, the effect of RDN on BP and eGFR was monitored, as well as the relationship between the safety and effectiveness of RDN. Seven studies with a total of 711 patients were analyzed, of which 329 were in the group in which PVI was performed with RDN, and 382 in the group with only PVI. Among them, 623 patients had paroxysmal AF, and 88 had persistent AF. According to these results, patients treated with both RDN and PVI had fewer AF recurrences compared to those treated with PVI (31.3% vs 52.9%, $p < 0.00001$). Systolic BP values were also statistically lower in patients with RDN and PVI, while there was no significant difference in diastolic BP between the two groups. In the six-month period, eGFR was significantly higher in patients treated with a combination of PVI and RDN. Complications occurred in 6.32% and 11.8% of patients treated with RDN + PVI and in patients treated only with PVI, respectively.[88] What is important to note is that it seems that the effect of RDN on the recurrence of AF episodes is not the same in all categories of AH, and it has been shown that the highest effectiveness, as well as the highest reduction of BP, is most pronounced in resistant AH.[89] Likewise, the effect of RDN on AF appears to be independent of BP.[90]

Another potential role for RDN is with regards to ***heart failure (HF)***. In HF, there is overactivity of the sympathetic system, which leads to an increase in peripheral vascular resistance with a consequent decrease in cardiac output, which results in organ hypoperfusion.[91] In addition, the increase in peripheral vascular resistance favors the occurrence of myocardial hypertrophy, fibrosis, and thus the occurrence of arrhythmias.[91] According to previous research, it has been shown that RDN inhibits the activity of neprilysin in the kidney and reduces the activity of the renin-angiotensin system.[92] The REACH pilot study studied the impact of RDN in 7 patients with chronic systolic HF and found that RDN improved HF symptoms and functional capacity measured by the 6-minute walk test.[93] Brandt et al included in their study 46 patients who underwent RDN, and the impact on left ventricular hypertrophy and on systolic and diastolic function was observed in patients who also had resistant AH. According to that research, RDN, in addition to its known effect on BP, led to a significant reduction in left ventricular mass, and at the same time improved diastolic function.[94] Also, it has been shown that RDN in patients with HF and preserved systolic function (HFpEF) improves circumferential strain measured by magnetic resonance of the heart, which is considered a surrogate indicator of diastolic function. Kresoja et al found that in patients with HFpEF reduced systolic and diastolic LV stiffness were partly normalized, concluding that RDN might be a potential therapeutic strategy for AH and HFpEF.[95] In conclusion, RDN appears to be a promising option for the treatment of AF as well as HF, considering the common mechanisms of AF and AH occurrence, especially an imbalance in the sympathetic nervous system. The promising results of previous reports support this assumption. However, to include it in the AF and HF treatment algorithm, it would be necessary to prove the same in a larger randomized study. This was also concluded by authors of the systemic review and meta-analysis on effect of RDN in patients with HFrEF who found that RDN can increase LVEF and walking distance.[96]

Criteria Required by an Individual Centre for Approval of Renal Denervation

Personnel and Procedure

Renal denervation can only be done in centres where different diagnosis of AH and treatment of severe forms of AH are possible. These centres must obtain a certificate from the Croatian Hypertension League. In these centres, independent of the RDN, regular interventions on blood vessels (>25 per year) must be carried out. Each centre must employ at least two physicians (interventional cardiologists or interventional radiologists) who have performed at least 10 RDNs with a proctor or with an experienced physician. At least 10 candidates for RDN from future centre must be presented on the monthly meetings of the RDN team in the ESH Excellence centre. Once the centre is approved, at least 15 RDNs must be performed annually at each centre. All those patients also should be presented and discussed at the monthly meetings of the multidisciplinary team of the ESH Excellence centre. In addition to nephrologists and cardiologists specializing in AH, a physician specializing in intensive care medicine, a vascular surgeon, an interventional radiologist, and a nephrologist in charge of hemodialysis must be available 24/7 in each centre.

Spatial Condition

In every centre there must be a stationary part and a radiology laboratory where angiographic procedures are possible 24/7. It is recommended that the centre has a dialysis department, and if there is none, then the collaborating centre that has dialysis must be within reach in less than 60 minutes. The centre must have a vascular surgery department and an intensive care unit.

Patient Selection

The criteria for selecting a candidate for RDN is specified before. Every patient who is a candidate for RDN must be presented and discussed at a monthly interdisciplinary meeting in cooperation with the ESH Excellence Centre for Hypertension and the Referral Centre for Arterial Hypertension of the Ministry of Health of the Republic of Croatia. Meetings can be held in a hybrid format.

Diagnostic Options

Each centre must be able to carry out diagnostic procedures to rule out secondary forms of AH, and the necessary diagnostic procedures specified before. If the centre does not have all diagnostic procedures to exclude all secondary forms of AH, then the patient is referred for additional diagnostic procedures to the Referral Centre for Arterial Hypertension of the Ministry of Health of the Republic of Croatia. In addition, the centre must be able to perform a CO_2 angiography. If it does not have this diagnostic method, it refers the patient with CKD or who is hypersensitive to iodine contrast agent to the RDN in the Referral Centre.

Therapeutic Options

In every centre, it is necessary to be able to treat severe resistant AH, as well as all secondary forms of AH. If the centre does not have the option of etiological treatment of certain forms of secondary AH (e g adrenalectomy, OSA…), then it refers the patient to the Referral Centre.

Patient Follow-Up After Renal Denervation

Each centre must ensure patient follow-up for one month after RDN, and then for 3, 6 and 12 months. After that, it is necessary to follow-up on the patient every 6–12 months. The follow-up protocol is specified before. Every patient who underwent RDN will sign informed consent and if agree his/her data will be entered into the Croatian registry of renal denervation, which is managed by the Croatian League for Hypertension. Patients who refused to be included into the registry will be followed in the same way as patients who will agree to be part of the registry.

Table 5 Areas of Scientific and Research Work in Renal Denervation in Croatia

1. Predictors of a Positive Response	2. Effects Beyond BP Lowering	3. Special Groups of Patients
– arterial stiffness (PWV measured in the office and 24h PWV, CAVI) – central aortic pressure (measured in the office and 24h CAP) – heart rate (measured in the office and using ABPM) – kidney function (eGFR) – salt intake (24-hour urine sodium excretion) –sympathetic/parasympathetic activity	– variability and circadian rhythm of BP – CAP –arterial stiffness (office, 24h PWV, CAVI) – sympathetic activity – kidney function (eGFR) – albuminuria (24.-hour urine) –metabolic effects (glycemia, insulin resistance, dyslipidemia, uric acid…)	– patients on a chronic dialysis program – kidney transplant patients – heart failure – atrial fibrillation – OSA – isolated systolic hypertension (in elderly and in youth) – patients with diabetes and a very high CV risk

Abbreviations: eGFR, estimated glomerular filtration rate; ABPM, ambulatory blood pressure monitoring, PWV, pulse wave velocity; CAP, central aortic pressure; CAVI, cardio-ankle vascular index; OSA, obstructive sleep apnea syndrome.

Prospective Research on Renal Denervation in Croatia and the Croatian Registry for Renal Denervation

The main scientific research interest in the entire professional community, including in Croatia, is to determine the predictors of a positive response after RDN. The next goal is to prove the effect of RDN on top of the effects on BP. The third objective is to analyze the effect of RDN in special patient populations. The next area of interest is to organize an educational platform that could become a model for other countries. The objectives of the scientific research work are shown in Table 5.

Croatian Registry of Patients Who Had Undergone Renal Denervation

All patients who have undergone RDN in the past period and all patients who will undergo RDN and who signed informed consent and agree that her/his data could be used will be entered into the Croatian Registry of RDN. The registry is in electronic form and data will be entered into it before the intervention and during follow-up. The registry will be prepared in such a way that the data can be automatically transferred to the GSR. The managers of the registry will prepare semi-annual reports on the state of the registry.

Collaborators

Other members of Task force for the resistant hypertension and renal denervation of the Croatian Hypertension League:

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Disclosure

The authors report no conflicts of interest in this work.

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