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GUIDELINES

Italian Society of Interventional Cardiology (GISE) and Italian Society of Arterial Hypertension (SIIA) Position Paper on the role of renal denervation in the management of the difficult-to-treat hypertension

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ABSTRACT

Renal denervation (RDN) is a safe and effective strategy for the treatment of difficult to treat hypertension. The blood pressure (BP)-lowering efficacy of RDN is comparable to those of many single antihypertensive medications and it allows to consider the RDN as a valuable option for the treatment of difficult to treat hypertension together with lifestyle modifications and medical therapy. A multidisciplinary team is of pivotal importance from the selection of the patient candidate for the procedure to the post-procedural management. Further studies are needed to investigate the effect of RDN on clinical outcomes and to better identify the predictors of BP response to RDN in order to recognize the patients who are more likely to benefit from the procedure.

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KEY WORDS: Denervation; Hypertension; Guideline.

Arterial hypertension is the leading risk factor for cardiovascular (CV) disease, and it is related to about two-thirds of all cerebrovascular accidents and half of all ischemic heart disease worldwide. It affects over one billion people worldwide and its global burden is rising due to escalating obesity and population aging.[1]

Lifestyle modifications and drug therapy are the mainstays of treatment.[2] Benefits of treatment are well established: a meta-analysis found that a 10 mmHg reduction in systolic blood pressure (SBP) reduced the risk of major CV events by 20%, coronary artery disease by 17%, stroke by 27%, heart failure by 28% and all-cause mortality by 13%.[3]

However, despite the availability of many effective and safe antihypertensive medications, globally only about one in five adults with hypertension have their blood pressure (BP) under control.[4] A common form of uncontrolled hypertension is resistant hypertension, which is defined as uncontrolled BP despite the use of ≥3 antihypertensive agents with different mechanisms of action, including a diuretic, usually thiazide-like, a long-acting calcium channel blocker, and a blocker of the renin-angiotensin system (RAS), at maximal or maximally tolerated doses. The diagnosis of resistant hypertension requires the exclusion of several possible causes of pseudo-resistant hypertension, including poor adherence to prescribed drugs, white coat-hypertension, clinical inertia and inaccurate BP measurement.[5]

The sympathetic nervous system plays a key role in the development of primary hypertension, and sympathetic activity is increased in many patients with resistant hypertension.[6] A crosstalk is present between the kidney and the central nervous system and involves both sensory afferent nerves and sympathetic efferent nerves (Figure 1).[7] Renal pathological processes increased afferent signalling nerves causing central sympathetic activation, that in turn through efferent nerves induces activation of the RAS, arteriolar vasoconstriction, increased heart rate (HR) and myocardial contractility. All these effects ultimately trigger BP elevation.[6] Catheter-based renal denervation (RDN), ablating both afferent and efferent renal sympatethic nerves, modulates the overactive signaling between the kidney and central nervous system, and as consequence represents an additional option in the armamentarium for the treatment of arterial hypertension.[8]

An unmet clinical need

The number of subjects aged 30–79 years with hypertension doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019, despite a stable age-standardized prevalence worldwide. Among them, the treatment rate was only 47% in women and 38% in men. Moreover, less than half of those treated, reached adequate control of

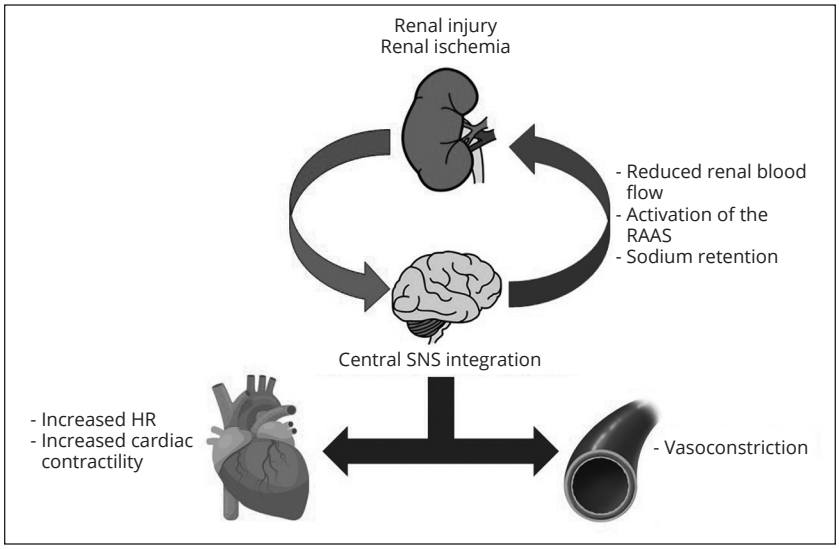

Figure 1.—Brain-kidney sympathetic crosstalk. Schematic representation of sympathetic tone crosstalk with afferent signaling from the kidney to the central nervous system and efferent signalling from the central nervous system to the kidney. Afferent signalling is triggered by different types of renal injury. Efferent signalling causes arterial hypertension acting through the kidney and the cardiovascular system.
SNS: sympathetic nervous system; RAAS: renin angiotensin aldosterone system.

BP values, with global control rates of 23% and 18% respectively for women and men.[4] Despite improvements in the diagnosis and treatment of hypertension, especially in middle and high-income countries, the prevalence of controlled BP still remains unsatisfactory.[4] The prevalence of controlled BP in the USA increased to 53.8% in 2013-2014 and then declined to 43.7% in 2017-2018, despite accepting a target control systolic BP value of 140 mmHg.[9] Failure to achieve goal BP was also observed in Italy, where over one decade of observation (from 2000 to 2011) only 33% of hypertensive patients achieved effective BP control.[10]

Non-adherence to pharmacological treatment remains one of the most important causes of uncontrolled hypertension.[11, 12] A large prospective italian study including more than 240.000 patients newly treated with antihypertensive drugs, investigated the incidence of cardiovascular events according to drug coverage, tracked by prescription registries. CV risk reductions of 20 and 25% were reported respectively in patients with intermediate (proportion of days covered from 51% to 75%) and high drug coverage (proportion of days covered >75%) as compared with patients with very low drug coverage (proportion of days covered ≤25%).[13]

Non-adherence to pharmacological treatment is a multifactorial phenomenon. Five categories of factors impacting adherence to prescribed medications have been identified: social and economic (age, education and socioeconomic status), healthcare system-related (patient-physician relationship, access to and cost of care), therapy-related (complex regimens, treatment changes, duration and adverse effects), condition-related (multiple comorbidities, symptom severity and quality of life) and patient-related (fear of dependence or adverse effects, lack of knowledge, denied diagnosis and forgetfullness).[11, 12]

A questionnaire-based cross-sectional survey was performed in about one thousand patients with elevated BP in Germany; almost 40% of those patients not on medication and almost 30% of those on drug therapy, were prone to choose one-time catheter-based RDN in the treatment of hypertension.[14] Similar results were observed in a survey conducted in Japan, which revealed that predictors of preference for RDN on logistic regression analysis were younger patient age, male sex, higher home or office SBP, poor antihypertensive drug adherence, the presence of heart failure and the presence of side effects during treatment with antihypertensive drugs.[15] Moreover, the majority of patients included in the questionnaire-based cross-sectional survey in Germany, reported that doctors were most likely to be their main source of information regarding medical problems and to influence their decision regarding medical therapies.[14] On the other hand, many clinicians accept unmet BP goals without taking decisive steps and changing therapeutic regimens, even in patients at moderate or high CV risk.[16, 17] In the USA a national survey of ambulatory care conducted from 2005 to 2012, revealed that among adults with uncontrolled hypertension, only one out of six patients experienced an intensification of their drug regimen by their primary care physician.[18] These results underline the need for a structured process, including patients' preferences and perspectives, in order to select the ideal therapeutic strategy for hypertensive patients.

To offset these difficulties observed in the real world of hypertensive patients, new non-pharmacological, device-based therapeutic approaches have been developed. The potential application of RDN in clinical practice has been tested in clinical trials, showing a BP-lowering efficacy both in patients with and without concomitant antihypertensive medication. Therefore, recent consensus documents from the European Society of Hypertension, the Italian Society of Hypertension, the Society for Cardiovascular Angiography and Interventions (SCAI), ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) have considered RDN as an innovative third option in the armamentarium of antihypertensive treatment after lifestyle modification and medical therapy.[19-22] The European Society of Hypertension (ESH) guidelines for the management of arterial hypertension considered RDN as a treatment option in patients with an estimated glomerular filtration rate (eGFR) > 40 ml/min/1.73m^2 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 (class of recommendation [CoR] II, level of evidence [LoE] B). Moreover, it's recommended that RDN should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure (CoR I, LoE C).[23]

Available data of clinical efficacy and safety

The SYMPLICITY HTN-3 trial failed to show a significant reduction of SBP in patients with resistant hypertension 6 months after RDN as compared with a sham control, despite a reduction in SBP of 14.1 mmHg.[24] The possible reasons for the failure are multifactorial and include frequent medication changes during the study period, use of first generation device, incomplete denervation, lack of experience of many operators, procedure variability and inadequate follow up duration.[25] After this trial, several changes in terms of concomitant medications, study populations and procedural aspects have been adopted according with the third European Clinical Consensus Conference for clinical trials in device-based hypertension therapies.[26] Since then, five sham-controlled randomized trials showed safety and efficacy of second generation radio frequency (RF) or ultrasound (US) systems in patients with or without concomitant medical therapy.[27-31] The reduction in office SBP ranged from -9.0 to -10.8 mmHg and in the diastolic blood pressure (DBP) from -5.0 to -5.5 mmHg, whereas the decrease in ambulatory BP ranges from -4.7 to -9.0 mmHg for SBP and -3.7 to -6.0 mmHg for DBP (Figure 2).[19] More recently also the RADIANCE II trial demonstrated a significant reduction in daytime ambulatory SBP at 2 months with US-based RDN (mean -7.9 mmHg) *vs.* the sham procedure (mean -1.8 mmHg) in the absence of antihypertensive medications.[32] A subgroup analysis of the Global SYMPLICITY Registry DEFINE showed that BP reduction after RDN was independent of the number and type of baseline antihypertensive

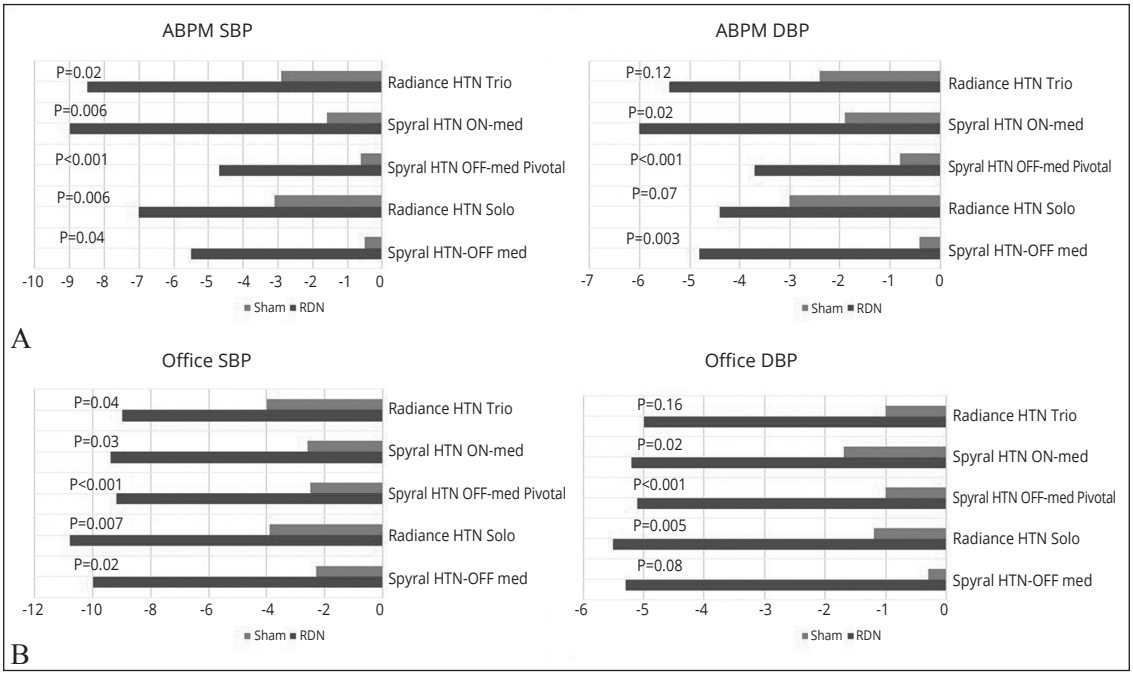

Figure 2.—Effect of RDN on BP control: A) Barr graph representing change in 24-h ambulatory blood pressure after renal denervation observed in sham-controlled randomized clinical trials of second generation; B) Barr graph representing the change in office blood pressure after RDN observed in the sham-controlled randomized clinical trial of second generation. Data are shown as mean BP change from baseline to the time point of each study primary objective. P values are given for difference between treatment and sham group adjusted for mean baseline BP.

medication classes.[33] The 24-hours ambulatory BP monitoring (ABPM) after RDN demonstrated efficacy throughout the entire observation period, in particular the night-time BP reduction is a better predictor of cardiovascular events reduction than the attenuation of morning BP rise.[34, 35]

Considering the large variability in BP response after RDN treatment, the identification of responders is a critical issue. Baseline BP prior to RDN was the only parameter that was consistently identified to predict BP response after RDN.[36] In the SPYRAL-HTN OFF MED trial the reduction in the 24-hour average SBP and DBP, as well as HR was significantly greater in patients with a median HR >73.5 bpm, than those <73.5 bpm, possibly identifying a subgroup of hypertensive patients, that could benefit more from RDN.[37] On the other hand, it has been demonstrated that RDN reduces plasma renin activity (PRA) and aldosterone level at 3 months, and higher baseline PRA levels (>0.65 ng/mL/h) were associated with a significantly greater reduction in office and 24-hour SBP.[38] Nevertheless, none of the predictors of BP response to RDN reported so far are sensitive and specific enough to allow an individualised patient selection.[22]

The durability of BP reduction effect after RDN procedure was sustained at 3 years, as shown in the SPYRAL HTN-ON MED, RADIANCE HTN-SOLO trial and the Global SYMPLICITY Registry.[39-41] The Global SYMPLICITY Registry is a prospective, open-label registry conducted at 196 active sites worldwide and enrolled 2237 hypertensive patients receiving the RDN treatment with the first-generation RF catheter. Baseline office and 24-h ambulatory SBP were 166±25 and 154±18 mmHg, respectively. SBP reduction after RDN was sustained over 3 years, including decreases in both office (-16.5±28.6 mmHg, P<0.001) and 24-hour ambulatory SBP (-8.0±20.0 mmHg; P<0.001).[41] A significant BP reduction was also confirmed in high-risk patients including elderly patients (age ≥65 years) and patients with atrial fibrillation, diabetes mellitus type II, severe treatment resistant hypertension, chronic kidney disease (eGFR <60 mL/min/1.73 m^2) and isolated systolic hypertension.[42] More recently, the final analysis of the SYMPLICITY HTN-3 trial, after the initial failure at 6 month follow-up, showed that patients in the RDN group had significantly larger reductions from baseline to 36-month follow-up in both office and 24h ambulatory SBP compared with the sham control group.[43] Two single-arm studies including patients undergoing RF-based RDN, have shown longer-term efficacy up to 10 years after the procedure.[44, 45] Durable BP reduction is also supported by preclinical data, that showed a lack of nerve function 180 days after RDN with sustained reduction of axon density and nerve atrophy in a normotensive swine model.[46]

Despite the efficacy in reducing BP, until now there are no available randomized controlled trials that have analyzed the direct effect of RDN on clinical outcomes. Epidemiological studies found a continuous linear relationship between elevated BP and adverse CV events.[47] A reduction of 5 and 10 mmHg of office SBP was associated with a decrease in major CV events respectively of 10 and 20% and of stroke by 13 to 26%, regardless of how this reduction has been obtained.[47, 48] Based on BP reduction observed in high-risk patients from the Global SYMPLICITY registry and events reductions from a published meta-regression analysis, it was estimated a significant absolute reduction in major adverse CV events over 3 years compared with the projected control (8.6% observed *vs*. 11.7% for projected control; P<0.01), primarily due to reduced stroke incidence.[49] Moreover, an analysis of Global SYMPLICITY Registry, showed that Time in Target range (TTR) of BP after RDN through 6 months was 30.6% and a 10% increase in TTR after RDN through 6 months was associated with significant risk reductions from 6 to 36 months of 15% for major adverse CV events (P<0.001).[50]

In addition to being an effective treatment, RDN is a safe and well-tolerated endovascular intervention. In all sham-controlled randomized trials, the rate of major adverse events in the RDN group was comparable to the sham group.[27-31] Femoral vascular access site-related complications (*e.g.*, haematoma, pseudoaneurysm, fistula, bleeding, etc.) were the most reported complications.[27-31] In the SYMPLICITY HTN-3 trial, the largest randomized trial, only one of 352 patients in the RDN group (0.3%)

had a vascular complication requiring treatment.[24] Vascular access site complications may be reduced designing RDN systems suitable for radial access. Complications related to renal artery ablation (*e.g*. renal artery dissection, spasm, post-procedural stenosis) have been infrequently reported.[27-31] In a large meta-analysis including 5769 patients undergoing RDN using RF, 26 patients (0.45%) with renal artery stenosis or dissection were identified of whom 24 (0.41%) required renal artery stenting with a 0.20% pooled annual incidence of stent implantation, which is similar to the reported natural incidence of renal artery stenting in hypertensive patients. Median time from RDN procedure to all renal intervention was 5.5 months and 79% of all events occurred within one year of the procedure.[51] No significant decrease in kidney function has been reported after RDN procedure: a meta-analysis of 48 studies found no differences in the eGFR after an average follow-up of 9.1 months.[52] Renal safety was also confirmed at 3 years follow-up in the Global SYMPLICITY Registry, with observed eGFR decrease within the bounds of the expected decline in patients with severe hypertension.[41] Renal safety data are not valid for patients with an eGFR < 40 ml/min/1.73 m^2, that were excluded from most of the trials.[27-31] However, few small single center, non randomized studies reported the efficacy and safety also in patients with chronic kidney disease (CKD) with an eGFR <40 mL/min/1.73 m^2.[53, 54]

Renal denervation devices: past, present and future

The concept of modulating blood pressure through sympathectomy dates back to the 1930's[55] and several years later the first in-human experience, involving 76 patients, was reported.[56] The first encouraging results reported in SYMPLICITY HTN-1 supported the development of devices with different energy sources.[57] However, this technological rush suffered a sharp slowdown with the release of SYMPLICITY HTN-3 data.[24] Nevertheless, in recent years, new clinical evidences clarified the role of this procedure in the treatment of hypertension.[27-32] Currently, technologies used for RDN in patients with hypertension as well as other conditions with similar sympathetic imbalance are essentially based on three different methods: RF, US and drug injection (Figure 3).[58-60] For the sake of brevity and clinical relevance, we hereby focus on devices that have already received CE mark and can thus be used for routine patient care.

Radiofrequency denervation

RF represents the most used ablation method. Basically, the energy used consists of an alternating electric current exerting an ablative action by both direct damage due to resistive heating to the more superficial tissues and by thermal conduction to deeper tissues. In practice, the applied high-frequency low-power RF energy heats the

	Spyral (Medtronic)	Paradise (RECor Medical)	Peregrine (Ablative solutions)
			
Mechanism	Radiofrequency	Ultrasound	Ethanol injection
Vascular access size	6 Fr	6 Fr	7 Fr
Catheter type	Four electrodes	Balloon with ultrasound transducer and cooling circuit	Three guided microneedles
Ablation targets	Main renal artery and branches	Main renal artery	Main renal artery
Treatment time per segment	45-60 seconds	7 seconds	n.a.

Figure 3.—Devices for percutaneous renal artery denervation. RDN devices and their characteristics.
n.a.: not available.

surrounding tissue and hence denatures the protein structure of the sympathetic nerve bundles within the vascular adventitia and perivascular adipose tissue. The SYMPLICITY-HTN-3 trial failed to show the effectiveness of the first-generation RDN device (Flex single electrode catheter) *versus* the sham procedure in hypertensive patients.[24] The first-generation device has been replaced by second-generation devices, featuring multi-electrode catheters. Unlike the single electrode catheter, which had to be rotated to treat different segments of the vessel, the electrodes in multi-electrode catheters are positioned to cover all four quadrants of the arterial circumference simultaneously (4 simultaneous quadrantic [4SQ] ablation), providing a more uniform procedure and a less operator-dependent function. The only available device in clinical practice is the Spyral (Medtronic, Minneapolis, MN, USA), which is a helical-shaped preformed microcatheter with four unipolar electrodes, that can be advanced on a 0.014" workhorse guidewire. Once the guidewire is retracted, the device resumes its original shape adapting to the diameter of the artery and allowing the treatment of a broad diameter range (3-8 mm), including the main artery distal segment, side branches and accessory vessels to achieve a complete treatment. When deployed all four electrodes are arranged approximately 90° from each other generating 360° ablation. Electrode cooling is provided directly by laminar blood flow during the ablation. The efficacy of treatment with this device in patients taking antihypertensive drugs was demonstrated in the SPYRAL HTN-ON MED randomized trial with a significant reduction at 6 months of both office and ambulatory blood pressure in device-treated patients compared to the sham-controlled group.[28] Similar results were also recorded in the SPYRAL HTN-OFF MED Pivotal trial in patients with uncontrolled hypertension in absence of antihypertensive medication.[30]

Ultrasound denervation

US represents another effective tecnhique employed for RDN. Notably, the energy supplied consists of >20 Hz frequency sound waves, converted into thermal energy once they reach the vessel wall. By virtually avoiding direct contact with the arterial wall, US denervation might minimize the risk of endothelial damage;[61] moreover, US-based RDN has higher depth of ablation than RF, making direct ablation of branch arteries unnecessary.[62, 63] The PARADISE system (RECor Medical, Palo Alto, CA, USA) consists of a small, flexible balloon catheter able to simultaneously deliver US energy and cool the artery wall, by circulating water in the balloon, in order to prevent damage during the process. The efficacy of treatment with this device in hypertensive patients who were not taking antihypertensive medications was demonstrated in the RADIANCE HTN SOLO trial with a significant reduction of daytime ambulatory SBP.[29] The efficacy was also demonstrated by the RADIANCE HTN TRIO in patients with hypertension resistant to a standardized triple combination pill.[31] Instead the REQUIRE trial did not show a significant difference in ambulatory BP reductions between RDN and a sham procedure in Asian patients with resistant hypertension,[64] due to incomplete exclusion of patients with primary hyperaldosteronism, inclusion of patients with poor medication adherence and incomplete blinding of medical staff.[65, 66] More recently, the results of the RADIANCE II trial indicate that, among patients with uncontrolled stage II hypertension, RDN with the Paradise system resulted in a greater reduction of daytime ambulatory SBP at 2 months in the absence of antihypertensive medications compared with a sham procedure.[32]

Drug injection

This method uses the direct injection of drugs into the vessel wall through microneedles, inducing selective neurolysis and purportedly reducing the risk of endothelial damage. Several substances have been studied for this purpose, including alcohol, botulinum toxin type A, guanethidine, and vincristine. The Peregrine system (Ablative Solutions, San Jose, CA, USA) is a catheter with 3 retractable micro-needles. Once positioning has been confirmed, all 3 micro-needles are deployed simultaneously for controlled delivery of 0.3 mL of dehydrated alcohol into the adventitia inducing a direct and permanent neurolysis. First-in-human experience showed favourable results in terms of safety and feasibility in a small series of 18 sub-

jects with refractory hypertension.[67] The efficacy and safety were also confirmed in an open-label trial enrolling 45 patients with uncontrolled BP.[68] Recently the TARGET BP OFF-MED trial, a randomised, blinded, sham controlled trial, confirmed the safety of the device, but did not show a statistically significant difference in 24-hour SBP at 8 weeks after the procedure between groups in absence of antihypertensive medications. However, after 12 months of blinded follow-up with medication escalation, patients achieved similar office SBP with a significantly lower medication burden in the RDN group (mean daily defined dose:1.5±1.5 *vs.* 2.3±1.7; P=0.017).[69] The randomised, sham controlled TARGET BP I trial for patients taking antihypertensive medication is currently ongoing.[70]

In summary, several methods can be used for RDN in hypertensive patients, each one with its own pros and cons. In RADIO-SOUND HTN trial endovascular US-based RDN of the main renal arteries was found to be superior to RF ablation of the main renal arteries only, whereas a combined approach of RF ablation of the main arteries, accessories and side branches was not different to US at 3 months.[63] At six months, 24-hour SBP values were significantly lower in the US group than in the other two groups. After drug optimization, at twelve months no difference was found between the groups.[71] A recent metanalysis revealed that there were no significant differences in the magnitude of blood pressure reduction between RF and US-based devices, although it was numerically greater in the second-generation of RDN trials than in first generation of RDN trials.[72] Ongoing trials and observational studies will inform on their comparative user-friendliness, efficacy and safety.

Diagnostic evaluation of the patient with difficult to treat arterial hypertension

The initial screening of patients candidate to RDN can be performed by a general practitioner, cardiologist, internist or a nephrologist with experience in hypertension management. However, it is recommended that patients are referred to dedicated outpatient hypertension centres with experience in handling patients with difficult to treat hypertension. The Renal Denervation Multidisciplinary Team (RDMT) plays a pivotal role in patients management, thanks to the different clinical skills required to identify the causes of failure of a conventional drug-based therapy. It is strongly recommended that the indication for the RDN procedure should be provided by RDMT, which should be composed by experts in hypertension management (cardiologist and/or internist and/or nephrologist), experts in RDN endovascular procedures (interventional cardiologist or interventional radiologist) and anaesthesiologists.[20-23] Such third-level reference centers should be certified by national hypertension societies (Table I).

Once the patient has been referred to the hypertension centre, the initial evaluation should include the assessment of the hypertension grade and of target organ damage, exclusion of secondary hypertension, pseudo-resistant hypertension and any contraindications to RDN, like severe CKD (Figure 4).

Office blood pressure values and HR should be carefully assessed, and the presence uncontrolled BP should be confirmed, during a medical evaluation, through 24-hour ambulatory blood pressure monitoring (ABPM). The ABPM parameters to be considered are mean 24 hours

TABLE I.—*Minimum requirements for RDN selection centers.*

Center	Description
Hypertension centre	• ESH Excellence Centers and/or Centers with specific SIIA certification or acknowledgement • Dedicated outpatient service for the difficult-to-treat patients • Medical and nurse staff with targeted education on the topic • Equipement assess 24-h BP, drug adherence and screen for main causes of secondary hypertension, including advanced imaging facilities • Coordination of the multidisciplinary team in charge of finalizing the indication to RDN
Interventional centre	• Certified operators (interventional radiologist or cardiologist) • Volume of renal procedures >10/year (RDN procedures >5/year) • Agreement with the regional healthcare system for reimbursement of the procedure

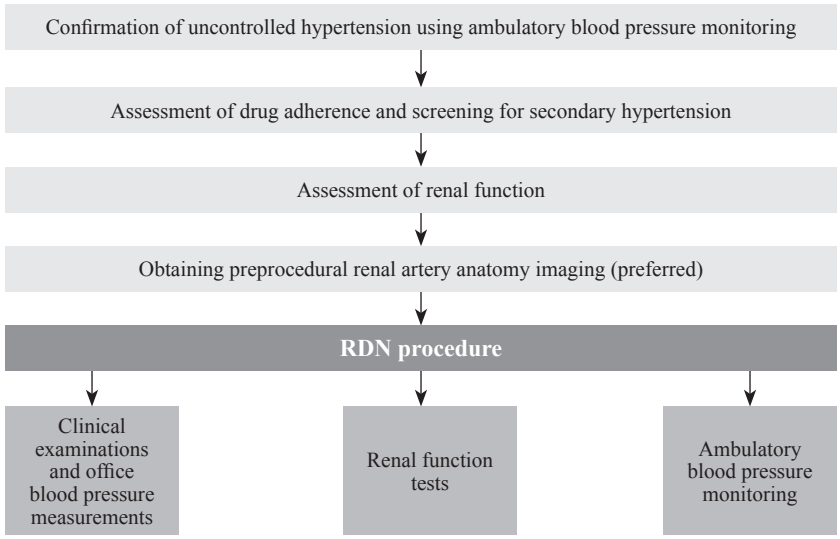

Figure 4.—Pre-and post-RDN assessment flowchart. Management of patients undergoing RDN.

SBP and DBP, HR and the number of valid readings.[2] Given the low reproducibility of ABPM recordings, to ensure reliable results, only test with >75% of readings should be considered as reliable.[73] The clinical assessment of the patient should be completed by the definition of the global CV risk and the assessment of target organ damage in order to define BP targets and optimize concomitant treatments.[2]

In the presence of uncontrolled BP values (office BP >140/90 mmHg) in a patient treated with three or more antihypertensive medications at optimal or maximally tolerated doses, non-adherence to treatment and the presence of secondary forms of hypertension should be excluded before confirming a diagnosis of resistant hypertension. Indeed, half of patients with a potential diagnosis of resistant hypertension are non-adherent to the prescribed antihypertensive medications and should be considered pseudoresistant.[74] To obtain an objective assessment of medication adherence, hypertension centres should determine medications levels in the urine or in the serum.[75]

Secondary forms of hypertension should be suspected and excluded in the following scenarios: early onset in patients without other risk factors, sudden onset, severe hypertension, resistant hypertension, excessive decrease in eGFR with a small dose of an angiotensin-converting enzyme (ACE) inhibitor and unexplained hypokalemia.[2] The most common causes of secondary hypertension include obstructive sleep apnea, CKD, renovascular hypertension and primary aldosteronism.[76] It is important to remember that primary aldosteronism is often difficult to recognize,[77] as some classic disease features, such as hypokalemia, might not be present or attributed to the diuretic treatment.[78]

During the evaluation phase, laboratory tests including serum creatinine and measured or estimated GFR should be performed in order to identify patients with a GFR $\leq$ 40 ml/min/1.73 m^2, who should not be considered for RDN treatment.

The position paper of the Italian Society of Hypertension on the role of renal denervation in the management of the difficult to treat hypertensive patient proposed two ideal types of patients that could be candidates for RDN (Table II).[20] The first one is represented by resistant hypertensive patient, in whom an association treatment with three or more antihypertensive drugs has failed in achieving the target BP (recommended), while the second is represented by Grade 1-2, systo-diastolic, essential hypertensive patient, untreated or uncontrolled by one or two BP-lowering drugs (possible).[20] Of note, while initially RDN was limited to patients with resistant hypertension, there is growing scientific evidence that it could be considered also in patients with grade 1 or 2 hypertension in order to optimize BP control in combination with drug therapy. This approach is frequently requested by the patients to avoid

TABLE II.—*Clinical profiles of patient candidates to RDN.*

Clinical profile	Additional features to be considered
Essential hypertensive patient uncontrolled by an association RAS-blocker/calcium-channel blocker/diuretic at maximally tolerated doses (recommended)	Patient preference, adverse effects of spironolactone, poor drug adherence despite extensive counseling, systo-diastolic hypertension, no extensive vascular damage, high/very high lifetime cardiovascular risk
Grade 1-2 hypertension uncontrolled by 1-2 BP-lowering drugs (possible)	Patient preference, multiple intolerances to BP-lowering drugs/adverse effects, poor drug adherence despite extensive counseling, high/very high lifetime cardiovascular risk, paroxysmal atrial fibrillation and planned ablation

drug-related side effects, reduce the number of daily pills and avoid non-adherence to prescription;[14, 15] moreover, it underlines the importance to discuss with the patients about the different therapeutic options available to reduce BP and the need to consider patients' preferences when taking treatment decisions.

Once the patient candidate for RDN has been identified, preprocedural phase should include non-invasive renal artery imaging with either contrast-enhanced computed tomography angiography (CTA) or contrast-enhanced magnetic resonance angiography (MRA) or Doppler ultrasound. CTA and MRA are the preferred imaging techniques to rule out the presence of renal artery stenosis or fibromuscular dysplasia and to evaluate the location of renal artery ostia, the presence of accessory renal arteries and anatomic eligibility, evaluating renal artery diameters. Understanding renal artery anatomy might have important implications on determining endovascular treatment strategy and potential future device selection and patient selection for RDN.

Consequently, RDN may be considered a treatment option in the following scenarios:

• resistant hypertension, defined as a blood pressure that remains above goal despite concomitant use of three antihypertensive agents of different classes including a diuretic, usually thiazide-like, a long-acting calcium channel blocker, and a blocker of the RAS, at maximal or maximally tolerated doses;

• poor adherence to multiple antihypertensive medications despite extensive counselling;

• intolerance to multiple antihypertensive medications;

• patient's preference after extensive discussion about limits and potential risks of the procedure.

Instead, exclusion criteria for RDN endovascular procedures include:

• secondary hypertension including renal artery stenosis;

• chronic renal failure with eGFR ≤40 mL/min/1.73 m^2;

• size of the main renal arteries and branches <3 mm or >8 mm in diameter;

• recent renal artery stenting (<6 months).

Procedural aspects of renal denervation with radiofrequency devices

Patient preparation

Preventive hydration with saline 0.9% is advised to minimize the risk of contrast-induced kidney injury independently of the basal renal function. Intravenous hydration should start a few hours before the RDN procedure with an infusion rate according to the left ventricular ejection fraction (LVEF): 1 mL/kg/h if the LVEF is normal or 0.5 mL/kg/h if LVEF <40%. The antihypertensive therapy should not be discontinued before the RDN procedure and a pre-load with aspirin the day before is advised as for any endovascular interventional procedure. The patient should refrain from eating at least for 8 hours before the procedure. Before starting the RDN procedure, intravenous analgesia and sedation are mandatory. If the anesthesia is not deep enough, the patient could move, interrupting the delivery of energy due to the loss of contact between the electrodes and the vessel wall. The suggested strategy is a conscious sedation according to the Monitored Anesthesia Care approach: low doses of opioids (*e.g.*, 1-3 mg of morphine or fentanyl 1-2 mcg/kg intravenously [IV]) and benzodiazepine (*e.g.*, midazolam 2-3 mg IV) can usually provide adequate analgesia and sedation with ret-

rograde amnesia. Monitoring of vital parameters is mandatory, and the necessary drugs to manage adverse reactions (*e.g.*, naloxone and flumazenil) should be available in the catheteterization laboratory. A specific informed consent, defined by the denervation team must be obtainded for each patient undergoing procedure.

The RDN procedure

Nowadays RDN is performed by femoral vascular access through a percutaneous 6-Fr sheat. Unfractionated IV heparin (100 UI/mL) is needed in order to maintain ACT >250 s during the procedure. In case of elevate arterial BP values, continuous infusion of IV nitrates or nitroprussiate should be considered. At the beginning of the procedure, if CTA or MRA images of the renal arteries are not available, an abdominal aortography should be performed, using a pig-tail catheter positioned in the abdominal aorta, at the level of the origin of the renal arteries (lumbar vertebrae L1-L2), with power injection of 10 ml of iso-osmolar contrast media at 10 mL/s. Aortic abdominal angiogram is useful to detect main and accessory renal arteries, and their origins (Figure 5) in order to choose the shape of the guiding catether. In most cases an internal mammary artery (IMA) catether is adequate; other catheters useful in cases with upward artery take-offs are the Judkins right or the Multipurpose. Once selectively engaged, a complete angiography of the kidney is obtained with 5 mL of iso-osmolar contrast media at 5 mL/s, and it could be used as roadmap for the procedure. Selective angiography is useful to identify the vessels suitable for RF-based RDN. The ablation target segments should include all the renal arterial branches with a diameter range between 3 to 8 mm located outside the kidney parenchyma. Accessory renal arteries also carry sympathetic nerves and should be treated if the arterial diameter allows the insertion of the ablation catheter. Indeed, BP decreases were found to be significantly greater when accessory arteries were treated.[79] The Spyral RDN catheter (Medtronic, Minneapolis, MN, USA) is a rapid exchange 6 Fr catheter that runs over a conventional 0.014" coronary guidewire. The use of wires with hydrophilic tip is not advisable due to risk of perforation of distal vessels. Attention should be paid to maintain the tip of the wire under control to avoid any placement into parenchymal vessels. In case of tortuous anatomies, extra-support wires or a second "buddy" wire may be needed. Most of the RDN procedures can be performed using a single posterior-anterior projection, but in tortuous anatomies the ideal target for energy delivery may be difficult to identify due to overlapping with other branches; in such cases, cranial or caudal skews of the flat panel are useful (Figure 6). Nytroglicerin has to be injected before the ablation to prevent spasm. Once the target site is reached with the ablating catheter, the wire has to be retrieved proximal to the electrodes before starting the delivery of radiofrequency in order to let the device resume its original helical shape adapting to the diameter of the artery. Ablation should be performed as many times within a segment as anatomy permits, starting distally and working proximally without overlapping treatment zones. RDN will be more effective when ablation is performed also in the distal portion of the vessels, than when it is performed only in the proximal region, due to the reduced distance between sympathetic nerves surrounding the renal arteries and vessel wall.[80] In case of previous renal stenting, performed more than six months before RDN, it

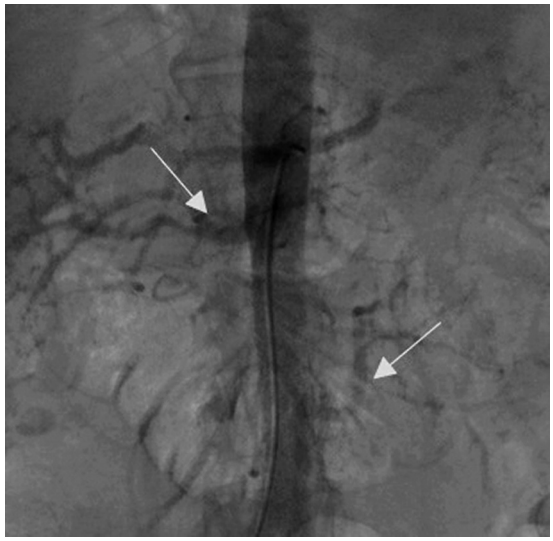

Figure 5.—Abdominal aorta and renal artery angiography. Angiography of the abdominal aorta showing the normal take off of the right renal artery and lower take off of the left renal artery.

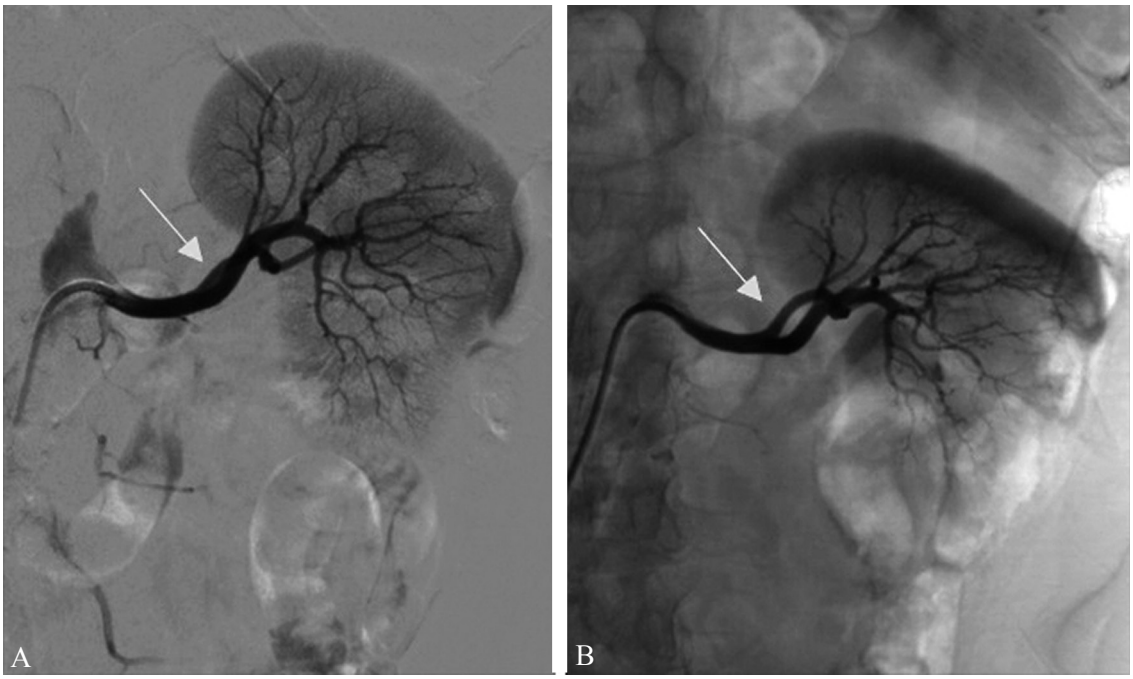

Figure 6.—Selective renal artery angiography. Left renal artery with two overlapping main branches (A). Caudal skew of the same artery with clear demonstration of two main renal branches (B).

is possible to treat the renal artery segments located distal and proximal to the stent. During the procedure it is essential to monitor the resulting impedance and temperature on the energy generator for each cycle. Before disengaging the guiding catheter, a selective angiography should be performed in the same baseline projection to exclude vessel injury. The same procedure should be performed contralaterally. Hemostasis of the vascular access site may be achieved through vascular closure device or manual compression.

Post-procedural care and discharge

In the first 12 hours following the procedure the patient should remain on bed rest with non-invasive monitoring of vital signs (BP, HR, temperature, respiratory rate) and pain control (checked with the VAS scale). The day after the procedure, complete blood count and renal function should be assessed. In case of renal function deterioration, hydration should be continued at 1 mL/kg/h if the LVEF is normal or 0.5 mL/kg/h if LVEF <40% and renal function reassessed at 48 and 72 hours post-procedure. Physical examination of vascular access site should be carried out to assess the efficacy of the hemostasis. In the absence of complications, the patient can be discharged the day after the procedure. Aspirin (75-100 mg) should be continued for one month post-procedure, then can be discontinued if there are no other indications to it. The use of dual antiplatelet therapy is not recommended if there is no other indication to it.[22]

Follow-up after the procedure

The RDMT should reevaluate the patient at 1,3,6,12 and 24 months after the procedure with assessment of office blood pressure, antihypertensive medications and blood tests including renal function (Figure 4).

ABPM should be performed at 6, 12, and 24 months following RDN to evaluate the 24-h BP response. Patients are unlikely to become medication free and changes of antihypertensive therapy should be guided by BP measurements during the follow-up.

Moreover, RDN was associated with a reduction of Left Ventricular Mass Index (LVMI) independent from both baseline BP and BP chang-

es;[81] therefore, an echocardiography could be performed after 12 months from the procedure to evaluate LVMI regression.

Routine renal artery imaging may not be necessary and should be obtained only in patients with procedure-related renal artery injury or clinical suspicion of renal artery stenosis, as indicated by an unexplained worsening of renal function or deteriorating hypertension. Each tertiary center should modify follow-up type and schedule according to patient clinical conditions.

Conclusions

RDN is a safe and effective strategy for the treatment of difficult to treat hypertension. The BP-lowering efficacy of RDN is comparable to those of many single antihypertensive medications and it allows to consider the RDN as a valuable option for the treatment of difficult to treat hypertension together with lifestyle modifications and medical therapy. A multidisciplinary team is of pivotal importance from the selection of the patient candidate for the procedure to the post-procedural management. Further studies are needed to investigate the effect of RDN on clinical outcomes and to better identify the predictors of BP response to RDN in order to recognize the patients who are more likely to benefit from the procedure.

Key messages

- Arterial hypertension is a common cardiovascular risk factor, but blood pressure control rates remain poor worldwide.
- Renal denervation is a safe and effective endovascular procedure for the treatment of difficult to treat hypertension.
- The Renal Denervation Multidisciplinary Team (RDMT) plays a pivotal role from the selection of the patient candidate for the procedure to the post-procedural care.

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Conflicts of interest
Francesco Versaci has a financial relationship with Sanofi and Translumina. All other authors have no conflicts of interest to declare.

Authors' contributions
All authors read and approved the final version of the manuscript.

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