

European Society of Hypertension position paper on renal denervation 2021

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This ESH Position Paper 2021 with updated proposed recommendations was deemed necessary after the publication of a set of new pivotal sham-controlled randomized clinical trials (RCTs), which provided important information about the efficacy and safety of endovascular device-based renal denervation (RDN) for hypertension treatment. RDN is effective in reducing or interrupting the sympathetic signals to the kidneys and decreasing whole body sympathetic activity. Five independent, fully completed, sham-controlled RCTs provide conclusive evidence that RDN lowers ambulatory and office blood pressure (BP) to a significantly greater extent than sham treatment. BP-lowering efficacy is evident both in patients with and without concomitant antihypertensive medication. The average decrease of 10 mmHg in office BP is estimated to lower the incidence of cardiovascular events by 25–30%, based on meta-analyses of RCTs using pharmacological treatment. Neither peri-procedural, nor short-term or long-term adverse events or safety signals (available up to 3 years) have been observed. Implementing RDN as an innovative third option in the armamentarium of antihypertensive treatment requires a structured process that ensures the appropriate performance of the endovascular RDN procedure and adequate selection of hypertensive patients. The latter should also incorporate patients' perspective and preference that needs to be respected in a shared decision-making process.

Keywords: hypertension, position paper, renal denervation, sympathetic nervous system

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; GSR, Global Symplcity Registry; RCT, randomized clinical trial; RDN, renal denervation; SNS, sympathetic nervous system

INTRODUCTION

Arterial hypertension is the most prevalent and important risk factor for death and disability worldwide, effecting more than one billion individuals and causing 10 million deaths annually. In addition to lifestyle changes and pharmacotherapy, renal denervation

(RDN) has emerged as the most advanced and promising device-based technology [1].

The 2018 European Society of Hypertension/European Society of Cardiology [ESC/ESH] Guidelines on the management of hypertension published in 2018 stated that 'the clinical evidence in support of RDN as an effective [blood pressure] BP lowering technique is conflicting' and that 'use of device based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and [randomized clinical trials] RCTs until further evidence regarding their safety and efficacy becomes available' [2]. In the following 3 years, new data

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on the efficacy and safety of device-based therapy have become available. It was deemed necessary by the European Society of Hypertension [ESH] Working Group on interventional approaches for the treatment of hypertension to provide an updated position paper on RDN. Proposed recommendations on the use of RDN for hypertension treatment are provided in Box 1 and in the summary of each chapter (given in *italics*).

This update (written by experts from the ESH including the ESH Working Group on device-based treatment of hypertension) seemed to be timely, not only because several sham-controlled RCTs have now been published but also in view of the expected increased uptake of device-based therapies such as RDN in clinical medicine. We have also considered that it cannot be foreseen when the next ESH/ESC Guidelines for the Management of Hypertension will become available.

THE EFFECTS OF RENAL DENERVATION ON SYMPATHETIC ACTIVITY

Overactivity of the sympathetic nervous system (SNS) contributes to the development and progression of hypertension. The kidneys play an essential and bidirectional role in the regulation of BP [3,4]. Increased activity of renal efferent sympathetic nerves decreases renal perfusion and glomerular filtration rate (GFR), increases tubular sodium reabsorption resulting in sodium retention and stimulates the renin angiotensin aldosterone system. Conversely, renal pathological processes, such as renal ischemia, injury or inflammatory and fibrotic changes result in increased afferent sensory signalling from the kidneys to integrative nuclei in the central nervous system. These in turn stimulate increased central sympathetic outflow, with the consequence of increased peripheral vascular resistance (vasoconstriction of the resistance vessels), thereby aggravation of BP-induced left ventricular hypertrophy, and a progression of cardiovascular and renal damage [3,4].

RDN interrupts or at least attenuates the crosstalk between the kidney and the central nervous system [3]. According to several animal studies, a substantial decrease of the norepinephrine content in the kidney was observed after RDN, thereby proving the concept that RDN decreases the efferent sympathetic signalling to the kidneys [4]. In humans, the sympathetic drive to the kidneys can be directly assessed by the norepinephrine spill-over technique. In the very first 10 patients with resistant hypertension, who were treated with radiofrequency RDN, an approximately 50% reduction in renal norepinephrine spill-over was observed [4]. RDN has also been shown to reduce plasma renin activity, and, most recently, plasma renin was identified as a predictor of the BP lowering efficacy of RDN in the randomized sham-controlled SPYRAL HTN-OFF MED study in drug-naive patients [5]. Thus, experimental and clinical data documented that RDN substantially decreases the sympathetic activity to the kidneys.

In humans, microneurography is the only direct method to assess postganglionic sympathetic nerve activity. In two studies in which this technique was applied, RDN reduced the nerve firing from the SNS progressively after 3 and 6 months in patients with treatment-resistant hypertension

[6,7], as well as in patients with uncontrolled hypertension and metabolic syndrome after 3 months [6–8]. When increased BP levels are accompanied by high sympathetic activity, as is commonly the case in hypertensive patients with chronic kidney disease, atrial fibrillation or heart failure, there is a strong rationale that RDN might represent a useful treatment, too.

In summary, we conclude that catheter-based endovascular RDN was found to significantly reduce central sympathetic outflow.

BLOOD PRESSURE LOWERING EFFICACY OF RENAL DENERVATION

First-generation studies

Proof-of-concept studies applying radiofrequency energy, high focused ultrasound energy and perivascular injection of alcohol found substantial decreases in 24-h ambulatory and office BP in patients with treatment resistant HTN [9]. Subsequently, several randomized, but open-label studies reported a significant reduction (albeit not in all studies) of ambulatory and office BP in the RDN group compared with a control group on antihypertensive medication [10]. In a series of first-generation sham-controlled RCTs, mixed results were reported. The Simplicity HTN-3 study included 535 patients with resistant hypertension and failed to meet the primary efficacy endpoint [11]. The lack of significance of this first-generation study, the Simplicity HTN-3 study, was related to poor methodology (e.g. high rate of and poorly verified drug changes in the run-in and treatment phase, lack of adherence to treatment) and incomplete RDN (no circumferential ablations).

Against this background, a Clinical Consensus Conference on device-based hypertension treatment was initiated and produced recommendations for the standardized assessment of device-based endovascular therapies [12]. The device technologies and techniques of RDN were adapted to allow more consistent and more complete (circumferential) ablation of the renal nerves (incomplete circumferential ablation was identified as one of the most relevant problems in Symplicity HTN-3) [13]. Stricter criteria for including study patients, for the run-in phase, and/or analysis of medication adherence (e.g. witnessed intake of the medication, if applicable) in each patient were recommended.

Second-generation studies

Following the recommendations of the expert group, second-generation RCTs have been designed and several of these were recently published. The Reduce HTN: Reinforce Study results were found difficult to interpret, as the study was prematurely stopped after including 50 patients of the 93 patients that were targeted [14]. In the five completed sham controlled RCTs, radiofrequency (Spyral catheter) and ultrasound (Paradise system) based RDN were uniformly found to be effective and well tolerated (Fig. 1) [15–19].

Of note, in the second-generation, sham-controlled RCTs, only minor changes in ambulatory and office BP were observed in the sham group: BP reduction ranged

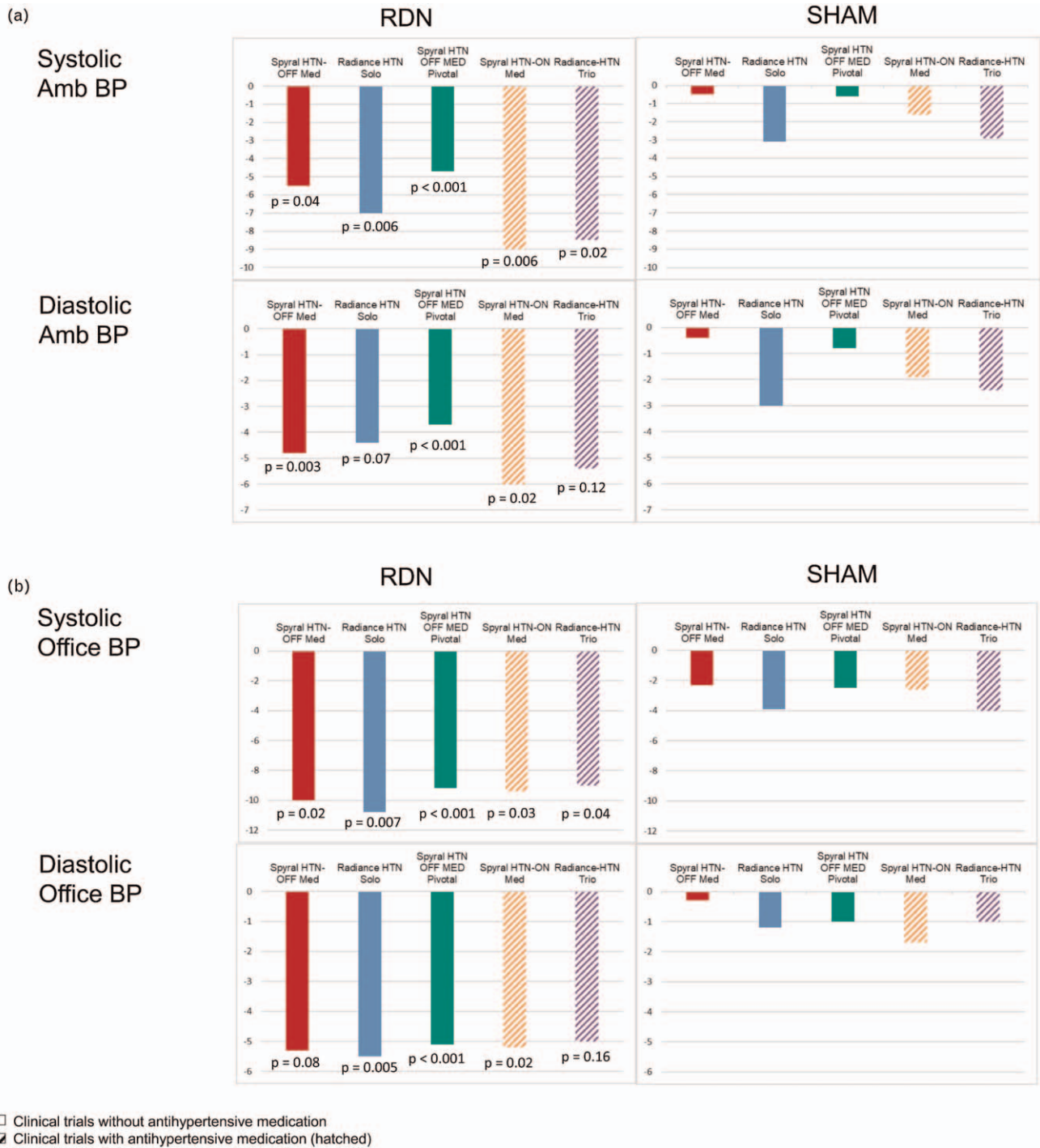


FIGURE 1 (a) Change in 24-h ambulatory blood pressure after renal denervation observed in sham-controlled randomized clinical trials of second generation. (b) Change in office blood pressure after renal denervation observed in sham-controlled randomized clinical trials of second generation. Data are 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.

from -0.5 to -3.1 mmHg for ambulatory BP and from -2.3 to -4.0 mmHg for office BP (Fig. 1) [15–19]. This is in contrast to the results of the Symplicity HTN 3 trial, in which changes in systolic office BP of -11.7 mmHg were observed in the sham control group [11].

Ambulatory blood pressure

In all second-generation sham-controlled RCTs, the primary objective was change in ambulatory BP, as ambulatory BP is

the best method to assess the BP load on the cardiovascular, cerebrovascular and renal system [2]. In comparison to the sham group, the reduction in ambulatory BP was significantly greater than in RDN group. The decrease in the RDN groups ranged from -4.7 to -9.0 mmHg systolic and from -3.7 to -6.0 mmHg diastolic (Fig. 1a) [15–19]. Furthermore, in SPYRAL HTN-OFF MED antihypertensive drug adherence was monitored using toxicological analyses, and after excluding those with nonadherence the 24-h

ambulatory BP difference between the sham and RDN group became numerically even larger [15]. Accordingly, in two trials in patients with resistant hypertension and high medication burden, BP-lowering effect of RDN was independent of adherence to antihypertensive treatment [19,20].

In the largest second-generation sham-controlled randomized study without antihypertensive medication at baseline ($N=331$), the SPYRAL HTN-OFF MED Pivotal trial [18], 166 patients were assigned to RDN and 165 to the sham procedure. The difference in 24-h ambulatory SBP between the two groups [difference -4.0 , 95% confidence interval (95% CI) -6.2 to -1.8 mmHg, $P<0.001$] was relatively modest in magnitude, though highly significantly different in favour of RDN. In the RADIANCE-HTN-TRIO, study patients with drug-resistant hypertension who received a single pill triple antihypertensive drug combination for 4 weeks (mandatory requirement) were randomized either to RDN or sham treatment. Significantly greater reductions were observed with RDN with respect to daytime ambulatory SBP (difference -4.2 , 95% CI -8.3 to -0.3 , $P=0.016$), compared with the sham group [19].

When analysing the ambulatory BP profiles, RDN was found to be associated with BP reduction throughout the entire 24 h in all sham-controlled RCTs [15–19]. The observation that night-time BP was also significantly reduced deserves special interest, as night-time BP has been repeatedly shown to be a better predictor of cardiovascular outcome than daytime BP [2,21]. Specific posthoc analysis of the morning BP rise that has been found to have an adverse prognostic significance also indicated that this morning surge is effectively attenuated after RDN [22].

Office blood pressure

From a physicians' and patients' perspective, efficacy of antihypertensive treatment is judged by the reduction in office BP, which is in most cases the BP value that primarily guides the physician to up and down-titrate antihypertensive medication. From a scientific perspective, we have an excellent database on the relationship between decreases in office BP and decreases in cardiac and vascular events of hypertensive patients (see below). Prospective data on the value of 24-h ambulatory BP reductions and associated cardiovascular prognosis are still lacking.

In light of these considerations, office BP changes are very informative about the BP-lowering efficacy of RDN. All second-generation sham-controlled RCTs reported superiority of RDN in reducing office BP compared with the sham group [15–19]. The decrease in the RDN groups ranged from -9.0 to -10.8 mmHg systolic and between -5.0 to -5 mmHg diastolic (Fig. 1b). In the sham group, the office BP decreased only slightly, an effect similar to the placebo effect observed in antihypertensive drug trials. In this context, it should be emphasized that, as shown by outcome-based RCTs, it is the reduction in office BP, that is the one including the sham/placebo effect, and not the difference between the two groups which is of prognostic relevance (see below).

In summary, in light of second-generation, sham-controlled RCTs, it is now established that RDN reduces consistently BP across a variety of hypertensive patients with mild to moderate as well as more severe hypertension, both

in the presence and absence of concomitant antihypertensive pharmacotherapy.

DURABILITY OF THE BLOOD PRESSURE LOWERING EFFECTS OF RENAL DENERVATION

The durability of the BP reduction with RDN has not yet been sufficiently investigated in the available RCTs all of which reported between 2 and 6 months, with the exception of RADIANCE SOLO, which reported after 12 months. In the sham-controlled RCTs, primary efficacy endpoints were BP measurements obtained at 2, 3 or 6 months after RDN, respectively. It was recommended that follow-up data of at least 12 months should provide data on the durability of the BP response [12]. But even within the RCTs, the proof of durability is challenging due to a variety of reasons. For example, in the RADIANCE-HTN-SOLO trials, standardized stepped-care antihypertensive medication was allowed for ethical reasons after primary endpoint collection at 2 month, which occurred in 65% of the RDN and in 85% of the sham group during the first 6 months of follow-up. Nevertheless, after the adjustment for number of medications, RDN reduced daytime ambulatory SBP to a significantly greater extent in the RDN than in the sham group [23]. In the RADIANCE-HTN SOLO trial, unblinding took place at 6 months and patients received antihypertensive medication at physicians' discretion. After 12 months, significantly fewer medications were prescribed in the RDN than in the sham group, whereas no difference in 24-h ambulatory BP was further noted compared with the sham group [24]. This illustrates the need to adjust for medication burden in order to properly compare the ambulatory and office BP reductions, and further emphasizes that other criteria should be developed to assess the durability of RDN.

In the international Global Symptomatic Registry (GSR) ($n=2652$, 3 years follow-up), the overall reduction in 24-h SBP at 3 years was -8.9 mmHg and for patients with resistant hypertension -8.7 mmHg [25]. Intriguingly, comparing the BP changes after 6 months, 1 year, 2 years and 3 years from RDN did not show any attenuation of BP reduction, and if any, even a slight further decrease appeared to occur. Reinnervation of the treated kidneys has been repeatedly discussed in relation to RDN. In an experimental study in sheep with hypertensive chronic kidney disease, regrowth of renal nerves and partial return of function were observed. The translation of these data into humans remains questionable. In long-term studies on patients after renal transplantation, no clinically meaningful reinnervation was observed [4].

In summary, we conclude that the antihypertensive effect of RDN in humans is durable, although reliable follow-up data are only available for up to 3 years. Thus, reinnervation does not appear to counteract to durability.

DOES RENAL DENERVATION IMPROVE CARDIOVASCULAR OUTCOME?

Long-term epidemiological studies have found a continuous log-linear association between elevated BP and

increased cardiovascular events across various population groups, irrespective of age, sex or established vascular disease [2]. Furthermore, RCTs have shown that reduction of BP by administration of BP-lowering drugs results in a reduced incidence of cardiac and vascular events, an effect that has been confirmed in large meta-analyses of RCTs with pharmacological interventions [26–28].

In 2021, no equivalent RCT is available or under way that analysed the effect of RDN on the incidence of cardiovascular events. We therefore refer to indirect evidence that estimated the BP-lowering effects of RDN on overall prognosis [26–28].

In three meta-analyses, pharmacological reduction in systolic office BP was associated with reduced incidence of major cardiovascular events, and, according to meta-regression analyses, even in a linear relationship [26–28]. A decrease of 5 and 10 mmHg in office SBP was associated with a decrease of major cardiovascular events by 10 and 20%, respectively and of stroke by 13 and 26%. This led to the concept that the protective effect of BP-lowering treatment is largely due to BP reduction *per se*, that is regardless of how it is obtained.

In the absence of outcome-based RCTs with RDN, the GSR, a worldwide database including patients after RDN with a follow-up of more than 3 years, was utilized to estimate a cardiovascular event reduction at 3 years after RDN [29]. The observed event rate in the 1749 patients with completed follow-up of 3 years was for major cardiovascular events 9.9%, and stroke 4.5%. The average decrease in office SBP over 3 years was -14.8 mmHg. This average reduction in systolic office BP was imputed in the meta-regression analysis and the relative risk reduction (estimated from the meta-analysis with pharmacological treatment [26]) was for major cardiovascular events 26% and for stroke 34% [29]. These estimates assume that baseline SBP would be maintained. Of note, the absolute risk reduction of major cardiovascular events and stroke was estimated to be 5.2% for resistant hypertension and 3.8% for type 2 diabetes [29].

In summary, on the basis of these estimates, RDN should be considered as an antihypertensive treatment option that reduces BP and contributes to improved cardiovascular prognosis of hypertensive patients.

SAFETY OF RENAL DENERVATION

Postprocedural surveillance of acute and chronic safety of device-based treatments has been recommended up to 3 years at least [9,12]. Peri-procedural adverse events comprise vascular access sites (femoral artery) related complications and unexpected events within 30 days after the procedure. In the two pivotal trials, no major device-related or peri-procedural related safety events were observed in the SPYRAL HTN-OFF MED pivotal trial and one peri-procedural adverse event (access site pseudoaneurysm successfully treated) was adjudicated in the RADIANCE-HTN TRIO trial [18,19]. Design of radial artery access systems for RDN has the potential to further diminish any vascular access site complications.

In all of the sham-controlled trials, the rates of major adverse events were similar in the RDN and sham

controlled groups and a meta-analysis of 48 study cohorts found no statistical different change in estimated GFR (eGFR) after an average follow-up of 9 months [30]. Long-term safety analyses are available from a sham-controlled trial, the RADIANCE-HTN SOLO, up to 12 months and from the Global Symplicity Registry up to 3 years, and in these data sets, no long-term safety signal has emerged [24,25]. Complying with the requirement of the Food and Drug Administration (FDA) to re-examine renal arteries with imaging techniques after 1 year from RDN will provide further safety data.

Immediately following RDN, a low incidence of acute micro-injuries was observed by optical coherence tomography and intravascular ultrasound, without any clinically significant sequelae [31]. In a meta-analysis specifically analysing renal artery adverse events (e.g. renal artery stenosis), the annual incidence of renal artery stenting following RDN was estimated at 0.20%, a rate comparable to the reported natural incidence of events in an untreated hypertensive population [32]. This analysis comprised 50 trials with 5769 patients and 10 249 years of data. Of note, in a subgroup of 396 patients from nine reports treated with radiofrequency RDN beyond the main bifurcation, no adverse events in the distal arteries were observed. In a separate analysis of 14 studies with 511 individuals using computed tomography after median of 11 months post procedure, only one significant renal artery stenosis was identified that required revascularization (0.2%) [32]. Systematic studies with imaging techniques further establish vascular safety following RDN [33].

In all of the sham-controlled RCTs, eGFR less than 40–45 ml/min per 1.73 m² was an exclusion criterion, due to initial safety concerns about possible damage to the endothelium by the energy delivery, contrast-induced nephropathy or long-term eGFR decline. Initial pilot data from a study including patients with an eGFR less than 45 ml/min per 1.73 m² reported no safety issues with RDN therapy, but due to the limited number of patients included, no statement can yet be made on the safety of RDN in patients with advanced renal impairment [4].

In summary, beyond few femoral access complications (hematoma, pseudoaneurysm), we conclude that no acute adverse safety events (e.g. acute renal failure, dissections, perforations, bleeding) were observed in the sham-controlled RCTs. Thus, RDN is considered to be a well tolerated endovascular intervention.

RENAL DENERVATION AND OPEN QUESTIONS

Several open questions in the field of device-based hypertension treatment need to be addressed [1,9,12]. Among these, identification of reliable peri-procedural and clinical predictors of the BP response to RDN represent major unresolved challenges. The waterfall plots clearly demonstrated the large variability in BP response after RDN treatment, as exemplified by the RADIANCE-HTN SOLO trial. Herein, the individual BP response in daytime ambulatory SBP at 2 months after RDN ranged from an increase in BP of more than 10 mmHg to a decrease of more than 20 mmHg in the RDN group. Similarly, a wide variation in

BP responses following RDN was observed in the other RCTs [15–19]. Baseline BP prior to RDN was the only parameter that was consistently identified to predict BP response after RDN. This phenomenon, however, has a nonspecific nature and applies to antihypertensive treatment in general. It is known as the biological law of initial value (Wilder's principle), and has also been observed with lipid lowering and blood glucose lowering treatments [34].

Intriguingly, there is an ongoing debate about whether or not patients with isolated systolic hypertension respond less to RDN. The most updated GSR analysis found no difference in office and 24-h ambulatory BP reduction in patients with isolated systolic hypertension as opposed to those with combined (systolic and diastolic) hypertension [25]. Accordingly, age above and below 65 years was not a predictor of BP response after RDN [25]. In contrast, several smaller studies identified arterial stiffness, as assessed by aortic calcification, central and brachial pulse pressure, and pulse wave velocity among others, as a predictor of poor BP response after RDN. Clearly, dedicated clinical trials in patients with isolated systolic hypertension should be conducted to examine the efficacy of RDN in this high-risk cohort.

Other suggested predictors of response to RDN have been suggested, such as number and type of medications at baseline, heart rate at baseline, abdominal obesity, plasma renin activity and aldosterone, and presence of obstructive sleep apnoea among others, but remain unconfirmed [10]. Requirements for robust identification of predictors for the BP response after RDN are, for example, to demonstrate that the inclusion of a predictor reclassifies a substantial portion of patients in terms of responders vs. nonresponders. Likewise, by applying receiver operating characteristic curves and area under the curve statistics, a substantially greater predictive value of BP response should be demonstrated by including potential predictors. In that sense, the average and standard deviation of night-time ambulatory BP has been identified as a potential robust predictor, which requires further corroboration in larger studies in both medicated and nonmedicated patients [35]. The BP response to endovascular electrical stimulation of the renal artery was used in a study to 'map' renal artery sites and identify responders, but currently, there is no evidence that this methodology can be used to provide reliable predictive information related to RDN induced BP reduction [36]. Whether genetic markers may be also of great value is currently under investigation.

Another important question relates to whether the various technologies to conduct RDN have a different benefit-risk-ratio, that is BP-lowering efficacy and safety. At the moment, RDN with radiofrequency energy and endovascular ultrasound have the most advanced programmes. The third technology, the Peregrine Catheter system (Ablative Solutions) facilitates the injection of alcohol directly in the perivascular space by three microneedles. In open-label studies, significant BP reductions were observed with this technique [37], but this has to be confirmed in sham-controlled RCTs that are currently conducted (TARGET BP OFF-MED and TARGET BP I).

So far, one open-label, single-centre study compared three groups with various technologies (Radiosound-HTN

study): Radiofrequency RDN of the main renal artery using the Spyral system was inferior to radiofrequency RDN of main renal artery as well as branches and also inferior to ultrasound based RDN [38]. However, no significant difference in BP reduction was found between radiofrequency-based ablation of the main renal arteries and subsequent side branches (as applied in the SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED Pivotal Study) as opposed to ultrasound-based RDN (as applied in the RADIANCE-HTN SOLO and RADIANCE-HTN TRIO studies). Accessory renal arteries also carry sympathetic nerves and should be treated, if the arterial diameter allows the insertion of the ablation catheter. Of note, BP decreases were found to be significantly greater when accessory arteries were treated.

In summary, extensive efforts are ongoing to identify clinical predictors of BP response and thereby to select hypertensive patients that benefit most from RDN. We recommend that open access to all individual databases of the various trials is urgently needed to perform a patient-based meta-analysis of predictors.

PATHWAY TO CLINICAL PRACTICE FOR RENAL DENERVATION

Prior to the use of endovascular device-based RDN in clinical practice, a structured approach for the implementation should be in place to inform about the selection of the appropriate patients and guarantee the best outcome from the intervention. Future guidelines will have to consider the results of the second generation, sham-controlled RCTs and the accumulating evidence that RDN safely reduces 24-h ambulatory and office BP (Fig. 1). The average reduction in systolic office BP is approximately 10 mmHg, which is estimated to reduce major cardiovascular events and, in particular, stroke by 25–30% [26–28].

Regulatory approval is a prerequisite to interact subsequently with reimbursement authorities. They have to define a threshold of cost effectiveness for device-based treatment based on established models. So far, health economic reports have been carried out, or are currently conducted regarding RDN in hypertension [39]. National healthcare costs related to hypertension and comorbidities differ significantly between the European Countries and the incremental cost-effectiveness needs to be calculated with respect to territory.

The authors want to stress that it is of great importance to establish a structured and transparent way of qualifying centres to perform RDN. In Germany, a consensus statement of the German Cardiac, Nephrology and Hypertension Society has been published on how RDN should be implemented into clinical practice [40]. RDN centres should undergo a qualifying process, in which the hospital facilities (e.g. 24-h access to diagnostics and treatment), access to qualified interventionalists (e.g. minimum of 25 interventions of the renal artery per year), capacity for comprehensive work up to select the appropriate hypertensive patients (ideally within an interdisciplinary institutional meeting) and structured follow-up of patients after RDN treatment are reviewed. Such a process should be conducted in accordance and agreement with the healthcare providers on a

national basis and may facilitate the pathway towards reimbursement of the RDN treatment.

In addition to the physicians' knowledge of hypertensive disease, patients' perspective and preference are also important determinants of controlling patients' hypertensive disease. In light of all these options for treating hypertension, patients' perspective and experiences with pharmacotherapy (efficacy as well as side effects) and preference for device-based therapy, such as RDN, needs to be respected in a shared decision process [41–43]. In an epidemiological survey, roughly one-third of hypertensive patients were prone to prefer RDN instead of pharmacotherapy to have their elevated BP controlled [41]. In particular, younger patients, male patients, those who have experienced side effects and admitted being nonadherent, were the ones that were more prone to prefer RDN over pharmacotherapy [41]. Patients' preference for RDN treatment was unrelated to the BP level and to the number of antihypertensive medications, whereas the physicians' preference for RDN is based on stage of hypertension and number of medications [42].

BOX 1: Position Statement in 2021

- On the basis of consistent results of several sham-controlled clinical trials, renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and blood pressure lowering drugs.
- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, that is to effectively reduce an elevated blood pressure and achieve blood pressure targets.
- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available up to 3 years.
- Renal denervation is an alternative or additive, not a competitive treatment strategy.
- A structured pathway for clinical use of RDN in daily practice is recommended.
- Patients' perspective and preference as well as patients' stage of hypertensive disease including comorbidities should lead to an individualized treatment strategy in a shared decision-making process, that carefully includes the various options of treatment, including renal denervation.

BOX 2: Major gaps in knowledge in 2021

- Predictors of blood pressure response to renal denervation therapy
- Predictors of RDN procedural efficacy
- Direct comparison of different ablation technologies
- Long-term durability of blood pressure lowering and safety beyond 3 years
- Safety in patients with estimated glomerular filtration rate <45 ml/min per 1.73 m²
- Randomized clinical trials in hypertensive comorbidities (e.g. chronic kidney disease, atrial fibrillation, heart failure)
- Cost-effectiveness analysis based on pivotal trials
- Patients' perspective, therapeutic preference and quality of life

In summary, we recommend a structured pathway for clinical use of RDN. As healthcare providers, physicians' perspective and patients' preference might be discrepant, we suggest to implement a standardized shared decision-making process to select the best treatment option for BP control including RDN.

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