Review

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Renal denervation in the antihypertensive arsenal – knowns and known unknowns

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Even though it has been more than a decade since renal denervation (RDN) was first used to treat hypertension and an intense effort on researching this therapy has been made, it is still not clear how RDN fits into the antihypertensive arsenal. There is no question that RDN lowers blood pressure (BP), it does so to an extent at best corresponding to one antihypertensive drug. The procedure has an excellent safety record. However, it remains clinically impossible to predict whose BP responds to RDN and whose does not. Long-term efficacy data on BP reduction are still unconvincing despite the recent results in the SPYRAL HTN-ON MED trial; experimental studies indicate that reinnervation is occurring after RDN. Although BP is an acceptable surrogate endpoint, there is complete lack of outcome data with RDN. Clear indications for RDN are lacking although patients with resistant hypertension, those with documented increase in activity of the sympathetic system and perhaps those who desire to take fewest medication may be considered.

Keywords: antihypertensive treatment, blood pressure, hypertension, refractory hypertension, renal denervation

Abbreviations: AAs, African Americans; ABT, Abbott; AF, atrial fibrillation; AHI, apnea/hypopnea index; AUC, area under curve; BAT, baroceptor activation therapy; BMI, body mass index; BP, blood pressure; CKD, chronic kidney diseases; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; DENERHTN, denervation for resistant hypertension; DREAMS, denervation of the renal arteries in metabolic syndrome; eGFR, Estimated glomerular filtration rate; ES, electrical storm; HR, heart rate; HRV, heart rate variability; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation; RDN, renal denervation; RNS, renal nerve stimulation; SAE, serious adverse events; SBP, systolic blood pressure; SD, standard deviation; VA, ventricular arrhythmia

INTRODUCTION

Renal denervation (RDN) has come of age; it has been more than a decade since RDN was first used to treat hypertension and hundreds of million dollars have been spent on researching this therapy. This effort has made it clear that RDN is not an ivory tower therapy but will have to be integrated into the antihypertensive arsenal. Thus, the practicing physician will have to know, when, where and how to resort to RDN as to achieve the greatest benefits (and the lowest risk) in each patient. Since RDN is an invasive procedure the risk/benefit ratio must be clearly defined. In the following we attempt to highlight a few clinical issues regarding the integration of RDN into the treatment of hypertensive cardiovascular disease.

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DEFINITION OF BLOOD PRESSURE ENDPOINTS

Current hypertension guidelines recommend the use of office and out-of-office ambulatory and home blood pressure (BP) measurements in the management of hypertension. These techniques have been used to evaluate the BP lowering efficacy of renal denervation as primary or secondary endpoint in the published randomized controlled trials [1–11], prospective observational studies [12–16], and retrospective clinical registries [17–20]. The primary efficacy endpoint was change in 24-h or daytime ambulatory BP except the two earlier SYMPLICITY HTN trials, in which office systolic BP at 6 months was a primary efficacy variable [1,2]. Though not considered as primary endpoint, night-time ambulatory [4,6,8–10], and home BP were also included in the secondary endpoints in several trials [1,3,9,10]. Systolic BP was exclusively used as the primary endpoint in the two SYMPLCITY HTN trials and in most of the subsequent randomized controlled trials [1,3,4,6,8–10]. Nonetheless, both systolic and diastolic BP were included as the primary endpoints in the SPYRAL HTN-OFF MED [5,6], and SPYRAL HTN-ON MED trials [7]. For both primary and secondary endpoints, usually only mean change in BP was analyzed. However, the proportion of BP response either defined as decrease or control to a target level was also assessed in the SPYRAL [5–7], and RADIANCE trials [8,9]. With regard to the duration of follow-up or timepoint of BP endpoints, BP at 6 months was the primary endpoint in most trials except that the SPYRAL [5–7], and RADIANCE trials [8,9] primarily evaluated BP lowering efficacy at 3 and 2 months, respectively. Nonetheless, BP beyond 12 months was also reported either in the publications of the principal results or subsequent analyses in several trials, such as the PRAGUE-15 [3] and SPYRAL HTN-OFF MED pivotal trials [6]. BP endpoints in the prospective observational studies and retrospective clinical registries were defined differently from the aforementioned randomized controlled trials.

First, BP was assessed only with the office measurement in the SYMPLICITY HTN-1 study [12,13], only with the ambulatory technique in the Austrian registry 18 and with both techniques in all the other studies [14–18,20].

Second, both systolic and diastolic BP were evaluated except in the RAPID study where only systolic BP was defined as the primary endpoint [16]. Third, much longer-term BP lowering effects were evaluated mostly for at least 12 months and in several studies up to 36 months [13,18,20]. Because of the possible placebo effect of the renal denervation procedure, ambulatory BP monitoring is obviously needed for the primary hypothesis testing. Whether systolic or diastolic BP is more appropriate as the primary endpoint remains under investigation.

METHODOLOGY

RDN involves catheterization of the renal arteries and using either a radiofrequency-based catheter system or ultrasound-based catheter system to ablate the nerves in the main body of the renal artery band some of its branches. Ablation results in reducing the sympathetic tone and of the activity of the renin-angiotensin-aldosterone system leading to a fall in systemic BP. Several factors have been identified to be involved in the completeness of denervation, such as the modality used (radiofrequency, ultrasound or perivascular alcohol infiltration), the number and location of ablation sites in the renal artery (proximal vs. distal artery vs. distal branches) [8,21–23]. Achieving completeness of renal nerve ablation is, therefore, considered to be key before RDN can fully be included in the arsenal of antihypertensive treatment options for clinical practice. Since the introduction of the Simplicity catheter [5], newer modalities have been designed to improve ablation.

Meta-analyses of the first generation of randomized controlled RDN studies did not show statistically significant BP lowering effects of RDN, whether or not SYMPLICITY HTN-3 [2] was included [24], and whether or not SHAM control was a part of the design [25]. However, the procedural problems that contributed to the failure of early RDN trials to lower BP could be overcome and new protocols were designed to assess the antihypertensive efficacy of RDN. The differences in design between the first ten RCTs included in the neutral meta-analyses [24,25] and the subsequent RCTs have been so extensive that it is in our opinion appropriate to distinguish between first and second generation RCTs of RDN in the treatment of hypertension [26]. The RADIOSOUND-HTN trial [27] provided the first head-to-head randomized comparison of radiofrequency-based versus ultrasound-based RDN techniques. In this trial, in patients with resistant hypertension, ultrasound-based RDN showed a larger BP reduction than radiofrequency-based RDN.

EFFICACY

RADIANCE-HTN SOLO [8] tested whether endovascular ultrasound RDN could reduce BP in patients with hypertension untreated with antihypertensive drugs for 4 weeks, whereas the SPYRAL-OFF [5] and ON MED trials [7] investigated whether RDN achieved by intravascular delivery of radiofrequency energy could reduce BP in patients off medication [5] or in patients on stable antihypertensive medication [7]. Interestingly, similar decreases in BP were obtained in RADIANCE-HTN SOLO and the SPYRAL studies (Table 1), in patients either off or on antihypertensive treatment. Thus, assuming that hidden drug use and variations in drug intake were not more common in the treatment group, RADIANCE-HTN SOLO [8] together with the SPYRAL-OFF [5] and ON MED trials [7] provide the first true trial evidence that RDN lowers BP. The designs, patient inclusion and exclusion criteria, baseline characteristics and ambulatory and office BP lowering effects were similar in all 3 trials (Table 1). The reasons for these standardizations of the protocols are likely that the same investigators were involved. Procedures were standardized and constantly improved in many aspects using the French DENERHTN study [4] as a pioneer and example to follow. The DENERHTN study also showed a 6 mmHg BP reduction compared to control [4] and these randomized studies taken together made us suggest that RDN lowers BP corresponding to one antihypertensive drug [28].

Recently SPYRAL-HTN OFF MED PIVOTAL [6], with a larger number of included patients than SPYRAL-HTN OFF

TABLE 1. Comparisons of the main characteristics (approximate average for the patients who were randomized to renal denervation and to SHAM control) and the net results of five new studies of intravascular renal denervation (Lancet 2017–2021).

Variable	RADIANCE-HTN SOLO	SPYRAL HTN-OFF	SPYRAL HTN-ON	SPYRAL OFF PIVOTAL	RADIANCE-HTN TRIO
No. randomized	146	80	80	331	136
Age (years)	54	54	53	53	53
% men	60	70	84	66	80
BMI (kg/m^2)	30	30	32	31	33
Office SBP (mmHg)	154	162	164	163	163
Office DBP (mmHg)	100	101	101	102	104
24-h SBP (mmHg)	143	152	152	151	145
24-h DBP (mmHg)	88	99	98	99	89
Net results (mmHg) expressed as difference in reductions between renal denervation and control (SHAM)					
Change Office-SBP	−6.5	**−7.7**	−6.8	−6.7	−5.0
Change Office-DBP	−4.1	−4.9	−3.5	−4.1	−4.0
Change 24h-SBP	−4.1	−5.0	−7.4	−4.1	−5.6
Change 24h-DBP	−1.8	−4.4	−4.1	−2.9	−3.0
Change daytime SBP	−6.3	−6.1	−4.0	−5.0	
Change daytime DBP	−2.6	−4.1	−4.0	−2.9	

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

MED [5], and RADIANCE-HTN TRIO [9], in which drugs for apparent treatment resistant hypertension were standardized in a 3-component single-pill (valsartan, amlodipine, hydrochlorothiazide) confirmed the significant BP reductions with RDN compared to SHAM (Table 1).

Novel results from 36 months of follow-up beyond the previously published 6 months data in the SPYRAL HTN-ON MED study (7) were recently published [129] At the outset 80 patients fulfilled the qualifying criteria and had been randomly assigned to undergo RDN ($n = 38$) or SHAM ($n = 42$). Patients and physicians were unmasked at 6 months and adjustments of medications allowed. Ambulatory BPs decreased from baseline by RDN, and were significantly lower than SHAM at 24 and 36 months, despite a similar intake of antihypertensive drugs. The medication at 36 months was 2.13 ± 1.15 (±SD) drugs in RDN and 2.55 ± 2.19 in SHAM ($p = 0.26$). Twenty-four of 31 patients in RDN and 25 of 27 patients in SHAM adhered to medication at 36 months. At 36 months, ambulatory systolic BP was ndash;18.7 ± 12.4 mmHg for RDN ($n = 30$) and -8.6 ± 14.6 mmHg for SHAM (n=32) with an adjusted difference −10.0mmHg (p=0.0039). Differences between RDN and SHAM at 36 months were −5.9 mmHg ($p = 0.0055$) for ambulatory diastolic BP, −11.0 mmHg ($p = 0.016$) for morning systolic BP, and −11.8 mmHg ($p = 0.0017$) for nighttime systolic BP. Of note, At 6 months, before unblinding, the difference in ambulatory BP was 7.7/4.1mmHg. The study reported no short-term or long-term safety issues. The authors concluded that radiofrequency RDN compared with SHAM resulted in a clinically meaningful and long-lasting BP reduction up to 36 months and that RDN could provide an adjunctive treatment modality in the management of patients with hypertension. Of note however, in SPYRAL HTN-ON MED trial, patients and physicians were unmasked at 6 months after RDN and despite the best efforts to get systolic BP to the target <130 mmHg in the SHAM group, it remained distinctly elevated at 36 months [129].

ADHERENCE TO DRUG TREATMENT

Poor adherence to drugs is very common in the management of chronic disease and it is often quite difficult to identify if not properly searched for. This is indeed a major confounder in the interpretation of the BP control in hypertension not only in clinical practice but also in clinical trials. Adherence is a dynamic process that involves compliant initiation of treatment, respect of prescribed dosages and persistence over time [29]. At each of these stages low adherence can interfere with the appropriate course of therapy. Full awareness of the multiple factors contributing to poor adherence in the management of hypertension (e.g. individual patient compliance, insufficient physician-patient interaction, adverse effects of drugs, long-term treatment, number of pills, coexistence of comorbidities) may limit its negative impact on the goals of therapy, particularly BP control [29]. In such a context, treatment simplification, as strongly recommended in the new European Guidelines

TABLE 2. Antihypertensive effects of beta-blockers, RAS blockers, calcium-channel blockers, thiazides, and renal denervation.

	Beta-blockers	RAS blockers	Calcium-channel blockers	Thiazides	Renal denervation
BP decrease, sustainability	years, decades	years, decades	years, decades	years, decades	months
BP paradox responders	yes	?	no	no	yes
BP variability	?	?	↓↓↓	↓↓	↓
BP decrease age dependent	yes	yes	no	no	yes
Heart rate	↓↓	no	no	no	↓
Plasma renin activity	↓↓	↓↓↓	?↑	↑↑	↓↓
Sympathetic activity	↓↓	↓	no	↑	↓↓
Morbidity and mortality	inconsistent evidence	↓↓	↓↓	↓↓↓	no evidence

[30] through the implementation of single-pill fixed-dose combination therapies, is currently viewed as an effective strategy to improve adherence and outcomes in the contemporary management of hypertension. One shortcoming in early clinical trials testing RDN may have been the lack of awareness regarding the impact of adherence to medical therapy. This may be responsible of uncontrolled fluctuations in BP with a subsequent misinterpretation of the efficacy of RDN [3,31].

The selection of patients as potential candidates for RDN has long been based on a presumed diagnosis of resistant hypertension, which could in fact also reflect a condition of pseudo-hypertension associated to poor adherence. For this reason, different methods to check medication taking, such as self-reported questionnaires, pill counts, clinical reports, prescription refills, electronic dispensers have been used with variable efficacy. In the most recent clinical studies, following the Consensus documents, positions of experts and of Regulatory Agencies, the detection of drugs (or metabolites) in urine specimens was implemented in clinical studies [7,30,32–35].

The assessment of the degree of adherence to the drug regimen is a key step to evaluate antihypertensive efficacy and to rule out pseudo-resistance. Clearly this has become a mandatory step for evaluating patients as possible candidates for RDN or to define the benefits due to RDN. In addition, appropriate adherence to antihypertensive drugs (>80%) may improve the results achieved with RDN. Conversely RDN may contribute to a reduction of the number of required BP-lowering agents, finally leading to treatment simplification and hence to a better compliance to therapeutic regimens.

DURATION OF THE BP-LOWERING EFFECT: DO NERVES REGENERATE AFTER RDN?

Histological examination of renal arteries of large animals proved that more complete denervation with newer devices can be obtained [36]. While more complete denervation seems associated with better short-term BP reduction, long-term data remain rather scarce. The largest international registries and sham-controlled trials report only BP data after a follow-up of 1–3 years maximum [37,129]. However, the small Oslo RDN study, that has reported the longest follow-up so far, indicates that BP lowering may not endure after longer follow-up. In this randomized study, including very carefully selected treatment resistant hypertension patients, daytime ambulatory BP increased again at 7 years follow-up after an initial decrease that sustained for 3 years, while BP was better controlled during the 7 years of follow-up in the drug treated as compared to the RDN patients [38]. These long-term findings provide important information in line with the concept that complete and persistent denervation may be crucial for BP control after RDN, but other factors including adjustments in BP-lowering medication deserve consideration. The long-term data may suggest that reinnervation of the kidney is responsible for the diminishing treatment effect of RDN.

To functionally assess the success of RDN in interrupting both afferent and efferent sympathetic signaling norepinephrine spill-over and renal 123 I-mIBG scintigraphy have been used [12,39]. These measurements can also be applied for establishing reinnervation of the kidney after RDN, but such efforts have not been reported in RDN patients to date. Most data showing that regeneration of nerves to the kidney does occur after complete denervation is derived from experimental and clinical experiences with kidney transplantation. Transplantation studies in dogs have shown that regeneration of renal nerves is completed in a time frame of 3–6 months [40]. In humans, already after a month after transplantation regenerating axons appeared distal to the graft's arterial anastomosis, according to a histologic study of 33 kidney grafts that were obtained after autopsy or surgery [41]. In this study, the number of regenerating nerves increased along with longer survival of the graft. Although histology suggest regeneration, it should be noted that discrepancies between early (partial) reinnervation and regaining sympathetic function might exist. In twelve kidney transplantation patients with a stable kidney function, renal 123 I-mIBG uptake, reflecting functional sympathetic innervation, was strongly associated with time after transplantation [42]. Yet 7 years after transplantation, uptake became comparable to nontransplanted hypertensive control patients These functional data might serve as a mechanistic explanation for the RDN findings previously discussed, where BP increased after 7 years of follow-up after initial better BP control [38].

Concerning RDN, knowledge of regeneration of the renal nerves is based on studies in large animals. Experiments in a swine model showed that progressive regenerative response occurs as early as 7 days after RDN, but at 90 days regenerated nerve tissue still displayed a disorganized architecture [43]. In sheep, it was shown that the absent renal sympathetic nerve activity after RDN, reflecting effective RDN, was completely restored after 11 months, while already after 5 months reappearance of sympathetic nerves in the renal tissue was demonstrated [44]. These studies, together with the experience from the transplantation field, indicate that both anatomical and functional reinnervation is very likely to occur after RDN, regardless of the modality used and the completeness of denervation. The time span, however, between anatomical and functional reinnervation seems to be different. Whether these observations can completely be translated to RDN patients and whether reinnervation from a mechanistic perspective is relevant for sustained BP control and associated CV morbidity and mortality awaits confirmation.

Sometimes finding from animals cannot be transferred in the humans and clinical experience also can differ from experimental results either in animals or in humans so large registries might be useful in gaining clinically useful information.

SAFETY

The three more relevant trials for the initiation of RDN in clinical practice SYMPLICITY 1, 2 AND 3, included a total of 752 patients [1,13,37]. In number 1 trial [13], one patient developed a renal artery stenosis requiring stenting, in

number 2 [1] in one patient there was an apparent progression of atherosclerosis in one renal artery that did not require any management and in the number 3 that was sham controlled there were no significant differences between the two groups of patients [37]. The excellent safety of RDN was then recognized and has also been shown in many other studies.

The second generation of RCTs was designed after the apparent failure of SYMPLICITY 3, five completed sham controlled RCTs using radiofrequency (Spyral catheter) and ultrasound (Paradise system) were found effective and well tolerated (Spyral HTN-OFF medication, Radiance HTN Solo, Spyral HTN OFF Medication Pivotal, Spyral HTN-ON Med, Radiance HTN Trio). The new catheters also showed an excellent safety [37].

With respect to changes in renal function, a meta-analysis reporting 2898 patients concluded that renal function does not significantly change up to at least 9 months after RDN [45]. The Global Simplicity Registry did not exhibit negative changes after three years [45]. Finally, the annual incidence of renal artery stenting was estimated as 0.20% similar to the incidence in untreated hypertensive population [46]

In summary RDN is a technique with an elevated level of safety provided the expertise of the interventionist is adequate.

COMPARISON TO ANTIHYPERTENSIVE DRUGS

A meta-analysis of 10 randomized clinical trials of RDN, published in 2017, generated disappointing results [24,25]. In all studies, the BP response to RDN was assessed on top of continued or optimized antihypertensive drug treatment in patients with resistant hypertension. In all 10 studies combined, the reductions in office and 24 h systolic BP averaged 3.6 mmHg (95% confidence interval, 12.8–5.6 mmHg; $P = 0.45$) and 1.0 mmHg (4.3–2.3 mmHg; $P = 0.54$). Meta-analysis of 24-h systolic BP in the 3 sham-controlled studies showed a reduction of 2.2 mmHg (4.7–0.3 mmHg; $P = 0.07$); for the seven studies without sham control, there was no reduction in 24-h systolic BP (+0.4 mmHg; 5.3 to 6.0 mmHg; $P = 0.90$). Based on these 2017 data, regulatory authorities would never approve any novel antihypertensive agent, given the small and unpredictable BP reduction and the absence of any long-term hard outcome data.

Based on the more recently generated evidence, perhaps the conclusion might be that RDN lowers BP to an extent approximately corresponding to one antihypertensive drug (Figure 1), weather RDN lovers BP is no longer a question (Figure 2). However, the constraints of RDN compared with the regular pharmacological treatment of hypertension remain staggering. RDN remains an invasive and expensive procedure, which health insurance does not cover even in the most affluent countries. RDN is a one-shot intervention, whereas the pharmacological approach can be easily tailored to a patient's profile by switching and combining drugs until the BP is controlled.

The deployment of RDN must also be viewed against the lower BP thresholds to initiate antihypertensive drug treatment and the lower targets that should be reached [47,30]. Even in treatment-resistant patients, there are pharmacological alternatives to RDN, with proven efficacy as demonstrated in the PATHWAY-2 trial (NCT 02369081) [48]. In this double blind, placebo-controlled, crossover trial, 335 patients were randomly assigned to sequential treatment with spironolactone, doxazosin, bisoprolol and placebo [48].

Eligibility criteria included: age ranging from 18 to 79 years; a seated clinic systolic pressure of 140 mmHg (135 mmHg in diabetic patients) or greater; a home systolic BP (18 readings over 4 days) of 130 mmHg or greater; and treatment for at least 3 months with the maximally tolerated doses of three antihypertensive agents. The average reduction in home systolic BP by spironolactone was 8.7 mmHg superior to placebo (95% CI, 7.7–9.7 mmHg), 4.3 mmHg superior to the mean of the other two active treatments (doxazosin and bisoprolol; 95% CI, 3.4–5.1 mmHg), 4.0 mmHg superior compared to doxazosin (95% CI, 3.0–5.0 mmHg), and 4.5 mmHg superior to bisoprolol (95% CI, 3.5–5.5 mmHg). Spironolactone was the most effective BP lowering treatment throughout the distribution of baseline plasma renin, but its margin of superiority and likelihood of being the best drug for the individual patient were greater in the lower than higher ends of the plasma renin distribution. In only 6 of 285 patients who received spironolactone, serum potassium exceeded 6.0 mmol/l on a single occasion [48].

COMPARISON TO OTHER DEVICE THERAPY

Multiple novel device-based therapies have been developed to lower BP. Most of these target sympathetic nervous system control of peripheral vascular resistance via some form of neuromodulation and/or mechanical aspects of the circulation [49]. None are yet approved for clinical use outside of clinical trials.

Baroceptor activation devices. Among the most clinically studied are implanted baroceptor activation therapy devices (BAT), originally identified as the Rheos system (CVRx, Minneapolis) [50]. This required surgical bilateral carotid sinus exposure and wrapping with an extravascular electrode connected to a subcutaneous stimulator. Baroceptor activation could be adjusted externally. Initial reports indicated sustained reductions of up to −21/−12 mmHg or more in patients taking more than three antihypertensive drugs. While this device appeared effective for many patients, serious adverse events (SAE) were unacceptably common, including operative site infection and neurologic effects. Changes in BP after discontinuing stimulation did not reach prespecified end-points and ABPM decrements after 3 months were −6/−4 mmHg, not reaching statistical significance. The Rheos system thereby failed to reach prespecified efficacy and safety endpoints in its pivotal trial. Since then, a second-generation BAT device has been developed with a lower profile, unilateral, more easily implanted, stimulating electrodes identified as 'Barostim Neo'. While this device still requires implantation adjacent to the carotid wall, it is less invasive and appears nearly as effective as bilateral stimulation. Initial uncontrolled studies of 30 patients identified an

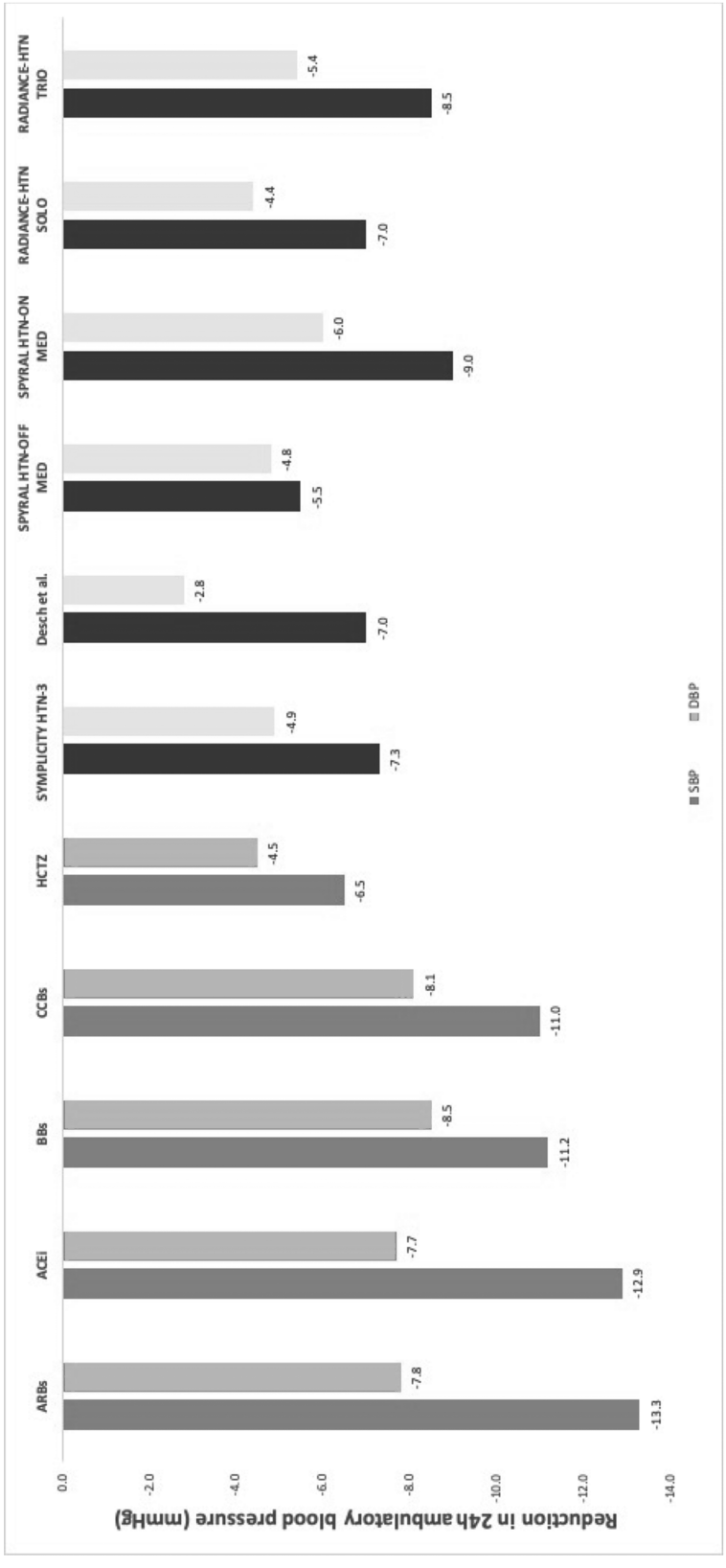

FIGURE 1 Reduction in systolic and diastolic 24 h ambulatory blood pressure (mmHg) achieved by individual antihypertensive drugs and those observed in sham-RCTs comparing renal denervation to sham intervention. Shown data available in [9,127,128]. RCT, randomized controlled trial.

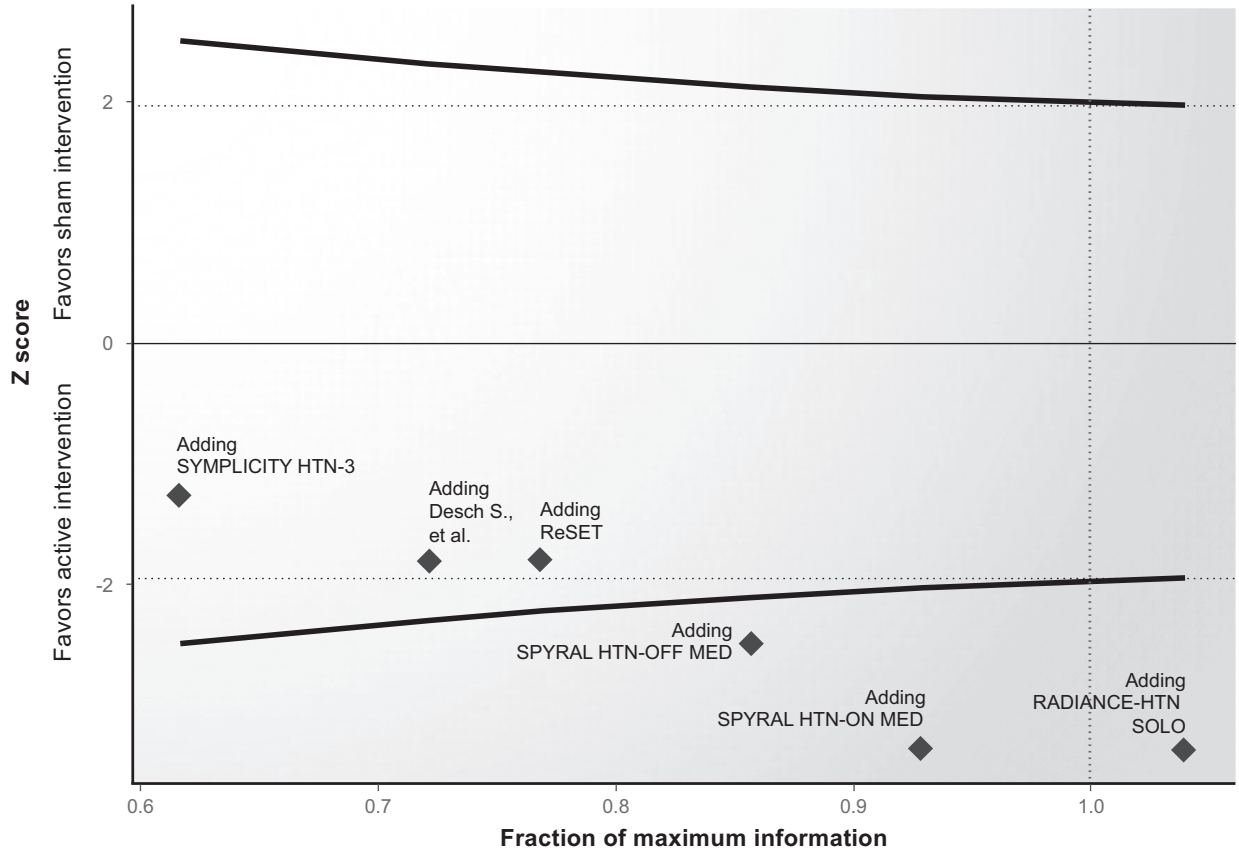

FIGURE 2 Sequential pairwise meta-analysis for mean change in 24-h ambulatory systolic blood pressure for sham-RCTs comparing renal denervation to sham intervention. Sequential pairwise meta-analysis for mean change in 24-h ambulatory systolic blood pressure is shown in the Figure for sham-RCTs comparing renal denervation to sham intervention. As heterogeneity was low, fixed effect meta-analysis was performed. The sham-RCTs were included in the sequential meta-analysis following the chronological order of publication and drawn boundaries were calculated using an adaptation of the continuous alpha-spending function. The sequential approach illustrates the trend of the accumulated evidence over time as the evidence becomes available in favor of renal denervation up to 6 months of follow-up. Crossing a boundary is indicative of strong evidence against the null hypothesis of equal mean differences between the interventions. As shown, the boundaries are already crossed following the addition of the 4th sham-RCT, with a summary mean difference favoring renal denervation of −2.76 (95% CI −4.93 to −0.59). Any additional sham-RCT available after that time-point, did not change the conclusive finding. CI, confidence interval; RCT, randomized controlled trial.

office systolic BP reduction of −26 mmHg. A long-term study of 60 patients identified ABPM reductions of −8/−5 mmHg after 24 months and reduced antihypertensive drug requirements [51,52]. Development of this device has been shifted to the management of congestive heart failure [53], although at least two investigator-initiated trials in drug-resistant hypertension continue.

Carotid sinus expanders. Devices to amplify baroceptor sensitivity have included implanted carotid sinus expanders. This device uses a unilateral, self-expanding nitinol stent (Mobius HD, Vascular Dynamics, Mountain View, CA) to increase the vascular stretch and wall strain in the carotid baroceptor leading to higher depressor responses to elevated pressures. Initial studies demonstrated reduced ABPM (−21/−12 mmHg) in 30 patients with resistant hypertension after 6 months. The long-term sustainability of BP changes has not yet been established. Implantation has been associated with some adverse effects, including some neurologic deficits thought to represent small embolic strokes [54].

Carotid body ablation. An additional approach has been carotid body ablation at the bifurcation of the common carotid artery. This has been achieved both by transvenous ultrasound via placement adjacent to the artery or unilateral surgical carotid body resection. Overall BP reductions were modest at 12 months, but half of the subjects had ABPM reductions above 10 mmHg at 3 months after surgical resection. The endovascular 'Cibiem' (Cibiem, Los Altos, CA) ablation system was found to be safe with ABPM reduction of −9/−7 mmHg at 6 months. If isolated systolic BP was excluded, ABPM fell −11/−7 mmHg [49].

Dual-chamber, rate-responsive implantable pacemaker (Moderato system, Orchestra BioMed) reduces stroke volume by changing the atrioventricular coupling interval. While this has been limited to individuals with indications for pacemaker placement, the application of programmable atrioventricular algorithms to modify BP may have promise. Further interventional neuromodulatory approaches include vagal nerve and deep brain stimulation. The latter derives from observations of autonomic sequelae in subjects undergoing DBS related to movement disorders (e.g. Parkinson's disease), chronic pain syndromes and psychiatric disorders.

Central iliac arteriovenous anastomosis by means of placement of 4 mm coupler stent lowers arterial pressure, likely in part by reducing blood volume and expanding

venous pressures. It is associated with a rise in cardiac output and reduced systemic and pulmonary vascular resistance. In a multicenter, randomized trial, there was reduction in office BP (−25/20 mmHg) and ABPM (−13/15 mmHg) as compared to no change in the control group at 12 months [55].

Similar results were observed in a subgroup of patients with prior renal denervation. Creation of these fistulae resulted in iliac vein stenoses, however, sometimes treated with venous stenting. Long-term follow up was reported to be associated with sequelae of cardiac overload and trials have been discontinued [32].

EFFECTS BEYOND BLOOD PRESSURE

HEART RATE

RDN by interrupting sympathetic activity between brain and kidney is expected to lower heart rate (HR). There are few studies that directly examine this effect. In SPYRAL HTN-OFF MED [56], Böhm *et al.* showed that at 3 months HR in RDN group was 2.5 bpm lower than in the sham group. Moreover, an HR >73.5 bpm predicted greater BP reductions. Similarly, Ukena *et al.* assessed HR with 24h-ECG at baseline and 6 months post-RDN [57]. They found that only in patients with higher baseline HR (>72 bpm), RDN had a significantly effect (−2.3 ± 7.1 bpm). They showed that in patients with high burden of premature atrial captures (PAC, ≥6/h), RDN reduced them (−12.4) too. They did not find any effect of RDN on heart rate variability (HRV). However, when assessed immediately after intervention (1 min), RDN was showed to be effective in reducing HRV [58]. There are also studies that did not show any significant effect of RDN on HR [59]. However, most of these studies suffer from some limitations, such as low patient numbers, lack of control group, lack of sham procedure, great number patients included under treatment of beta blockers, to name just few. Taken together, these data showed that RDN could be effective to lower HR only in patients with higher baseline HR and conceivably this can be used to better assess patient eligibility undergoing RDN.

EFFECTS OF RDN IN ARRHYTHMIA

Hypertension is one of the most important risk factors for developing atrial fibrillation (AF). The prevalence of AF increases with age as does arterial hypertension [60]. Sympathetic nerve activity is an important mechanism involved in the control of BP and AF [61]. RDN was shown to be effective in reducing sympathetic activity [62]. Several clinical studies have tested the hypothesis that concomitant renal denervation may improve the outcomes of catheter ablation of AF. Ukena *et al.* performed a meta-analysis in uncontrolled hypertensive patients where they assessed the effect of RDN in addition to pulmonary vein isolation (PVI) in patients with AF. Six studies with a total of 689 patients were included in the analysis. RDN was performed using a radio-frequency catheter system. They showed that concomitant RDN to PVI in patients with AF was associated with reduced recurrence rates of AF [63]. RDN performed in patients with persistent AF was shown to be effective also on ventricular HR control [64]. In another nonrandomized study (AFFORD study) where the effect of RDN (without PVI) was evaluated in 20 hypertensive patients with paroxysmal or persistent AF, the authors noted a reduction of AF burden [65]. In patients with chronic kidney disease, PVI + RDN was associated with augmentation of AF event-free rate, reduction of AF burden, and improvement of renal function [66]. However in two randomized well controlled studies (Adjunctive Renal Denervation to Modify Hypertension and Sympathetic tone as Upstream Therapy in the Treatment of Atrial Fibrillation: HFIB-1 and HFIB-2), RDN as an adjunctive upstream therapy during PVI, failed to demonstrate any benefit [67]. In contrast, the ERADICATE-AF study, a randomized clinical study (patients were randomized in PVI (using cryoballoon) alone or PVI + RDN) performed in patients with paroxysmal AF and arterial hypertension, showed that RDN when added to PVI increased the likelihood of freedom from AF at 12 months [68]. One drawback of this, as well as other studies was that no sham arm was included, as it is standard in most RDN studies performed in patients with hypertension. Moreover, as BP was not controlled, it is not known whether the antiarrhythmic effect of RDN is caused by reduction of BP per se or by BP-independent mechanisms.

Concerning ventricular arrhythmia (VA), recently Hawson *et al.* published a meta-analysis including seven studies [69], only one of them randomized [70], none of them with sham procedure, with a total of 121 pooled patients. The authors assessed the efficacy of RDN in patients with refractory VA or electrical storm (ES). RDN was shown to significantly reduce implantable cardiac defibrillator therapies, the number of VA episodes, antitachycardia pacing episodes and shocks.

Future well designed randomized studies with sham procedure and control of BP are needed to answer the question whether RDN will truly reduce the recurrence of cardiac arrhythmias.

HEART FAILURE

Chronic activation of the sympathetic nervous system is an important factor in the pathogenesis of heart failure, amenable to modulation by successful RDN. In a large animal model, renal denervation led to a significant increase in natriuretic peptides through inhibition of renal neprilysin activity whilst also modulating RAAS signaling, reducing plasma renin and angiotensin II. Similar effects were seen when administering beta-blockers in this animal model [71].

While it is intriguing to hypothesize, that RDN may serve as a treatment option for heart failure patients who do not tolerate or adhere to standard medical therapy, clinical evidence for heart failure patients with reduced or preserved ejection fraction is currently lacking.

Amongst 20 trials registered under clinicaltrial.gov, only 2 trials investigating renal denervation in heart failure patients have been completed (REACH-Pilot, RDT-PEF), 4 have been terminated early, the status for most trials ($n = 10$) is currently listed as unknown.

The REACH-Pilot study was the first to explore the effect of RDN in seven patients with chronic heart failure and a mildly reduced left ventricular ejection fraction (LVEF), averaging

43% [72]. The open-label, nonrandomized study suggested that RDN may safely be performed in heart failure patients. Symptomatic relief and improvement of 6-min walk tests were reported. The other completed trial, RDT-PEF [73], was a randomized, open-controlled, single-center study, terminated early due to recruitment difficulties. After screening 10 228 patients, 25 patients with HFpEF were randomized 2:1 between RDT and optimal medical therapy. Underpowered, the study was not able to determine the effect of RDN on the planned endpoints of QoL, exercise function, biomarkers and left heart remodeling.

A single-center report recently described that in a retrospectively identified cohort of HFpEF patients ($n = 99$, avg. LVEF 64%), RDN led to an improvement of diastolic dysfunction and hemodynamics [74]. Bias associated with the retrospective study design, lack of randomization and adequate control group – patients without heart failure served as controls, a sham procedure was not performed – require careful interpretation of these hypothesis-generating results. Evidence of RDN in patients with a reduced LVEF <40% is even more scarce, stemming from the Symplicity HF trial [75]. Designed as a feasibility study, the authors safely performed RDN in 39 patients, while observing reductions in NT-proBNP and 120-min glucose tolerance tests.

Whether RDN will ever play a role in heart failure therapy remains to be seen. In recent years medical therapies of HF have evolved, setting a high bar. Unlike RDN, pharmacological therapies have proven beneficial not merely by improving surrogate end-points, but by significantly reducing cardiovascular morbidity and mortality in large, randomized, and placebo-controlled studies.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is highly prevalent in patients with hypertension and in particular in those with apparent or true resistant hypertension [76,77]. Thus, in true resistant hypertension, OSA was found to be present in 45% of patients [77]. Considering the role of the sympathetic nervous system in the pathophysiology of the OSA-induced increase in BP [78] and the ability of RDN to reduce the sympathetic drive, it appeared reasonable to evaluate the effect of RDN on BP and sleep parameters in patients with resistant hypertension and OSA. A decrease in BP and an improvement of the apnea/hypopnea index (AHI) after RDN was first reported in a small group of 10 patients with resistant hypertension and OSA [79]. Several years later, the same authors confirmed their initial findings in a multicenter, open-label, randomized proof-of-concept trial, which compared radiofrequency-based RDN to no intervention, in 60 patients with true RHTN and moderate-to-severe OSA [80]. In this study, reductions in the apnea-hypopnea index after RDN correlated significantly with baseline AHI and baseline body mass index, but not baseline BP. In a posthoc analysis of the SYMPLICITY HTN-3 trial, renal denervation reduced the 6-month office systolic BP in 94 subjects with self-reported OSA (-17.0 ± 22.4 vs. -6.3 ± 26.1 mmHg, $P = 0.01$) with a relevant effect during the night [81]. One meta-analysis pooled available data from several small studies that had assessed the effect of RDN on OSA severity in patients with OSA and came to the same conclusions [82]. However, in another small study of 20 patients with OSA and resistant hypertension, RDN lowered BP, but did not improve sleep apnea severity [83]. The SIMPLICITY Registry included 205 patients with OSA. In this patients group, RDN induced significant 6-month reductions of both office and ambulatory systolic BP respectively by 14.0 ± 25.3 mmHg (office) and by 4.9 ± 18.0 mmHg (ambulatory) [84]. The 6-month change in SBP from baseline was not statistically different between OSA and non-OSA patients and was independent of continuous positive airway pressure (CPAP) therapy [84]. In all these studies, RDN was safe. Taken together, available data suggest that RDN may help lowering BP in hypertensive patients with OSA and might have some favorable effects on the AHI.

INSULIN SENSITIVITY AND DIABETES

A sustained activation of the sympathetic nervous system (SNS) is a common feature in patients with obesity, metabolic syndrome and type 2 diabetes [85–87]. Thus, there was also a good rational to explore the impact of RDN on glucose metabolism and insulin sensitivity. In 10 patients with resistant hypertension and OSA, Witkowski *et al.* reported a significant decrease in plasma glucose concentration 2 h after glucose administration and a reduction in hemoglobin A1 C level 6 months after RDN suggesting an improvement in glucose tolerance [79]. Mahfoud *et al.* made a similar observation with significant decreases in fasting glucose and insulin and C-peptide levels 3 months after renal denervation in patients with resistant hypertension [88]. These changes in glucose tolerance were observed in the absence of any changes in body weight or lifestyle. In a small group of patients with resistant hypertension and OSA, Daniels *et al.* found a decrease in 2 h post load plasma glucose but changes in other metabolic indices were not statistically significant [83]. RDN also improved insulin sensitivity in some nondiabetic patients with treatment-resistant hypertension [89] and in two patients with polycystic ovary syndrome [90]. However, Miroslawska *et al.*, did not confirm these findings while assessing the 6-month impact of RDN on insulin sensitivity and insulin in resistant hypertension [91]. The same authors actually confirmed the absence of significant changes in insulin resistance and plasma adipokines, 2 years after renal denervation in the same patient population [92]. The Denervation of the Renal Arteries in Metabolic Syndrome (DREAMS)-study investigated prospectively the effects of RDN on insulin sensitivity and BP in 29 patients with metabolic syndrome [93]. In this study, RDN did not lead to a significant improvement of insulin sensitivity up to 12 months after treatment. Yet, a significant reduction in ambulatory BP was observed. A review and meta-analysis investigated the metabolic effects of RDN according to the current evidence [94]. The outcomes of interest were changes in fasting glucose, insulin, C-peptide, hemoglobin A1C, homeostatic model assessment-insulin resistance, cholesterol, and triglyceride levels before versus after RDN, and also RDN versus the control group. The main conclusions were that catheter-based RDN

had no impact on glucose metabolism. However, RDN induced a statistically significant but clinically negligible improvement in HDL-C and triglycerides levels. Thus, whether RDN should be used to restore glucose metabolism and insulin sensitivity remains to be confirmed in specifically designed randomized prospective studies.

CHRONIC KIDNEY DISEASES

SNS regulates several renal functions that contribute to the regulation of BP such as renin secretion, renal tubular sodium handling and renal hemodynamics [87]. Hence, activation of the SNS, which occurs already in early stages of kidney diseases [95], plays a role in the development of hypertension and in chronic kidney disease (CKD) progression [96]. Moreover, hypertension is not only highly prevalent in CKD patients but also often resistant to treatment, needing multiple drug therapies [97]. Preliminary results from small, uncontrolled studies have shown that renal denervation safely lowers BP in CKD patients [98]. In addition, some data suggested that the procedure might retard the deterioration of kidney function irrespective of the BP effect [99,100]. Data of the global SIMPLICITY registry have confirmed that RDN is safe and effective in lowering office and 24 h ambulatory systolic BP in CKD [101]. The BP lowering effect of RDN was greater in patients without CKD than in those with CKD. However, based on the same dataset, Ott *et al.* [102] concluded that after adjusting for baseline data, 24-h systolic and diastolic ambulatory BP reductions induced by RDN were similar in patients with and without CKD, whereas office systolic but not diastolic BP was reduced less in patients with CKD. Regarding renal function, a first analysis of the SIMPLICITY registry showed that between baseline and 3 years, estimated glomerular filtration rate (eGFR) declined by 7.1 ml/min/1.73 m^2 in patients without CKD and by 3.7 ml/min/1.73 m^2 in patients with CKD, suggesting some beneficial effect of RDN on GFR [20]. However, in a later analysis, although patients without CKD had a greater decrease in eGFR during the first year after the intervention, the decline in eGFR was found to be comparable in the two groups at 3 years [102]. This observation is in line with the results of a meta-analysis of 52 studies and a qualitative review of an additional 14 studies, reporting on 2898 patients in total including all types of patients with resistant hypertension, which concluded that renal function does not change significantly up to at least 9 months after renal denervation [45].

Thus, RDN can be considered as a safe and effective way to lower BP in patients with CKD and resistant hypertension. Yet, several important information are still missing to promote this procedure in CKD:

- Firstly, we lack information on the percentage of RDN-treated patients reaching recommended BP targets as defined by recent guidelines.
- Secondly, one does not know whether RDN effectively reduces the occurrence of cardiovascular events and truly prevents the progressive loss of kidney functions.
- Lastly, data on long-term renal safety, measured with adequate methods, are still missing.

Therefore, the use of RDN in CKD should be limited to well selected patients in whom BP targets are very difficult to reach with conventional therapeutic approaches.

CLINICAL IMPLICATIONS

Several meta-analyses and systemic reviews that have been conducted to determine effects of RDN in patients with resistant hypertension yielded conflicting results. While some showed no benefit on office or 24-h ABP [24,103,104], more recent meta-analysis which includes newer trials such as RADIOSOUND and RADIANCE-HTN TRIO showed a significant reduction in 24-h ABP, particularly when RDN was conducted in both main renal arteries and the side branches [105]. The heterogeneity in the outcomes among these trials and meta-analyses are likely related to adherence to antihypertensive medications which are typically low in patients with apparently resistant hypertension [106–109].

Observation studies from hypertension referral centers and clinical trial population showed that prevalence of nonadherence, as captured by biochemical monitoring of antihypertensive drug levels, is very high between 50% and 80% [106–109]. Thus, when antihypertensive drug regimen is optimized and standardized with once daily combination therapy to maintain medication adherence throughout the study, a small benefit of RDN in improving BP control is more evident and similar in magnitude to adding an antihypertensive agent from a different class.

RDN will likely offer a similar effect on BP among patients with resistant hypertension to those with untreated hypertension but the magnitude of BP lowering is not as large as once perceived (24 h systolic BP reduction of 1–10 mmHg, office systolic BP reduction of 7–10 mmHg) [105]. This reduction will be relatively minute among those with severe resistant hypertension with baseline systolic BP of 180 mmHg or above despite 5 or more antihypertensive drugs as other factors such as secondary causes of hypertension (primary aldosteronism, obstructive sleep apnea) or unrecognized medication nonadherence are likely to have a larger role on BP control which cannot be modified by RDN.

Beyond resistant hypertension population, previous studies have also attempted to determine subgroups who are likely to benefit the most from RDN. Sex has not shown to be a predictor of RDN response in most meta-analyses. Similarly, race/ethnicity has not been shown to be predictor of response. Analysis from the SYMPLICITY HTN3, which enrolled 26% African Americans (AAs), showed that AA race did not independently predict systolic BP response in either sham or RDN [110]. The REQUIRE trial which was exclusively conducted in Japan and South Korea showed that renal denervation reduced 24-h systolic BP by 6.6 mmHg 3, which is similar to responses in non-Asian population. However, this reduction did not achieve statistical significance as the same BP response was observed in the sham controlled arm [10]. Higher baseline 24-h diastolic BP was suggested as an independent predictor of diastolic BP response after RDN [111] while presence of isolated systolic hypertension is predictive of lack of BP responses [37]. However,

subsequent analysis from the RADIOSOUND trial did not confirm this finding [11]. Secondary analysis from the SPYRAL HTN-OFF MED showed that subgroup of patients with elevated baseline heart rate of 70 beats/min experienced a significant reduction in 24-h systolic BP by 6.2 mmHg after RDN while the group with slower heart rate showed no reduction in BP when compared to sham controlled arm [112]. Another post hoc analysis from the DENER-HTN also showed that higher nighttime BP and standard deviation (SD) of nighttime systolic BP are independent predictors of BP improvement after RDN [113]. This finding from the DENER-HTN is confirmed in a recent analysis from the RADIANCE HTN-SOLO but the area under curve (AUC) calculated from the receiver operating characteristic curves of nighttime BP or SD of nighttime BP in detecting responders is modest (0.65–0.72) [114]. However, baseline heart rate was not shown to discriminate responders from nonresponders in the RADIANCE HTN-SOLO trial [8]. The inconsistent findings among these studies in identifying predictors of response maybe related to relatively small samples size from each cohort and difference in patient's baseline characteristics as well as the unmeasured confounding influences. For example, the responder group in the SPYRAL HTN-OFF MED with elevated baseline heart rate is more likely to be cigarette smokers who were not on any antihypertensive drug during the trial.

Because of heterogeneity in BP response to RDN, the cost analysis of the intervention is difficult to ascertain. In one economic analysis, addition of RDN to usual antihypertensive medication therapy is cost effective only in patients aged 60 years or older with resistant hypertension and 10-year predicted cardiovascular disease risk of at least 13.2% assuming that RDN will result in a sustained reduction in office systolic BP by 5.73 mmHg which was reported in SYMPLICITY HTN3 trial [115]. Another economic evaluation showed that the cost-effectiveness of RDN plus medical therapy compared to medical therapy alone was estimated at 408 021 euros per patient avoiding CV event at 10 years assuming a sustained reduction of ambulatory systolic BP of 5.9 mmHg based on the DENERHTN study [116].

Additional cost analysis of RDN using newer generation device is still needed to assist with shared decision making in healthcare.

Based on these clinical trials to date, RDN maybe more suitable for a selected group of patients without severe form of hypertension (systolic BP below 180 mmHg) or advanced chronic kidney disease (estimated glomerular filtration rate above 40 ml/min/m^2) who have experienced side effects to multiple drug regimen or expressed desire to take fewest medications as much as possible. Share decision making should be made with the patients and referring physicians to avoid unrealistic expectations as most patients will not achieve a 20 mmHg reduction in BP. Optimizing medication regimen and screening for secondary hypertension should be routinely performed prior to consideration for this procedure as it was conducted in most sham-controlled trials with successful outcomes [4,9].

A somewhat more promising approach in predicting the antihypertensive response seems to be renal nerve stimulation (RNS)-induced BP increase before and after RDN. De Jong *et al.*, in a small study documented that RNS-induced maximum BP increase before RDN had a correlation of $R = 0.61$ ($P = 0.020$) for systolic and $R = 0.71$ ($P = 0.004$) for diastolic ABPM changes 3–6 months after RDN [117]. The drawback is that RNS must be performed under general anesthesia at 4 sites in the right and left renal arteries.

GUIDELINES

Summarizing what International Hypertension guidelines say about renal denervation for the treatment of hypertension is straight forward, they do not say very much. The evaluation of treatment of hypertension with drug therapy, through randomized clinical trials is one of the most studied areas in clinical medicine. Guideline developers have benefited from a wealth of data from clinical outcome trials, demonstrating the effectiveness of drug treatments at reducing cardiovascular morbidity and mortality. Consequently, this has become the gold standard for recommending a new treatment. This is a high bar for new device-based treatments such as renal denervation because the studies with device-based treatments have been relatively small and of short duration, thus, assessing the impact of the intervention on morbidity and mortality has so far, been impossible, and is unlikely to happen. It could be argued that BP lowering per se, is a powerful surrogate for future benefit, irrespective of the means of achieving it. This concept has been applied to treatment recommendations in existing guidance for most lifestyle interventions advocated for hypertension, and also for the drug treatment of resistant hypertension. However, drug therapy for hypertension is now largely generic and low cost and economic considerations assume increasing importance in guidelines. To this end, the BP lowering efficacy of renal denervation appears modest, and the predictability (i.e. who will respond?) and durability of any BP lowering response remains uncertain. The inconsistency in the findings of some of the early RCTs also fueled concern about the efficacy, at the time major guidelines in the US and Europe were being developed for release in 2017 and 2018 respectively. This has been compounded by the recognition that much of the so called 'unmet need' to address poor BP control rates, relates to untaken medication, i.e. problems of adherence to multipill drug treatment, and that the recommendation in current guidelines advocating for wider use of single pill combinations of therapy should begin to address deficiencies in BP control. Mindful of all these considerations, none of the existing hypertension treatment guidelines across the world formally recommend renal denervation for routine clinical use to treat hypertension, outside of the context of clinical trials. Most of the current international hypertension guidelines have not even considered or commented on renal denervation for the treatment of hypertension. The position of various guidelines covering all regions of the world are summarized the table below. Whether this will change when new guideline committees begin considering their guideline updates, remains open to question because the challenges outlined above

Hypertension guideline	Year of publication	Recommendation on renal denervation	Recommendation grading
Dutch Society of Internal Medicine – Guideline for hypertension treatment in the 2nd and 3rd line care	2012	Use of device-based therapies is not recommended for treatment of hypertension	Very low: (GRADE)
Australian National Heart Foundation Hypertension Guideline	2016	Not reviewed or discussed	N/A
American College of Cardiology/American Heart Association Hypertension Guidelines	2017	Not reviewed or discussed	N/A
Guidelines on the management of arterial hypertension and related comorbidities in Latin America	2017	Renal denervation mentioned in discussion of resistant hypertension but suggested results of ongoing trials required and no formal recommendation	N/A
European Society of Cardiology/European Society of Hypertension Clinical Practice Guidelines for the Management of Arterial Hypertension	2018	Use of device based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available	III C
Chinese Hypertension Guideline	2018	Not reviewed or discussed	N/A
NICE (UK) Hypertension Guideline 2019	2019	Not reviewed or discussed	N/A
Japan Hypertension Guidelines	2019	Comment..... But no formal recommendation	N/A
Hypertension Canada	2020	Not reviewed or discussed	N/A
International Society of Hypertension	2020	Not reviewed or discussed	N/A

REGULATORY AGENCIES

A recent European Society of Hypertension position paper confirms the long-term safety (at least 3 years) and efficacy of RDN [118]. Although RDN is approved in Europe, commercialization has been limited and there is no approval in the United States, Japan, or Australia. RDN has recently been noted to demonstrate marked improvement in outcomes from the disappointing results of Medtronic's first pivotal, randomized, blinded trial against a sham procedure in 2014. Since that time, advances in technology and newer data have confirmed the potential for regulatory approval and commercialization in the near future for the Medtronic Spyral Catheter and potentially other devices. Nevertheless, at the present time, the Medtronic Symplicity device is the only RDN system commercially available globally and has regulatory approval in over 60 countries. Although other devices also have CE Mark approval in Europe, there is no significant commercial RDN use in any geography or marketing commercial despite regulatory approval [119].

In addition to Medtronic, two smaller competitors: ReCor Medical/Otsuka and Handok Kalos may be considered for regulatory approval in the future. ReCor's Paradise is an investigational device in the US, but approved for sales in the EU and bears a CE mark. In addition, Medtronic's on-medication large-scale study is expecting results in 2021∗, which could support FDA approval along with earlier HTN Off-Med trial results [120].

It is most probable that any FDA approval will be for the use of RDN in combination with antihypertensive pharmacotherapy. Most promising is Medtronic's Symplicity Spyral, which may be considered for FDA approval in late 2022. On the other hand, other competitors may not be in position to seek FDA approval as urgently.

Earlier catheters from both Boston Scientific (BSX) and Abbott (ABT) do not appear to be on track for US authorization. Although ReCor Medical may follow Medtronic's submission to the FDA for its RDN system shortly, despite breakthrough device designation, the company may need more robust data to get final approval. The FDA Breakthrough Devices Program is designed to help patients get more timely access to newer therapies and technologies for life-threatening or irreversible diseases [118].

ETHICAL ASPECTS

The advent of new biologicals and technologies has revolutionized medical research and treatment. Ethical research on these modalities requires clinical equipoise; i.e., uncertainty within the expert medical community about whether the new treatment is preferred to established ones [121]. Once efficacy has been demonstrated, use of the new treatment in the clinic is guided by the analogous concept of benefit/risk ratio. In certain circumstances, the prognosis of the disease is so dismal that it is perfectly ethical for the physician to offer high-risk, even potentially fatal therapies (e.g., new biologicals for incurable cancer), whether the patient ultimately accepts them or not.

How do we apply ethics to renal denervation? Once proof of concept trials confirmed BP reduction without or with concomitant medications, its potential benefit became the reduction of risk from incompletely controlled hypertension. However, although to be expected from experience with other antihypertensives, improvement in outcomes has not been demonstrated yet and additional putative benefits (insulin resistance, arrhythmia, sleep apnea, renal function) remain to be proven.

Downsides of RDN include 20–30% of nonresponders who cannot be preidentified, modest BP reduction like that of drug monotherapies, diminished effect in isolated systolic hypertension, increasing salt-sensitivity of BP [122], and the possibility of long term reinnervation discussed above. Although generally safe, RDN is still a costly and invasive procedure. Access artery hematomas and pseudoaneurysms, renal artery dissections, plaque progression and stenoses, and acute renal injury have been described. Not enough follow-up is available to assess long-term (decades) risk of ischemic nephropathy or renovascular hypertension.

The benefit/risk ratio for RDN in resistant hypertension may prima facie be considered analogous to the cancer example above, because of the very high cardiovascular risk of this population despite four-drug treatment [123,124]. However, up to 50% of these subjects are misdiagnosed (poor BP recording technique, white coat effect, high-salt diet, use of pressors), have a treatable secondary cause, or have not been given proven drug therapies such as spironolactone or amiloride [125,126]. Also, nonadherence to therapy must be ruled out (e.g., ambulatory BP monitoring after witnessed intake of medications). Provided a diagnosis of true resistant hypertension is thoroughly made, RDN appears to be an ethical choice in these patients.

What about patients who refuse drug therapy or escalation because of 'intolerance', 'multiple allergies', or unspecified reasons? They present an ethical conundrum, and it is likely that regulatory agencies will recommend a process (evaluation by allergist and desensitization, psychiatric evaluation, etc) before RDN is offered as an alternative therapy. When recommended, the consent process should go well beyond the pro-forma, usual preprocedure documentation, with a thorough discussion of known and unknown risks by the recommending physician.

Proof of concept has required clinical trials in which RDN was given to otherwise untreated hypertensive patients. However, ethical use of RDN as first line therapy in the clinic is trumped by the more than one hundred efficacious drug therapies for which there are outcome data. Although RDN BP responses are larger in untreated patients than in those with resistant hypertension, they are still not larger than those of drug monotherapies and lack outcome data.

Ultimately, regulatory agencies will dictate the indication for clinical use of RDN. They will likely use the differential characteristics of the patient groups defined above in making such determination. Currently, from an ethical point of view, RDN can be justified in 'end of the rope' situations in selected patients with resistant hypertension. In contrast, in the great majority of hypertensive patients, RDN's benefit/risk ratio is tilted against its ethical use.

UNRESOLVED CLINICAL ISSUES

1. Unpredictability of antihypertensive response. Despite some few markers (such heart rate, renin, renal nerve stimulation) it remains clinically difficult to predict who responds to RDN and who does not, and who even has a paradoxical increase in BP.
2. Paltry overall decrease in BP. RDN lowers BP to an extent approximately corresponding to one antihypertensive drug.
3. Duration of antihypertensive effect. Safety data on RDN are available for up to 3 years and in CKD, but long-term efficacy data in terms of BP reduction are still unconvincing.
4. Renal reinnervation with time? Experimental studies indicate that anatomical and functional reinnervation is very likely to occur after RDN, regardless of the modality used and the completeness of denervation.
5. Can RDN be repeated? If so, how often? Does repeated RDN lead to scarring of renal arteries? At present there are only anecdotal data on this question.
6. Synergism/antagonism with antihypertensive drug classes. As long as the antihypertensive response to RDN cannot be predicted, potential synergism/antagonism with drug therapy remains an educated guess.
7. Reversibility of antihypertensive effect when there is risk of hypotension. In contrast to standard antihypertensive therapy RDN effects cannot be adjusted when BP becomes too low.
8. Absence of outcome data. Although BP is an acceptable surrogate endpoint, some drug classes are known to reduce outcome less well than others. This is particularly true for drugs interfering with the sympathetic nervous system.

TAKE HOME MESSAGE

RDN lowers BP at best to an extent approximately corresponding to one antihypertensive drug. However, the constraints of RDN compared with the regular pharmacological treatment of hypertension remain staggering. RDN is an invasive and expensive procedure, which so far has not been approved by many regulatory agencies including the FDA and is not covered by most health insurances. Clear indications for RDN are lacking although patients with resistant or refractory hypertension and those who desire to take fewest medication possible may be considered. Similarly, selected hypertensive patients exhibiting disorders characterized by increased activity of the sympathetic nervous system such as certain arrhythmias, heart failure, obstructive sleep apnea, insulin resistance, chronic kidney disease may be good candidates for RDN. Despite a history of >10 years RDN outcome data are lacking. At present RDN remains a one-shot intervention, whereas the pharmacological approach can be tailored to a patient's profile by switching and combining drugs until the BP (or sympathetic activity) is titrated to the desired level.

The present review documents that more than a dozen years of intense RDN research has provided us with some solid knowns and research will continue to tackle the known unknowns. However, in the ongoing RDN saga, as always in science, there will be many unknown unknowns. (Box 1).

Box 1 Take home message

- RDN lowers BP at best to an extent approximately corresponding to one antihypertensive drug. However, the constraints of RDN compared with regular pharmacological treatment of hypertension remain staggering.
- RDN is an invasive and expensive procedure, which so far has not been approved by many regulatory agencies including the FDA and is not covered by most health insurances.
- Clear indications for RDN are lacking although patients with resistant or refractory hypertension and those who desire to take fewest medication possible may be considered.
- Similarly, selected hypertensive patients exhibiting disorders characterized by increased activity of the sympathetic nervous system such as certain arrhythmias, heart failure, obstructive sleep apnea, insulin resistance, chronic kidney disease may be good candidates for RDN.
- Despite a history of >10 years RDN outcome data are lacking. At present RDN remains a one-shot intervention, whereas the pharmacological approach can be tailored to a patient's profile by switching and combining drugs until the BP (or sympathetic activity) is titrated to the desired level.

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