

## THE PRESENT AND FUTURE

### JACC STATE-OF-THE-ART REVIEW

# Renal Denervation Update From the International Sympathetic Nervous System Summit



## JACC State-of-the-Art Review

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### ABSTRACT

Three recent renal denervation studies in both drug-naïve and drug-treated hypertensive patients demonstrated a significant reduction of ambulatory blood pressure compared with respective sham control groups. Improved trial design, selection of relevant patient cohorts, and optimized interventional procedures have likely contributed to these positive findings. However, substantial variability in the blood pressure response to renal denervation can still be observed and remains a challenging and important problem. The International Sympathetic Nervous System Summit was convened to bring together experts in both experimental and clinical medicine to discuss the current evidence base, novel developments in our understanding of neural interplay, procedural aspects, monitoring of technical success, and others. Identification of relevant trends in the field and initiation of tailored and combined experimental and clinical research efforts will help to address remaining questions and provide much-needed evidence to guide clinical use of renal denervation for hypertension treatment and other potential indications. (J Am Coll Cardiol 2019;73:3006-17)  
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The initial results from the Symplicity HTN-1 (1) and HTN-2 (2) trials moved catheter-based renal denervation (RDN) on to center stage in the cardiovascular field. In these initial trials, RDN was demonstrated to be safe and effective in lowering blood pressure (BP) in subjects with resistant hypertension via a reduction in renal and central neural sympathetic activity (3,4). However, the sham-controlled Symplicity HTN-3 trial (5) failed to demonstrate superiority of RDN in reducing BP compared with a sham group at 6 months post-procedure. These unexpected findings have been discussed extensively and controversially in the published literature. The failure of the trial was attributed to several possible confounding factors, including issues related to patient selection and medication adherence, suboptimal procedural performance, and operator experience (6,7). The Symplicity HTN-3 results significantly affected other research studies and clinical trials in the field. It was not rectified until the multicenter, randomized-controlled DENERHTN (Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension) study showed a clear signal for supremacy of RDN and a standardized stepped-care antihypertensive treatment approach over the same standardized stepped-care antihypertensive treatment alone (8). Importantly, the prevalence of nonadherence to antihypertensive drugs at 6 months was high (~50%), but was not different in the renal denervation and control groups (9) in this study.

Nonadherence to antihypertensive medications is highly variable over time in clinical trials (10,11). Tomaszewski et al. (12) demonstrated that a significant proportion of patients in a specialist center show at least some degree of nonadherence that correlates with their BP. Furthermore, patients with undeclared/unrecognized nonadherence frequently undergo numerous additional diagnostic tests in

specialist centers to identify the causes of their apparent poor response to antihypertensive medications (12). The SPYRAL HTN-ON MED (Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomized trial) proof-of-concept randomized trial (13) showed adherence rates of ~60% and variation for individual patients throughout the study.

A recent study suggested that patients with apparent treatment-resistant hypertension should be formally evaluated for nonadherence prior to any further changes in medication. Indeed, the investigators observed a mean drop in 24-h ambulatory BP monitoring of 19/9 mm Hg after supervised administration of antihypertensive medications, highlighting the potential utility of “directly observed therapy” clinics (14). Poor adherence with prescribed medication in general may be considered an expression of patient’s preference, which could potentially be overcome by alternative one-off interventions such as RDN (15,16).

More than a decade after the publication of the original proof-of-concept study, 4 important recent trials have sparked renewed interest in RDN: the DENERHTN trial (8), the SPYRAL HTN-OFF MED (Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications [SPYRAL HTN-OFF MED]: a randomized, sham-controlled, proof-of-concept trial) (15), and RADIANCE-HTN SOLO (Endovascular ultrasound renal denervation to treat hypertension [RADIANCE-HTN SOLO]: a multicenter, international, single-blind, randomized, sham-controlled trial) (16) trials in drug-naïve hypertensive patients, as well as the SPYRAL HTN-ON MED trial (13) in hypertensive patients on concurrent antihypertensive therapy. All

#### ABBREVIATIONS AND ACRONYMS

**DOCA** = deoxycorticosterone acetate  
**DS** = Dahl salt-sensitive  
**RDN** = renal denervation  
**RSNA** = renal sympathetic nerve activity  
**RVLM** = rostral ventrolateral medulla

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demonstrated a convincing and clinically significant reduction of ambulatory BP in comparison with respective sham control groups (Figure 1). Evidence is therefore now available from 3 consecutive and adequately designed, randomized, sham-controlled trials confirming the BP-lowering efficacy of catheter-based RDN approaches (17).

With pivotal trials now underway for several RDN devices, it is perhaps pertinent for the hypertension community to develop strategies on exactly how to best allocate the limited resources to ensure the availability of RDN for those individuals who are likely to benefit most. To achieve this goal, intensive research efforts are required to address the most critical unresolved issues (Central Illustration). These issues and related recent research findings are discussed in the following text.

### MECHANISMS OF RDN-INDUCED BP LOWERING

**RENAL EFFERENT NEURAL SIGNALING.** The renal efferent sympathetic nerves are mostly adrenergic (18). Norepinephrine release mediates vasoconstriction of the renal vessels, as well as sodium and water

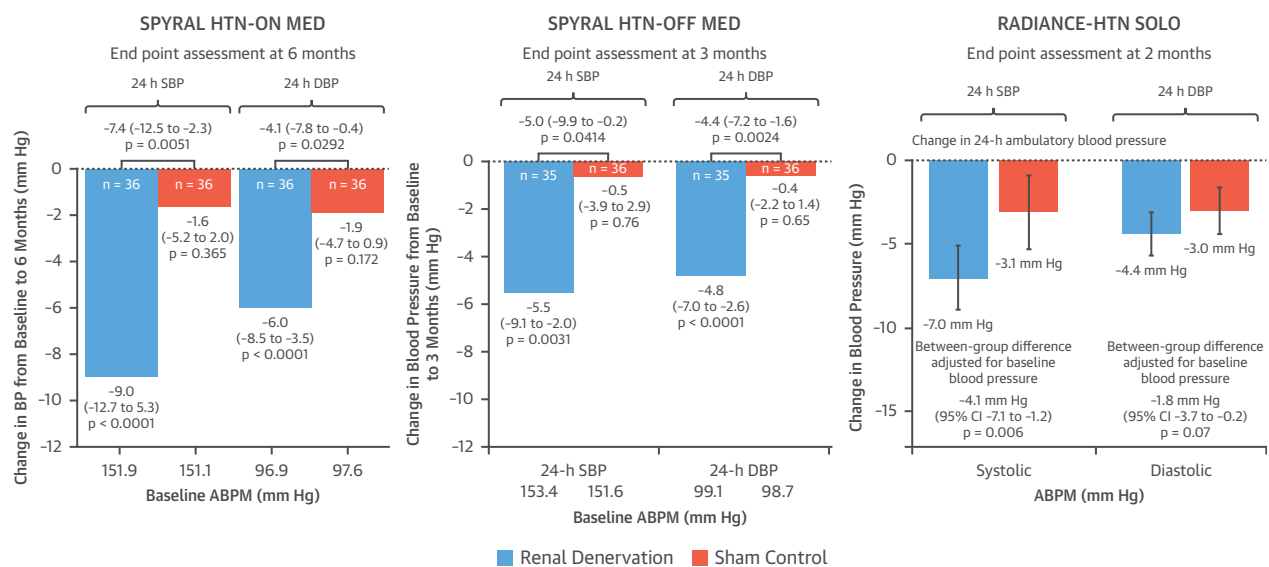
### HIGHLIGHTS

- Sympathetic nervous system activation is a key contributor to elevated BP.
- Catheter-based RDN reduces BP in both treated and drug naïve patients.
- Improved trial design, patient selection, and optimized procedural approaches contributed to these positive findings.
- Future research will focus on reducing the variability of the BP response and indications beyond hypertension.

reabsorption at renal tubular epithelial cells, and renin release from juxtaglomerular cells (19).

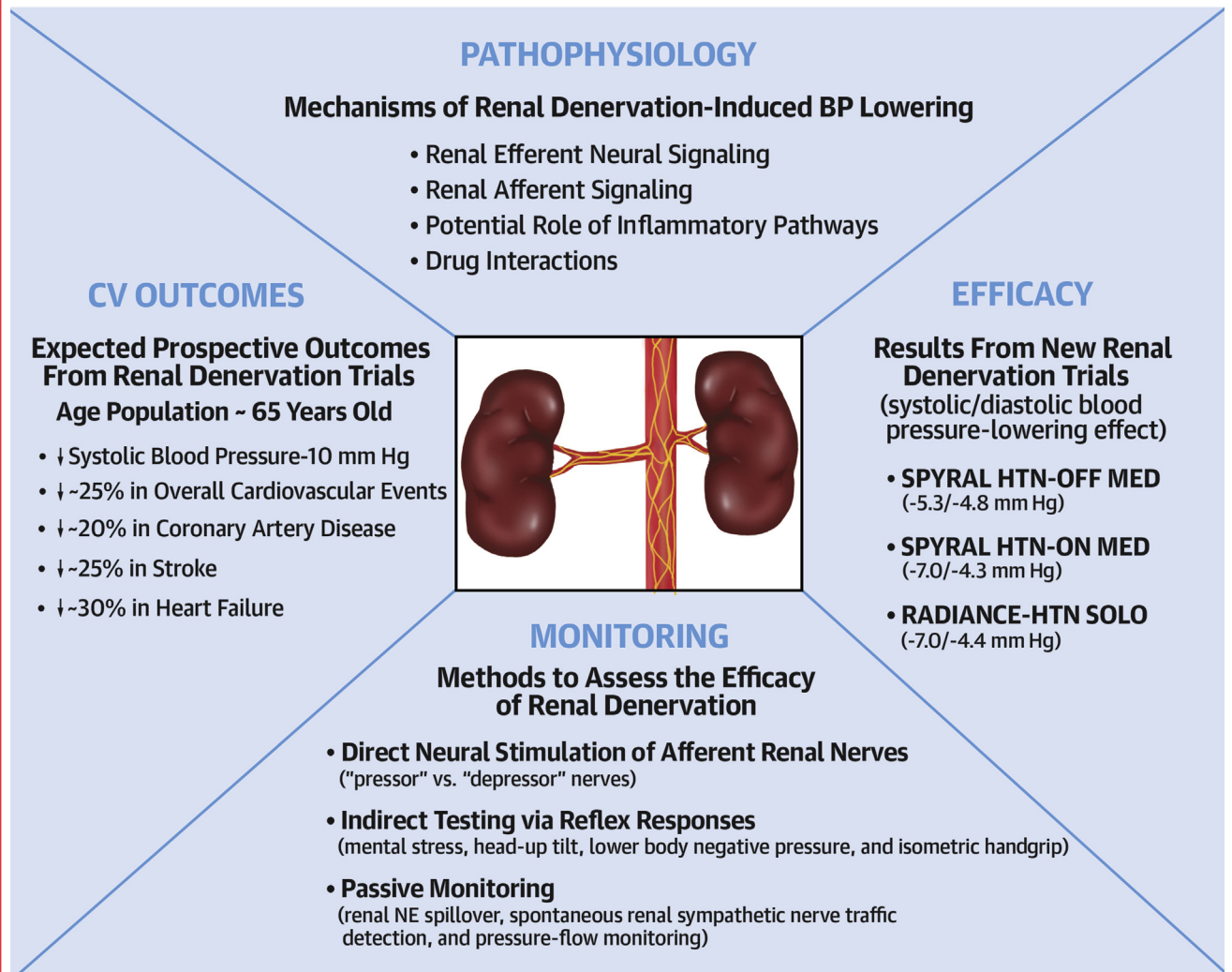
Interference with the neural drive to the kidneys by global suppression of central sympathetic outflow through chronic electrical activation of the carotid baroreflex (20) or by renal-specific sympatho-inhibition through RDN has been shown to abolish hypertension (21). RDN increases renal sodium and water excretion by suppressing sympathetically mediated renin secretion and/or renal tubular sodium

**FIGURE 1 Results From Recent Renal Denervation Randomized, Sham-Controlled Clinical Trials**



Comparison of changes in 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) in renal denervation versus sham-control groups in 3 recent randomized, sham-controlled clinical trials. Reprinted with permission from Kandzari et al. (13), Townsend et al. (15), and Azizi et al. (16). ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CI = confidence interval; SPYRAL HTN-ON MED = Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomized trial; SPYRAL HTN-OFF MED = Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomized, sham-controlled, proof-of-concept trial; RADIANCE-HTN SOLO = Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicenter, international, single-blind, randomized, sham-controlled trial.

**CENTRAL ILLUSTRATION** Areas of Ongoing Research in the Field of Renal Denervation

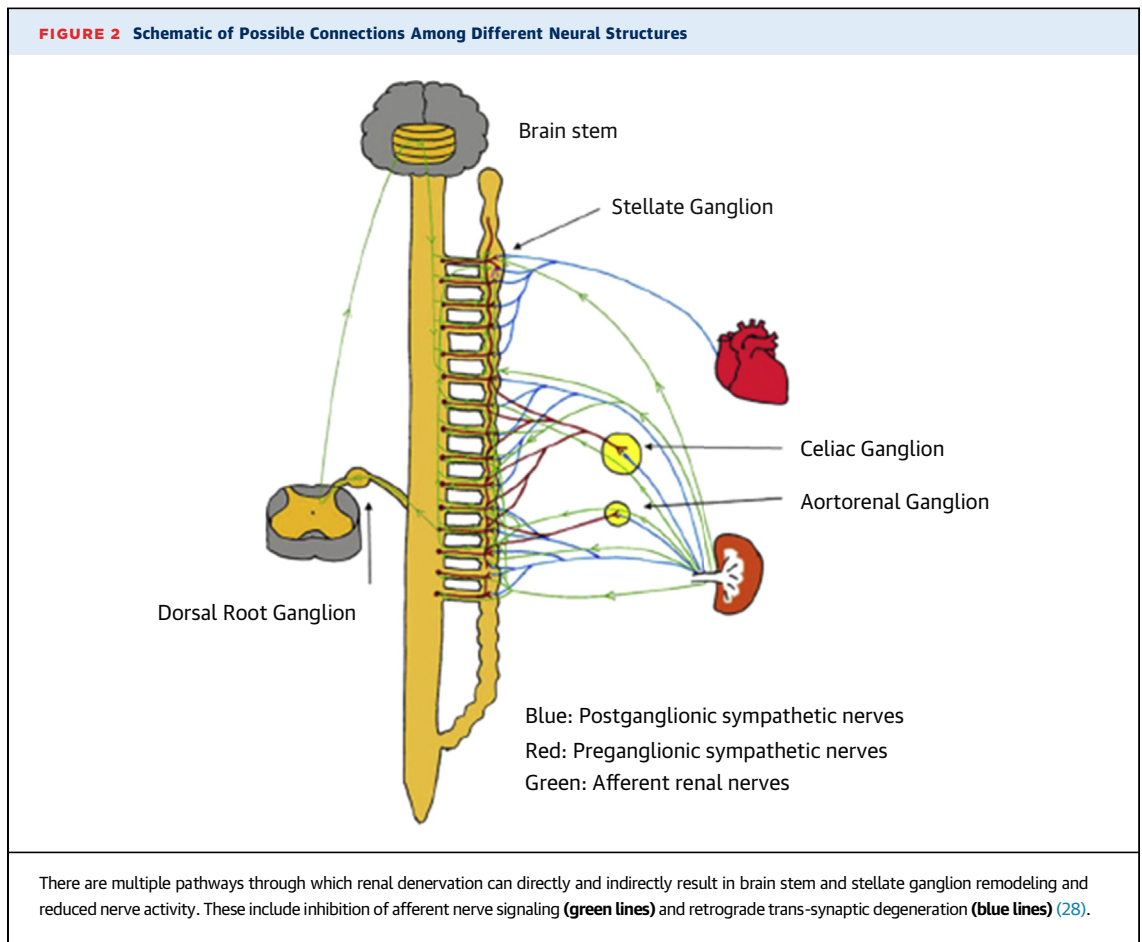


Kiuchi, M.G. et al. *J Am Coll Cardiol.* 2019;73(23):3006-17.

BP = blood pressure; NE = norepinephrine; RADIANCE-HTN SOLO = Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicenter, international, single-blind, randomized, sham-controlled trial; SPYRAL HTN-ON MED = Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomized trial; SPYRAL HTN-OFF MED = Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomized, sham-controlled, proof-of-concept trial.

reabsorption (22). However, Foss et al. (23) found no differences in daily or cumulative sodium and water balance between sham and RDN rats. This is consistent with previous reports that RDN decreases BP in normotensive Sprague Dawley rats independent of sodium balance or renin release (24,25). It is important to note that RDN did not affect the salt sensitivity of arterial pressure in Sprague Dawley rats (22) or Dahl salt-sensitive (DS) rats. Combined with their

findings that afferent renal nerves do not play a role in the DS rat model, these data point toward reduced activity of the renin-angiotensin system and possibly reduced renal vascular resistance being involved in the antihypertensive effect of RDN in the DS rat (26). In a canine model of obesity hypertension, the abolition of hypertension by RDN emphasized the importance of increased renal sympathetic nerve activity in the pathogenesis of obesity-induced

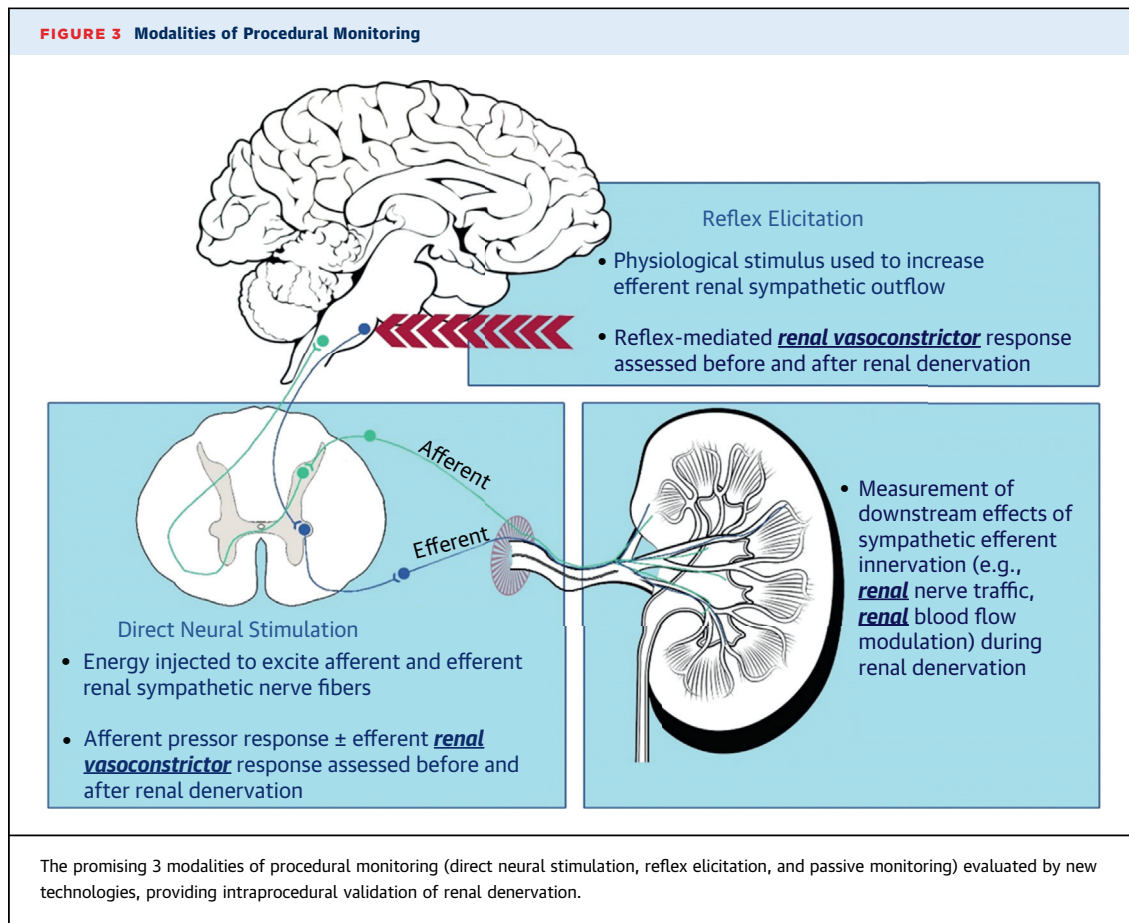


hypertension, and highlighted the role of renal-specific suppression of sympathetic activity in mediating the antihypertensive effects of baroreflex activation. The chronic neurohormonal responses to prolonged baroreflex activation and bilateral RDN in this experimental model suggested that the inhibition of the renin-angiotensin system contributes to the sustained BP-lowering during both global and renal-specific sympathoinhibition (21).

The rostral ventrolateral medulla (RVLM) is an important regulator of efferent renal sympathetic nerve activity (RSNA). The level of RSNA is reliant on the neuronal activity in sympathetic premotor nuclei in the brainstem and hypothalamus, including the RVLM and rostral ventromedial medulla as well as the paraventricular nucleus. The notable reduction in BP after the destruction of premotor neurons in the RVLM highlights its importance (27). Inhibition of RSN signaling after RDN with downstream effects on the renin-angiotensin system cascade are likely contributors to the BP-lowering efficacy.

**RENAL AFFERENT SIGNALING.** Recently, Tsai et al. (28) demonstrated in ambulatory canines that bilateral RDN, possibly via interrupting afferent renal innervation, led to substantial brain stem and bilateral stellate ganglion remodeling at 8 weeks post-procedure. These changes were associated with reduced  $^{18}\text{F}$ FDG-uptake in the brainstem, left stellate ganglion nerve activity, and atrial tachyarrhythmia events. The authors concluded that neural remodeling in the brain stem and stellate ganglion may partially explain the described anti-arrhythmic effects of RDN (28).

Trans-synaptic degeneration is a phenomenon in the central and peripheral nervous system that may remain active both at the level of the insult and in remote brain structures for as long as 1 year after a trauma (29). These progressive alterations may underlie some of the long-term functional consequences after initial injury (i.e., RDN) as shown in Figure 2, which summarizes the various direct and indirect connections between renal sympathetic nerves and the stellate ganglion. Meckler et al. (30) showed that



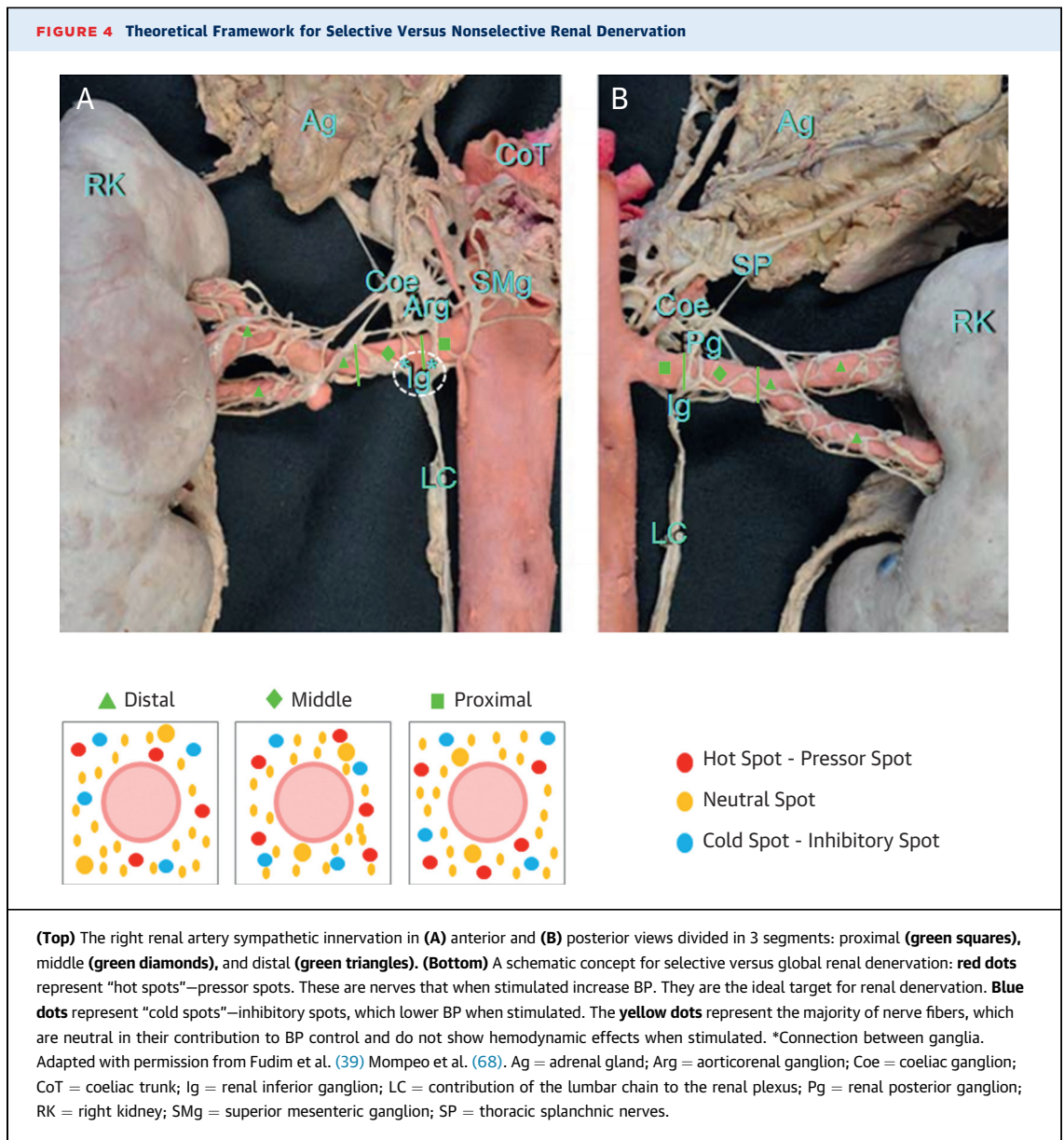
approximately 10% of renal sympathetic neurons in cats originated from the thoracic chain ganglia. In view of the connections between these 2 structures, RDN may directly result in retrograde cell death of the stellate ganglion. Furthermore, the application of fluorescent dyes in the renal nerves results in fluorescent labeling of the sympathetic cell bodies in paravertebral and prevertebral ganglia (31-33).

Because the sympathetic preganglionic neurons that project to the stellate ganglion are dispersed in spinal cord segments T1 to T10 (34), there is ample opportunity to inter-relate with the preganglionic cells that link indirectly with sympathetic nerve fibers surrounding the renal arteries. However, it is likely that some other pathways contribute to the trans-synaptic degeneration (28), because the ganglion cells of renal afferent nerves situated in thoracic and lumbar spine dorsal root ganglia also link to the posterior and lateral hypothalamic nuclei and the locus coeruleus (35,36). Overall, these findings indicate that persistent effects of RDN may well be mediated by remodeling of critical brain stem areas and the stellate ganglia.

### METHODS TO ASSESS THE EFFICACY OF RDN

Unlike coronary interventions, current RDN devices provide no feedback to the interventionalist regarding technical success of the procedure. As a consequence, the degree of denervation varies widely (37), and inadequate renal denervation was likely implicated in the failure of Symplicity HTN-3 to show a BP benefit beyond that of a sham control procedure (5,6). Despite more recent positive clinical trials (13,15,16) intraprocedural validation of adequate renal sympathetic nerve ablation remains a fundamental challenge in the field.

Validation of successful RDN in preclinical studies has been achieved in a number of ways, including assessment of histopathology, direct neural stimulation, reflex elicitation, and passive monitoring (Figure 3). Although histopathology is considered the gold standard for validation of RDN in preclinical studies, this approach is unsuitable in patients. Three other modalities are the subject of exciting new developments that may translate to the clinic to provide intraprocedural validation of RDN.



**DIRECT NEURAL STIMULATION OF AFFERENT RENAL NERVES.** Although the BP variability could merely be due to differences in the level of RDN that has been achieved in individual patients (i.e., “completeness” of nerve damage), another possibility is that some of these renal nerve fibers may act as “pressor nerves,” that is, promoting increases in BP when activated, whereas activation of sympatho-inhibitory afferent “depressor nerves” may lead to a fall in BP. Predominant ablation of *pressor nerves* would be expected to produce the largest fall in BP, whereas ablation of *depressor* nerve fibers might result in no effect or even a rise in BP after RDN. The

net effect on BP may therefore vary substantially. Although currently mainly a theoretical working concept without exact knowledge about spatial arrangement of these fibers and other anatomic and physiological features, identification of potential “ideal” ablation sites appears highly attractive.

It is possible to activate renal nerves using a catheter placed in the renal artery (38). Sites in the renal artery that upon stimulation do not exert an acute BP rise (or even a BP fall) may reflect areas of convergence of sympatho-inhibitory (*depressor*) nerves, the ablation of which should ideally be avoided. In contrast, those sites at which stimulation results in a

clear BP rise (*pressor nerves*) would be considered preferential ablation sites. Clearly, with unselected RDN, the possibility of ablating sympatho-inhibitory depressor (cold spot) or neutral (neutral spot) nerve fibers seems likely and may counteract BP-lowering effects achieved by ablating pressor nerves (hot spots) (39) (Figure 4).

Lu et al. (40) reported that renal nerve stimulation in both proximal and middle regions of the renal artery in dogs promptly increased systolic BP >10 mm Hg. However, during stimulation of the distal portions of the renal artery, BP did not increase. Only the proximal “responsive” sites were ablated and resulted in a systolic BP reduction of 24 mm Hg at 3 months of follow-up ( $p = 0.001$  vs. baseline). As a result, targeted selective ablation not only prevented similar BP response with stimulation at the previously responsive sites, but also attenuated the response to stimulus at the ipsilateral midrenal arterial sites, suggesting that afferent renal nerves are likely to play an important role in BP reduction.

Recently, Tsioufis et al. (41) reported a first-in-man study, in which 20 hypertensive patients underwent renal nerve stimulation using the ConfidenHT system. Bilateral renal nerve stimulations were performed at 3 to 4 sites/artery at 2 and 4 mA, respectively. Stimulation with 2 mA resulted in a maximum increase of  $8 \pm 6$  mm Hg in systolic BP (based on 119 stimulations;  $p < 0.001$ ) while stimulating with 4 mA resulted in a maximum increase in stimulus-evoked BP of  $10 \pm 8$  mm Hg (based on 61 stimulations;  $p < 0.001$ ). The mean increase in systolic BP did not vary between mid, distal, or branch sites when stimulating at 2 mA but was significantly higher at ostial ( $23 \pm 14$  mm Hg) than in nonostial locations ( $9 \pm 7$  mm Hg) when stimulating at 4 mA ( $p = 0.003$ ). This suggests that renal nerve stimulation might help in optimizing treatment effects (41).

In the SPYRAL HTN-OFF and HTN-ON MED trials, a large number of ablations were performed safely (>40 ablations) in the main renal artery and its branches, and this approach appeared to be effective and consistent in lowering BP. However, these findings do not oppose the concept of “hot spots,” as the higher number of ablated sites may improve the chance of hitting pressor nerves. Moreover, the successful RDN achieved through a circular lesion in the main renal artery by the endovascular ultrasound system used in RADIANCE-HTN SOLO suggests that interruption of the renal nerves in any segment of the renal artery may be sufficient to achieve RDN or it has deeper penetration beyond the artery.

**INDIRECT TESTING VIA REFLEX RESPONSES.** Whereas direct renal nerve stimulation uses energy,

reflex elicitation uses a physiological stimulus to excite the efferent renal sympathetic nerves and thus, reflex-mediated renal vasoconstriction before and after RDN is used to assess intervention success. In patients, renal sympathetic neural vasoconstriction has been shown in response to mental stress (42), head-up tilt (43), and lower body negative pressure (44), and recent reports of isometric handgrip (45) exercise-driven renal vasoconstriction in patients undergoing RDN are promising.

Contrasting from direct neural stimulation, reflex elicitation (42-45) is not painful, and thus, can be performed in conscious patients. It also assesses the integrity of the entire efferent limb of the renal sympathetic innervation, avoiding complexities arising from relationships between stimulation and denervation loci. However, this modality also has limitations, as repeatability of reflexes may be impacted by habituation, sensitization, and intra-procedural sedative and analgesic medications.

**PASSIVE MONITORING.** Passive monitoring techniques detect spontaneous efferent renal sympathetic nerve activity or its downstream effects, which are attenuated after successful RDN. The classic example is renal norepinephrine spillover, which was used to demonstrate renal sympathoexcitation in hypertensive patients (46) and to validate achieved RDN in a small group of patients (37). Although renal norepinephrine spillover is unsuitable to be used broadly for intraprocedural monitoring, new technologies based on passive monitoring approaches are being developed. One early-stage device detects spontaneous renal sympathetic nerve traffic from within the renal artery lumen (Autonomix Medical, Doylestown, Pennsylvania) (47). Additionally, to overcome the strong and confounding influence of autoregulatory mechanisms on traditional measures of renal vascular tone (48,49), novel means of renal sympathetic vascular control are under investigation for intraprocedural feedback (48,50,51).

Unlike other modalities, passive monitoring does not require a stimulus-response profile, which is inherently time-consuming and challenging to reproduce. However, passive monitoring techniques can be influenced by any factor that changes renal sympathetic outflow, including patient anxiety, autonomic reflexes, and pharmacological agents used for analgesia and sedation.

## DO RENAL NERVES REGROW FOLLOWING RDN?

In 2013, Mulder et al. (52) reported that substance P and calcitonin gene-related peptide content of



<b>TABLE 1 Baseline-Adjusted Fall in ABPM</b>				
Trial	24-h ABPM			
	Systolic	p Value	Diastolic	p Value
SPYRAL HTN-ON MED	-7.0 mm Hg (-12.0 to -2.1)	0.0059	-4.3 mm Hg (-7.8 to -0.8)	0.0174
RADIANCE-HTN SOLO	-7.0 ± 8.6 mm Hg (-7.1 to -1.2)	0.006	-4.4 ± 5.8 mm Hg (-3.7 to -0.2)	0.07
SPYRAL HTN-OFF MED	-5.3 mm Hg (-8.6 to -2.0)	0.0020	-4.8 mm Hg (-6.8 to -2.8)	0.001

Values are mean (95% confidence interval) or mean ± SD (95% confidence interval).

ABPM = ambulatory blood pressure measurements; CI = confidence interval; RADIANCE-HTN SOLO = Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicenter, international, single-blind, randomized, sham-controlled trial; SPYRAL HTN-ON MED = Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomized trial; SPYRAL HTN-OFF MED = Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomized, sham-controlled, proof-of-concept trial.

sensory nerves in the denervated kidney gradually returned toward that of the innervated kidney over a period of 12 weeks after RDN. This followed a similar time course as the return of neuropeptide Y and tyrosine hydroxylase content in sympathetic nerves. Whether restoration of neurotransmitter content demonstrated herein is associated with restoration of function of both efferent sympathetic and afferent sensory nerves remains to be demonstrated (52).

Booth et al. (53) reported that in sheep, functional reinnervation was demonstrated by the finding that electrical stimulation of the whole renal nerve resulted in normal afferent and efferent renal nerve responses, in contrast to the lack of responses acutely post-RDN.

Anatomical and biochemical studies indicated that 1 week after catheter-based RDN, the renal levels of markers for sympathetic efferent and afferent sensory nerves were significantly reduced, but by 11 months post-RDN, the levels had returned to pre-RDN levels, suggestive of reinnervation of both the sensory renal afferent nerves and the sympathetic efferent nerves (53). It is currently unknown whether the control of the renal vasculature, renin release, and sodium excretion in response to changes in RSNA is normal in the reinnervated kidney and whether there are changes in the central neural pathways controlling RSNA following RDN. However, Singh et al. (54) demonstrated in a hypertensive chronic kidney disease sheep model that BP, renin, and sodium excretion responses to blood loss were markedly blunted 2 and 5 months post-RDN.

Conversely, Mauriello et al. (55) reported evidence of neural sprouting as early as 5 months after human kidney transplantation. In all likelihood, nerve sprouting stems from sympathetic ganglia, because neural regeneration appears to be limited to sympathetic efferent nerve fibers. Complete periadventitial renal nerve regeneration in hypertensive subjects to reach levels seen in native arteries, being paralleled

by worsening of hypertension-related lesions in distal arterioles, seems to be achieved within 24 months following renal transplantation. Indeed, nerve density in kidney transplant arteries tends to reach levels similar to those in native renal arteries (55).

Reinnervation in humans following catheter-based RDN has not been demonstrated, which raises the question of underlying mechanisms capable of chronically maintaining a sustained decrease in BP despite potential reinnervation. Reduced renal vascular resistance, decreased intrarenal levels of renin, reduced RSNA burst size and burst incidence, changes in central autonomic nuclei, and others are possible explanations that require further exploration.

**THE POTENTIAL ROLE OF INFLAMMATORY PATHWAYS.** Some studies propose that renal inflammation may be directly triggered by amplified RSNA, as there is much evidence that inflammation of the vasculature, brain, and kidneys contributes to chronic increases in BP (56-58). Recently, a study reported that angiotensin II (AngII)-induced hypertension in mice is decreased by RDN and that this is paralleled by reduced renal inflammation independently of the BP (59). Because specific ablation of renal afferent nerves had no effect on the pathogenesis of hypertension in this study, it was suggested that the antihypertensive effect of RDN was due to ablation of efferent renal sympathetic nerve-mediated renal inflammation (59). Similarly, Banek et al. (60) also reported that RDN attenuates hypertension and renal inflammation in the rat deoxycorticosterone acetate (DOCA)-salt model of hypertension. Importantly, they also stated that resting afferent renal nerve discharge is elevated in DOCA-salt rats, and they hypothesized that this is caused by an increase in certain inflammatory cytokines in the kidney (60). Another finding was that afferent-specific renal nerve ablation attenuated the development of hypertension in this model to the

same degree as total RDN (60). The authors concluded that although renal inflammation may have its onset in efferent renal sympathetic nerves, hypertension was driven by augmented afferent renal nerve traffic, probably secondary to renal inflammation (60). A subsequent study from the same group demonstrated that afferent-specific renal nerve ablation also decreased arterial pressure in the established phase of DOCA-salt hypertension to the same degree as total RDN (61). However, neither method of ablation reversed renal inflammation in the established phase of this model, suggesting the presence of other mechanisms responsible for the inflammation.

Although there is a shortage of clinical studies directly measuring renal inflammation after RDN, there are several studies in which markers of peripheral inflammation were evaluated. Kampmann et al. (62) reported similar cardiovascular and inflammatory responses in hypertensive humans who underwent catheter-based RDN, where all measured circulating inflammatory cytokines (tumor necrosis factor- $\alpha$ , interleukin [IL]-6, and IL-1 $\beta$ ) remained unaffected 6 months post-treatment, despite a significant decrease in arterial pressure. In contrast to these results, a clinical report from Zaldivia et al. (63) described a reduction in circulating inflammatory cytokines (MCP-1, IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , and IL-12) several months after catheter-based RDN in hypertensive subjects. Further clinical and preclinical investigations are necessary to elucidate the anti-inflammatory effect of RDN.

## DRUG INTERACTIONS

The recent 3 sham-controlled trials, SPYRAL HTN-OFF MED and RADIANCE SOLO (in which patients were not on concurrent medication), and SPYRAL HTN-ON MED (in which 29% of individuals were using 1 drug, 18% were taking 2 pills, and 53% were using 3 types of antihypertensive medications), demonstrated a significant baseline-adjusted fall in ambulatory BP, although background treatment and baseline BP levels differed between them (Table 1). Similar BP responses in SPYRAL HTN-OFF and RADIANCE-HTN SOLO suggest that multiple lesions in the main renal artery and its branches is equivalent to circumferential lesion to main renal artery only, albeit the depth of lesions may be relevant in this context. Further studies are needed to elucidate if spironolactone and/or clonidine cause any drug interaction with RDN or if their response can predict responders to RDN,

as clonidine reduced BP ( $p < 0.001$ ) and plasma noradrenaline concentrations ( $p < 0.05$ ) significantly 7 and 30 days after therapy onset. The BP-lowering effects of clonidine are related to the centrally mediated and/or direct suppression of peripheral noradrenergic activity, indicating the utility of clonidine in cases of hypertension where the sympathetic nervous system is hyperactive (64). Thus, the premise that patients with greater sympathetic dependence (clonidine-sensitive) may represent a more susceptible population for RDN.

## POTENTIAL EFFECT ON CARDIOVASCULAR OUTCOMES

Reduction in target organ damage by pharmacological treatment is closely linked to a decrease in the time-averaged BP it causes. In a meta-analysis including 613,815 patients from 122 studies, reduction of office systolic BP by 10 mm Hg was related to a reduction in cardiovascular events by 20%, overall mortality by 13%, coronary artery disease by 17%, stroke by 27%, and heart failure by 28%, respectively (65). In the HOPE-3 study, patients with baseline office systolic BP of  $>143.5$  mm Hg had a reduction of systolic BP by  $-5.8/-3.0$  mm Hg (due to pharmacological therapy) associated with a 28% lower incidence of cardiovascular events compared with the placebo group (66). In another meta-analysis of 147 randomized trials comprising 464,000 patients, a reduction in 10 mm Hg systolic and 5 mm Hg diastolic office BP was related to a decrease of coronary heart disease and stroke events by  $\sim 22$  and 41%, respectively, depending on the age of the patient (67).

Although not proven by prospective outcome trials in the context of RDN, a  $\sim 10$  mm Hg decrease in office systolic BP achieved in RDN trials in which the average age of the population was  $\sim 65$  years, if maintained long-term, would be associated with a reduction in cardiovascular events by  $\sim 25\%$ , especially heart failure and stroke.

## SUMMARY

The positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED reignited the RDN field. However, several unsolved issues remain to be addressed appropriately, including identifying those patients who may benefit most, defining the durability of effects on BP and safety in the long-term, determining the mechanisms of the BP reduction to optimize response, and developing tests

and technologies to establish the extent of renal artery denervation, ideally at the time of intervention.

Filling in these blanks will help to advance the field further and ultimately determine the clinical utility of RDN. Here, we have summarized some of the most relevant issues identified by a group of clinical and experimental scientists to facilitate this critical task.

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**KEY WORDS** blood pressure, cardiovascular disease, hypertension, renal denervation, sympathetic nervous system