

Renal Denervation in Asia

Consensus Statement of the Asia Renal Denervation Consortium

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Abstract—The Asia Renal Denervation Consortium consensus conference of Asian physicians actively performing renal denervation (RDN) was recently convened to share up-to-date information and regional perspectives, with the goal of consensus on RDN in Asia. First- and second-generation trials of RDN have demonstrated the efficacy and safety of this treatment modality for lowering blood pressure in patients with resistant hypertension. Considering the ethnic differences of the hypertension profile and demographics of cardiovascular disease demonstrated in the SYMPLICITY HTN (Renal Denervation in Patients With Uncontrolled Hypertension)-Japan study and Global SYMPLICITY registry data from Korea and Taiwan, RDN might be an effective hypertension management strategy in Asia. Patient preference for device-based therapy should be considered as part of a shared patient-physician decision process. A practical population for RDN treatment could consist of Asian patients with uncontrolled essential hypertension, including resistant hypertension. Opportunities to refine the procedure, expand the therapy to other sympathetically mediated diseases, and explore the specific effects on nocturnal and morning hypertension offer a promising future for RDN. Based on available evidence, RDN should not be considered a therapy of last resort but as an initial therapy option that may be applied alone or as a complementary therapy to antihypertensive medication.

Key Words: Asia ■ blood pressure ■ cardiovascular diseases ■ denervation ■ population

Recent multicenter international sham-controlled clinical trials have demonstrated statistically and clinically significant reductions in blood pressure (BP) after renal denervation (RDN) in patients with uncontrolled hypertension¹⁻³ and have added important scientific perspective to the neutral results of the earlier SYMPLICITY HTN-3 trial.⁴ The clinical positioning of this innovative treatment should now be considered within the overall clinical hypertension management strategy.⁵

Hypertension profiles and the demographics of hypertension-related cardiovascular disease (CVD) vary with ethnicity. In Asia, the impact of hypertension on CVD is greater, and the rate of uncontrolled hypertension is higher than in Western countries.^{5,6} The goal of hypertension management strategies should be towards perfect 24-hour BP control, thus reducing the rate of CVD events in Asia towards zero.⁷ However, to date, there has been no discussion or

consensus on the positioning of RDN for Asian hypertension management.

The Asia Renal Denervation Consortium (ARDeC) consensus conference was recently convened to share up-to-date information and regional perspectives on the scientific evidence for renal denervation. The consortium consisted of Asian physicians who actively perform RDN in a variety of regions, including Hong Kong, Japan, Korea, Malaysia, Singapore, Taiwan, Thailand, and Vietnam, and was convened independent of any clinical or healthcare organization. The goal of the consortium was to achieve consensus recommendations on RDN that might help inform healthcare professionals in Asia. Individual members reported on various aspects of RDN for hypertension focusing on four major questions as detailed below, followed by group discussion of the data and consensus recommendations. Here, we report the consensus from the first ARDeC conference, held in 2019.

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Current Evidence

First-Generation Clinical Trials

The early proof-of-concept SYMPLICITY HTN-1 and the randomized controlled SYMPLICITY HTN-2 trials reported dramatic BP reductions following RDN.^{8,9} Initial enthusiasm stalled after the release of results of the SYMPLICITY HTN-3 study.⁴ SYMPLICITY HTN-3 was a blinded, randomized controlled trial in which 535 subjects with uncontrolled treatment-resistant hypertension were randomized to RDN or a sham procedure. No statistically significant differences between the 2 groups were observed at the 6-month follow-up, although office and 24-hour BP had decreased significantly in both groups. Post hoc analysis of SYMPLICITY HTN-3 identified several confounding factors that could help to explain the unexpected neutral results, especially the significant decrease in BP seen in the sham-control group.¹⁰ First, the use of medications to treat hypertension and the possibility of patient noncompliance with treatment were not adequately addressed in the study protocol. Second, the study population was predominantly North American with a significant proportion of Afro-Americans. Third, substantial procedural variability may have occurred due to inexperience among study investigators. Considering all these limitations, the SPYRAL HTN clinical trial (Global Clinical Study of Renal Denervation With the Simplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension) program was initiated to reliably determine the efficacy of RDN for the treatment of hypertension.

The efficacy of RDN was further supported by the results of the multicenter, open-label, randomized controlled French DENERHTN study (Renal Denervation for Hypertension), comparing RDN with stepped-care standardized antihypertensive treatment in 121 patients with resistant hypertension.¹¹ At the 6-month follow-up, there were significantly greater reductions in daytime ambulatory BP in the RDN group versus control.¹¹

In addition to randomized trials, the Global SYMPLICITY Registry (GSR) has enrolled over 2700 real-world patients and >2300 have now been followed for 3 years.¹² The GSR data showed that, when used in routine clinical practice outside a clinical trial setting, the BP response to RDN was consistent with the results obtained in randomized trials. The safety record within GSR has been very good, and the registry has recorded significant office and 24-hour BP reductions out to 3 years in multiple high-risk subpopulations including the elderly, and patients with diabetes mellitus, chronic kidney disease, isolated systolic hypertension, and arrhythmias.^{13,14}

Second-Generation Trials

After carefully considering the shortcomings of the SYMPLICITY HTN-3 trial, newer second-generation RDN devices were evaluated in randomized trials. The SPYRAL HTN-OFF MED trial was a multicenter, international, single-blind, randomized, sham-controlled trial using the second-generation multielectrode Symplicity Spyral catheter system and including 80 patients with mild to moderate hypertension not currently prescribed antihypertensive medication (either drug naïve or discontinued medication).³ Three-month changes in office and ambulatory systolic BP (SBP) and diastolic BP from baseline were

statistically significant in the RDN group (Figure 1), and there were no significant changes in BP from baseline in the sham-control group ($P < 0.05$ for between-group comparison).

SPYRAL HTN-ON-MED was also a multicenter, international, single-blind, randomized, sham-controlled trial, conducted at the same enrolling centers as SPYRAL HTN-OFF MED.² Patients with mild to moderate hypertension who had been prescribed 1–3 standard antihypertensive drugs were enrolled. Treatment with RDN was associated with statistically significant changes in BP from baseline to 6 months with no significant change in the sham-control group (Figure 1). No major procedural or clinical safety events were observed in either the OFF-MED or ON-MED trials.^{2,3} Both trials have been extended to collect additional safety and effectiveness data (SPYRAL Pivotal trial and ON-MED IDE trial).

The RADIANCE-HTN SOLO trial was a multicenter, international, single-blind, randomized, sham-controlled study of the ultrasound catheter-based Paradise renal denervation system in patients with moderate uncontrolled hypertension.¹ A significant reduction in daytime and 24-hour ambulatory BP was observed in the RDN versus sham (Figure 1), with no major procedural or clinical safety events observed in either group.¹

The single-blind, single-center, 3-arm randomized RADIOSOUND-HTN (Randomized Comparison of Ultrasound Versus Radiofrequency Denervation in Patients With Therapy Resistant Hypertension) study compared 3 different RDN techniques, including radiofrequency ablation of the main renal artery (RFM-RDN), radiofrequency ablation of the main renal artery, branches, and accessories (RFB-RDN), and ultrasound-based ablation of the main renal artery (USM-RDN), in patients with resistant hypertension.¹⁶ Reductions in daytime SBP were greater with USM-RDN versus RFM-RDN, and there was no significant difference between USM-RDN and RFB-RDN. The proportion of patients with a ≥ 5 mm Hg reduction in BP was not significantly different between the 3 groups.¹⁶

Several additional RDN catheter systems have been developed and are currently in the early stages of clinical testing. The Peregrine catheter ablation system (Ablative Solutions, MI) includes a 3-needle delivery system to perform chemical RDN via microdoses of dehydrated alcohol.¹⁷ In the first-in-man trial, mean office SBP decreased from 175 to 151 mm Hg (-24 mm Hg). The IberisBloom radiofrequency energy-based RDN catheter system (Terumo, Tokyo, Japan) incorporates a 4-electrode catheter design, similar to the SYMPLICITY device. A single-arm registry is currently ongoing, and a randomized trial is planned. Golden Leaf (Shanghai Golden Leaf Med-Tec Co, Shanghai, China) has also developed a 6-electrode basket design radiofrequency energy-based RDN catheter.¹⁸ One study showed that office and ambulatory SBP significantly decreased by 11.5 and 7.5 mm Hg, respectively, at 3 months. A sham-controlled randomized trial is planned.

Notably, a recent meta-analysis based exclusively on sham-controlled trials showed a significantly greater reduction in daytime ambulatory SBP in second-generation RDN trials compared with first-generation RDN trials (mean difference in 24-hour SBP: -4.9 mm Hg [95% CI, -7.1 to -2.6 mm Hg]).¹⁹ Another meta-analysis also indicated significant office and ambulatory BP-lowering effects of RDN in randomized trials after removing the confounder of unplanned

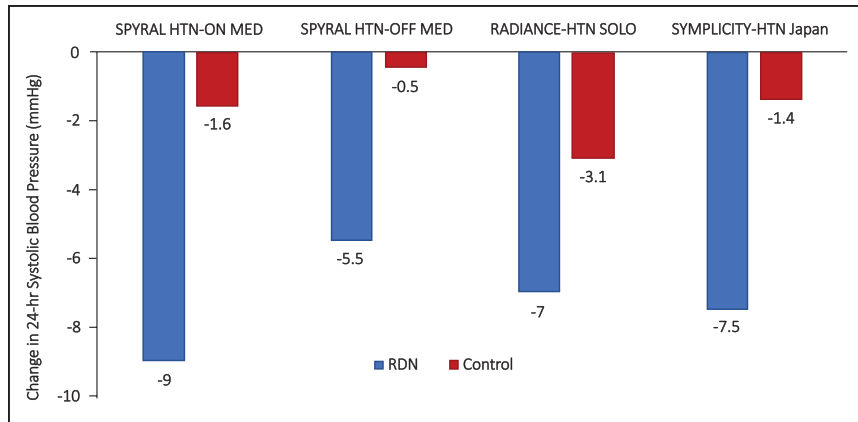


Figure 1. Comparison of 24-h systolic blood pressure (SBP) changes from baseline to follow-up in recent randomized renal denervation trials. SBP reductions in the SYMPLICITY HTN-Japan study (the only randomized trial of renal denervation [RDN] in a predominantly Asian population) were similar to those in the global trials despite use of first-generation single electrode RF catheter technology.^{1-3,15}

medication changes (mean difference in 24-hour SBP: -6.1 mmHg [95% CI, -8.7 to -3.5 mmHg]).²⁰

There are currently few data on the effects of RDN on hard clinical outcomes, although early reports of surgical splanchnicectomy showed improved mortality compared with a matched control group, independent of BP reduction.²¹ Nevertheless, the relationship between decreased BP and reductions in cardiovascular risk is well-established, and relatively modest reductions in office SBP are strongly associated with cardiovascular risk reduction.²² Data from a systematic review and meta-analysis calculated that a 10 mmHg reduction in SBP was associated with a 13% reduction in all-cause mortality, a 27% reduction in the rate of stroke events, and 28% reduction in the risk of developing heart failure (all independent of baseline BP).²² Thus, although prospective outcome trials of RDN are highly desirable, these may be challenging to practically design and execute, and use of surrogate end points may provide a more feasible approach to determining the clinical value of RDN.

Summary: First and Second Generation RDN Trials

- Early clinical trials of RDN have repeatedly demonstrated the efficacy and safety of this treatment modality for lowering BP in patients with resistant hypertension.
- All second-generation RDN trials showed that RDN significantly reduced BP without any major safety concerns.
- Recent meta-analyses showed a significantly greater reduction in daytime ambulatory SBP in second- versus first-generation RDN trials.
- Several ongoing pivotal trials will further evaluate the safety and efficacy of RDN in large populations of patients with hypertension.

What Is the Asian Perspective for RDN?

The characteristics of hypertension and hypertension-related CVD show key racial differences in Asian populations.⁶ First, stroke occurs more frequently than myocardial infarction in Asian (particularly East Asian) countries,²³ whereas myocardial infarction is more common than stroke in the rest of the world.²⁴ Second, although East Asian populations are generally slimmer than whites, the prevalence of hypertension in Asia is similar to global rates.²⁵ Cutoff values for both body mass index and waist circumference and the presence of hypertension and other metabolic syndrome features were lowest in East Asian populations and highest in South Asian

populations.²⁶ This suggests that Asian populations, particularly East Asians, are prone to developing obesity-related metabolic derangements, including hypertension. Third, masked hypertension, which includes morning hypertension and nocturnal hypertension, is more prevalent in Asians than in Westerners,^{27,28} and masked hypertension is associated with increased CVD risk.²⁹⁻³¹ Comparing the baseline 24-hour BP profiles of resistant hypertension between Japanese patients enrolled in SYMPLICITY HTN-J and white and black patients enrolled in the SYMPLICITY HTN-3 with identical enrollment criteria, Japanese patients had significantly higher morning BP and more pronounced morning BP surge, despite similar inclusion criteria and office BP across the 3 ethnic groups.¹⁵ Masked hypertension is a hallmark of obesity-related hypertension,³² which causes increased circulating blood volume (and therefore nocturnal hypertension) due to decreased sodium excretion and decreased baroreceptor sensitivity (and therefore morning BP surge) due to increased sympathetic activity.^{33,34} In addition, the nondipper/riser pattern of nocturnal BP is more common in Asians than in Westerners.³⁵ Finally, East Asian populations have at least a 2-fold higher sensitivity to the β -blocking effects of propranolol than white populations.³⁶ Overall, these observations suggest that Asian populations might be more sensitive to sympathetic modulation, thereby making RDN an attractive BP-lowering strategy.

SYMPLICITY HTN-J was the first prospective randomized study to focus specifically on the uncontrolled Asian hypertensive population.^{37,38} Differences in SBP reductions after RDN of only the main renal artery using the first-generation RF catheter were not significantly different from those seen in the control group (receiving standard pharmacotherapy), potentially due to a lack of statistical power due to early discontinuation of the trial. However, the magnitude of reductions in 24-hour SBP after RDN were similar to those achieved in the subsequent sham-controlled SPYRAL HTN-OFF-MED, -ON-MED, and RADIANCE-HTN SOLO trials using next-generation technology (Figure 1).³⁷⁻⁴⁰ Although Japanese patients were included in both SPYRAL HTN trials,^{2,3} the numbers enrolled were too small to detect any ethnic differences in the BP-lowering effect. Recently, the effectiveness of ablation of both the main renal artery and its branches has been shown to be superior to that of main renal artery ablation only for reducing norepinephrine content in the kidney in pre-clinical studies, and for BP reduction in clinical studies.^{16,41}

These data suggest that RDN might be as effective, or perhaps even more effective, in Asians than in Westerners.

Time-trend analysis of SYMPLICITY HTN-J showed that reductions in ambulatory BP after RDN occurred consistently over the 24-hour period, including nighttime and in the morning (Figure 2). Given that nighttime and early morning hypertension are associated with higher CVD risk independently of office BP in Asian patients with hypertension,⁴²⁻⁴⁶ the clinical implications of RDN therapy could be greater in Asian countries. Notably, the recent long-term follow-up results of SYMPLICITY HTN-J showed significant and marked reductions in office BP with RDN, without significant procedural complications in Japanese patients (Figure 3).

The first reported comparison outcomes of RDN in an Asian population were from the Korean Registry,⁴⁷ a sub-analysis of the GSR.¹² Following RDN of both renal arteries, overall registry data showed that office SBP was significantly reduced at 6 months (168.3±13.9 at baseline to 148.8±18.4 mmHg at 6 months; $P<0.001$) and 12 months (141.0±17.2 mmHg; $P<0.001$ versus baseline). Changes in SBP at 6 and 12 months were -19.4 ± 17.2 and -27.2 ± 18.1 mmHg, respectively (both $P<0.001$ versus baseline).⁴⁷ Comparing BP reductions between patients from GSR Korea and a matched subset

of white GSR patients (n=169), changes in SBP at 6 months were similar in the 2 groups (-19.4 ± 17.2 versus -20.9 ± 21.4 mmHg, respectively; $P=0.547$ [unadjusted] and $P=0.998$ [adjusted for baseline BP]), but at 12 months SBP reductions were greater in Koreans versus whites (-27.2 ± 18.1 versus -20.1 ± 23.9 mmHg, respectively; $P=0.004$ [unadjusted] and $P=0.002$ [adjusted]). No procedure- or device-related adverse events were reported in the Korean subgroup.⁴⁷ Multivariate analysis adjusting for all baseline characteristics and baseline medication classes identified a significant association between higher baseline office BP and a greater reduction in SBP at both 6 and 12 months.⁴⁷ Importantly, Korean patients were more likely than white patients to have a greater reduction in 12-month SBP,⁴⁷ suggesting a potential role for racial differences in the effects of RDN. Long-term follow-up of GSR Korea also showed that long-term SBP reductions were greater in Korean than in white patients.⁴⁸

Recently, another analysis of the GSR was reported for the Taiwan subgroup (GSR-Taiwan).⁴⁹ Of the 26 patients enrolled (mean age 59.1 ± 13.8 years), 8 were treated with the Symplicity Flex catheter and 18 were treated with the Symplicity Spyrax catheter. Baseline office SBP was 168.2 ± 19.8 mmHg and diastolic BP was 89.0 ± 14.3 mmHg. Office BP reductions after

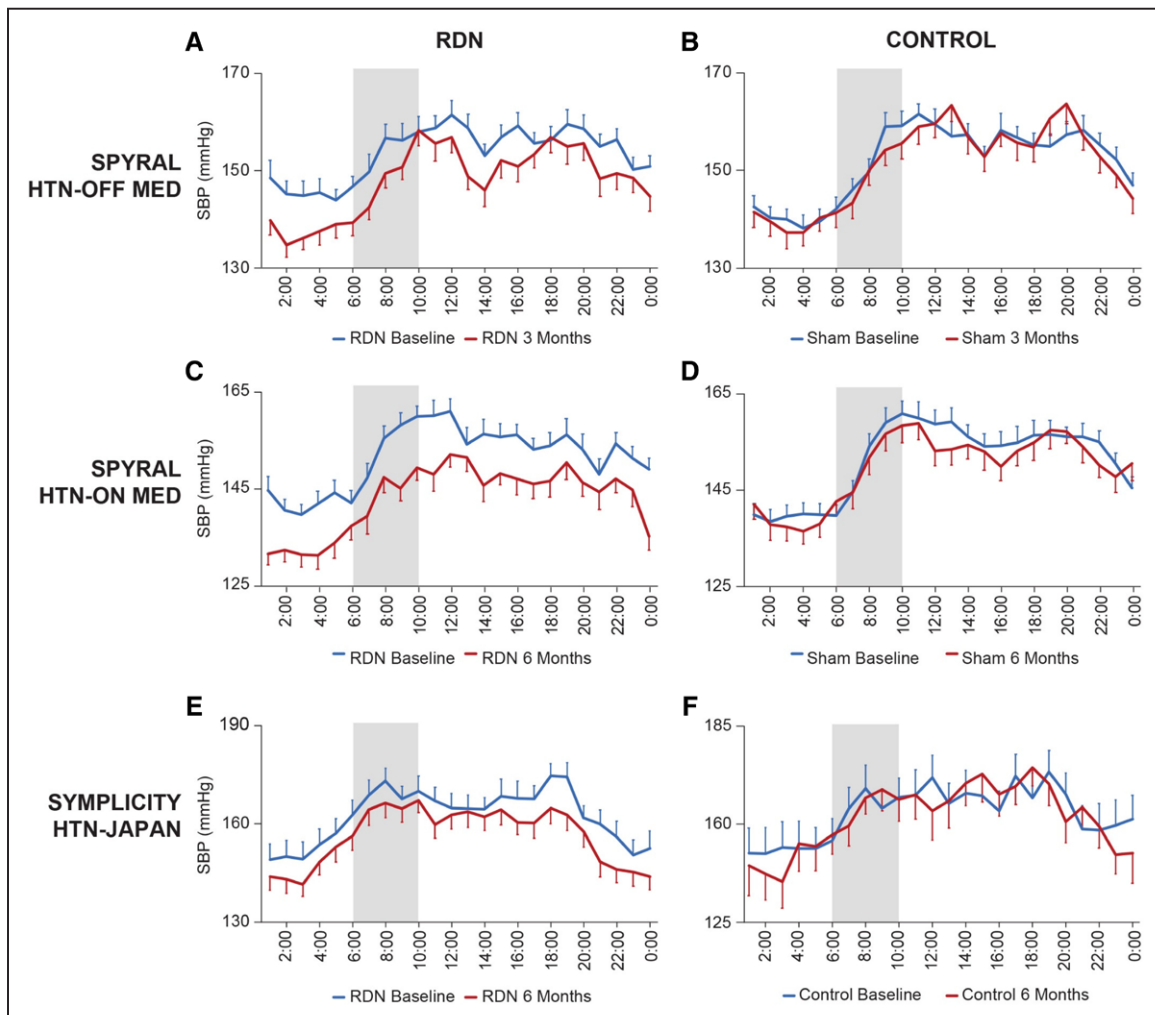


Figure 2. Ambulatory systolic blood pressure (SBP)-lowering effect of renal denervation (RDN) based on 24-h diurnal variation in different clinical trials. Blood pressure reductions showed similar 24-h patterns between the SPYRAL HTN-OFF MED (A,B) SPYRAL HTN-ON MED (C,D) and SYMPLICITY HTN-Japan (E,F) trials.^{1,2,37}

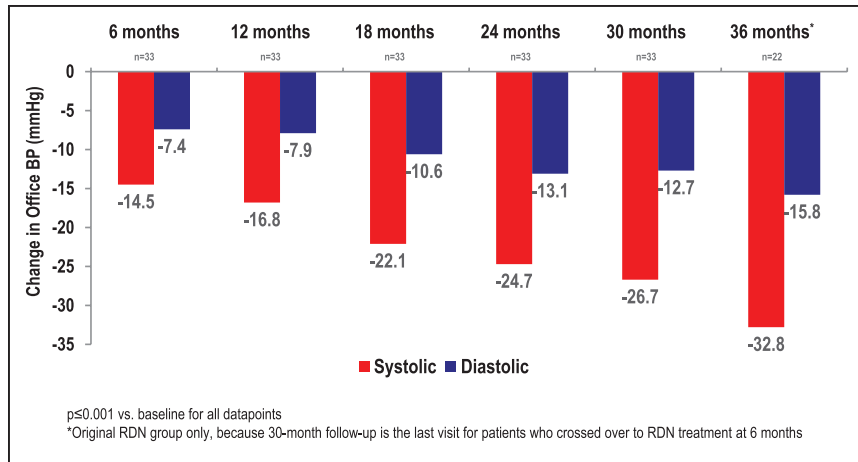


Figure 3. Change in office blood pressure (BP) after renal denervation (RDN): 3-y follow-up of SYMPLICITY HTN-J.³⁷

RDN were sustained for up to 3 years in the Symplicity Flex group and up to 2 years in the Symplicity Spyral group. In the Symplicity Flex group, office SBP reductions at 3 months and 3 years were 14.9 ± 14.7 and 29.7 ± 25.9 mmHg, respectively (both $P < 0.05$ versus baseline). In the Symplicity Spyral group, reductions in office SBP at 3 months and 2 years were 21.2 ± 28.7 and 42.4 ± 10.7 mmHg, respectively (both $P < 0.05$ versus baseline). Collectively, these analyses indicate that RDN should be a promising hypertension management strategy option in Asia.

Summary

- Long-term follow-up in the SYMPLICITY HTN-J study showed that significant reductions in BP were sustained for at least 3 years after RDN without any significant intervention-related adverse effects.
- Subanalyses from the Global SYMPLICITY Registry showed significant and sustained BP reductions after RDN in the Korean and Taiwanese subpopulations.
- The proportion of Korean GSR patients with a substantial reduction in 12-month SBP was greater than that for white patients.

Which Patients Are Most Likely to Benefit From RDN?

The promising results of RDN in Asian populations may partly be due to higher salt sensitivity and higher salt intake in Asians than in Westerners. Dietary modifications are important and may be effective to reduce salt intake, but meaningful and persistent dietary changes often fail. Meanwhile, the risk of end-organ damage due to uncontrolled hypertension remains high. Reduced baroreflex sensitivity increases BP variability that may be further exacerbated by higher salt intake.³⁸ Chronic baroreflex failure may further lead to an adverse pressure-natriuresis response.³⁸ Likewise, age-related baroreflex failure leads to extended increases in BP levels and BP variability in Asians with higher salt sensitivity and higher salt intake. In addition, nondipper and riser pattern of nocturnal BP partly depend on the increased circulating volume which is associated with higher salt sensitivity and salt intake.

Available data from Asian populations also suggest that RDN is a feasible BP-lowering strategy for uncontrolled hypertension across multiple clinical scenarios including

antihypertensive-naïve patients, those on treatment and patients in whom treatment has been discontinued. In the Asian prospective J-HOP (Japan Morning Surge - Home Blood Pressure) study, morning and nocturnal uncontrolled hypertension were associated with increased risk of CVD, especially stroke, regardless of office BP control status.⁴⁵ Because of the fact that the BP-lowering effects of antihypertensive drug therapy generally decrease overnight before typical morning dosing, nighttime and morning BP control may represent a relative blind spot for current antihypertensive medication regimens.¹⁵ Thus, RDN could be applied as both adjunctive and alternative complementary therapy for the management of hypertension.

RDN affects both sympathetic efferent and afferent sensory nerve pathways to reduce BP (Figure 4).^{5,50} Sympathetic efferent nerve ablation inhibits the renin-angiotensin-aldosterone system resulting in increased renal blood flow, reduced salt sensitivity, and decreased urinary excretion of sodium. Especially at nighttime, the circulating volume decreases to lower BP because the nondipping pattern of nocturnal BP is a compensation mechanism designed to excrete excess sodium for patients with increased circulating volume.^{33,34} Thus, RDN should be effective in Asians with higher salt intake and higher salt sensitivity, but prospective studies are needed to clearly define the direct effects of sodium and volume status on the response to RDN in Asian populations. Furthermore, afferent nerve ablation suppresses the central sympathetic outflow to increase baroreceptor sensitivity. As a result, exaggerated BP variability, such as morning BP surge and sleep-triggered BP surge, are decreased.

Combined Hypertension Versus Isolated Systolic Hypertension

Previous studies have shown that baseline BP, diastolic BP variability,⁵¹ combined systolic-diastolic hypertension,⁵² 24-hour ambulatory heart rate,⁵³ renal artery vasodilatation,⁵⁴ aortic pulse wave velocity,⁵⁵ and central pulse pressure⁵⁶ were potential predictors of response to RDN. Although none of these are direct measures of sympathetic activity, the observation that patients with combined systolic-diastolic hypertension were more responsive to RDN was considered in the design of 3 RDN 2.0 trials. Evidence that isolated systolic hypertension patients may respond less well to RDN mainly

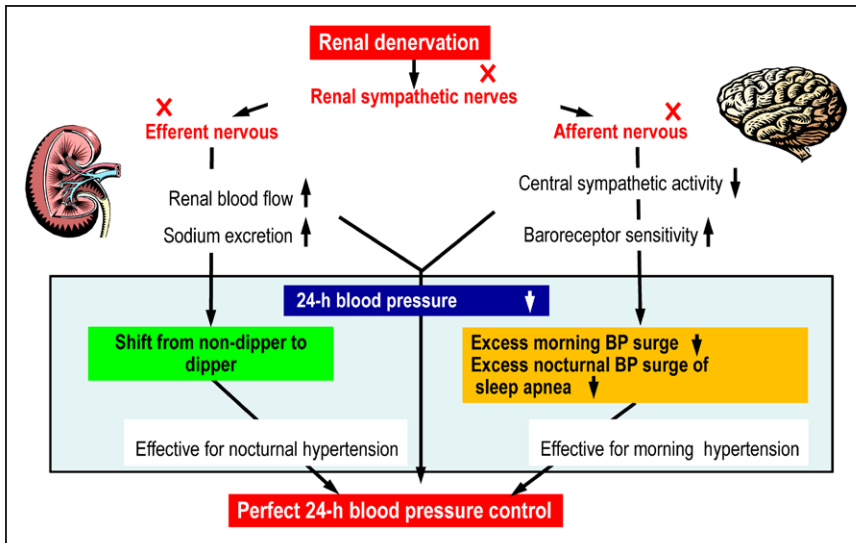


Figure 4. Potential mechanisms for the effects of renal denervation (RDN) on 24-h diurnal blood pressure variation.⁵⁰ RDN may contribute to the achievement of perfect blood 24-h pressure control via distinct efferent and afferent mechanisms that might differentially effect daytime, nighttime, and morning blood pressure control.

comes from pooled data from SYMPLICITY HTN-3 and GSR, and other studies.⁵² However, these data have a number of limitations, including the retrospective nature of the analyses. Furthermore, significant differences in baseline BP, heart rate, and demographic variables including age and comorbidities make meaningful statistical comparisons between patient groups challenging, despite multivariate adjustments. Indeed, a recent subanalysis of a prospective, randomized trial of RDN using both RF and ultrasound techniques found no difference in ambulatory BP reductions between patients with isolated systolic hypertension and those with combined hypertension after appropriate adjustment for baseline BP, which is typically higher in the combined hypertension cohort.⁵⁵ Thus, the hypothesis that RDN is less effective in isolated systolic hypertension remains unproven and warrants further investigation. Interestingly, baseline heart rate may also be a useful identifier of neurogenic hypertension because a recent post hoc analysis of the SPYRAL HTN-OFF MED study showed that higher baseline 24-hour ambulatory heart rate (>74 beats/min) predicted greater BP reductions after RDN.⁵³

In summary, the search for reliable predictors to identify responders to RDN is important. However, current predictors of a more pronounced BP response to RDN, including baseline BP, combined uncontrolled hypertension, lower pulse pressure (<100 mmHg),⁵⁵ and higher 24-hour ambulatory heart rate, are based only on evidence from retrospective post hoc analyses. Whether these findings can be replicated in prospective studies awaits verification.

Uncontrolled Versus Treatment-Resistant Hypertension, Versus Patient Preference

Evidence from randomized controlled trials and meta-analyses of RDN, which have included a substantial number of patients from Asia, clearly showed that the BP-lowering efficacy of RDN was related to baseline BP and independent of the number of prescribed antihypertensive medications. Therefore, RDN should not be reserved only for patients with resistant hypertension. RDN could serve as a complementary BP-lowering strategy in situations where BP targets are clearly difficult to achieve and maintain.

Masked uncontrolled hypertension, defined as controlled office BP but uncontrolled home or ambulatory BP, occurs in $\approx 30\%$ of treated hypertensive patients.⁵⁷ Masked uncontrolled hypertension includes morning and nocturnal uncontrolled hypertension and is more frequent ($\approx 50\%$) in Asian populations,²⁸ potentially due, in part, to higher salt intake and higher salt sensitivity.^{6,33,58} Home and ambulatory BP measurements should be routinely required, particularly for Asian patients with hypertension. Given the 24-hour sustained BP reductions including nighttime and morning BPs achieved in the SYMPLICITY HTN-J, SYMPLICITY HTN-3, and 3 RDN 2.0 trials,^{37,38} it would seem reasonable to recommend RDN, in addition to antihypertensive dosage adjustment.⁵⁹

Although clinically meaningful BP reductions can be achieved by various lifestyle interventions and antihypertensive agents, nationwide BP control rates remain poor worldwide and are <50% in many Asian countries.⁶⁰⁻⁶² Similar to other chronic diseases, one essential reason for the unsatisfactory control rates of hypertension is poor lifestyle/medication adherence, either by intention (patient preference), forgetfulness or other educational, psychological or socioeconomic factors.⁶³ The impact of nonadherence on long-term hypertension control is tremendous and often underestimated,^{63,64} as reflected by the marked difference in hypertension control rates between hospitalized patients compared with general populations. To reduce this gap, patient preference regarding long-term medication therapy should be carefully explored and considered in determining the most appropriate antihypertensive strategies for an individual patient as part of a shared decision-making process.⁶⁵ Those who are intolerant of or nonadherent to antihypertensive agents for any reason could be managed using RDN given its excellent safety profile and sustained BP-lowering efficacy.

Ethnicity

Significant ethnic differences in various aspects of hypertension could impact the responsiveness to RDN.⁶⁶ Asia-specific features of hypertension and the response to RDN have been summarized above. Given the susceptibility of Asian populations to hypertension and the fact that responses to RDN

appear to be at least equivalent, if not greater over the longer-term, to those in whites, RDN might be particularly beneficial in Asian populations.

Summary: Practical Population for Treatment With RDN

- Asian patients with hypertension, including those with resistant hypertension
- Patients with masked uncontrolled hypertension
- Patients with uncontrolled hypertension and established atherosclerotic cardiovascular disease (stroke, coronary artery disease, aortic dissection, etc) and heart failure
- Patients intolerant of, or nonadherent to, antihypertensive drug therapy
- Patients with combined uncontrolled hypertension, lower pulse pressure (<100 mmHg), or increased 24-hour ambulatory heart rate (>74 beats/min)

How Can the RDN Procedure be Optimized Further?

Anatomic studies in animals showed that complete 4-quadrant ablation was correlated with circumferential destruction of nerves along renal arteries, translating to reduced renal tissue norepinephrine levels.⁶⁷ In addition, human autopsy studies demonstrated that the periarterial sympathetic nerves converge from proximal to distal along the renal arteries.⁶⁸ The afferent sympathetic fibers are mainly located at the proximal segment with decreasing ratio of prevalence of afferent/efferent fibers in the direction from proximal to distal. Furthermore, periarterial sympathetic nerve fibers are closer to the arterial lumen at the distal segment. At distal regions, ≈75% of nerves are within 3 mm of the lumen, which is well within the range of damage for radiofrequency ablation. Animal studies show that combined main artery plus side branches ablation produced the greatest drop in renal norepinephrine.⁴¹ Similar findings have been reported in human clinical studies.⁶⁹ The presence of accessory branches also affects the completeness of ablation.⁷⁰ The total number of lesions delivered is also crucial because it was recently shown that increased number of ablations was a predictor of office SBP reduction at 6 months in SYMPLICITY HTN-3.¹⁰ These observations suggest that both main artery and distal branch ablations are important for complete nerve destruction.

Identification of Nerve Destruction

A safe, accurate, and clinically practical method to identify complete nerve destruction after a renal denervation procedure remains an unmet need. Accurate measurement of sympathetic activity may provide an alternative study end point or, more importantly, immediate feedback on procedural success by estimating the completeness of nerve destruction. The rate of norepinephrine spillover, as determined by radiotracer dilution, is a well-established physiological method for measuring sympathetic activity *in vivo*.⁷¹ RDN reduced renal norepinephrine spillover by 47% and total body norepinephrine spillover by 28% at 15 to 30 days after the procedure. In the SYMPLICITY HTN-1 trial, therefore confirming its effect on efferent renal nerves.⁹ However, such testing is not commonly available in hospital laboratories. Measurement of muscle

sympathetic nerve activity (MSNA) is another marker of central sympathetic activity measured by microneurography of postganglionic sympathetic nerves. Hering et al⁷² showed the reduction of MSNA at 3 months after RDN in a small number of patients, thereby documenting an effect on afferent renal nerves.⁷³ However, these findings were not reproduced in subsequent studies.^{74,75} Also, reductions in MSNA were not correlated with reductions in BP after RDN.⁷² Therefore, conclusive evidence is still required to show whether the measurement of MSNA is clinically useful in guiding the RDN procedure.

Direct assessment of sympathetic activity either by norepinephrine spillover or MSNA seems impractical in daily practice. Noninvasive measurement of autonomic activity via cardiac baroreflex sensitivity assessed from R-R interval analysis or from SBP values by phase rectified signal averaging indicated that impaired cardiac baroreflex sensitivity predicted response to RDN.⁷⁶ However, assessment of cardiac baroreflex is limited to patients who are in sinus rhythm and also requires noninvasive equipment that can continuously monitor arterial pressure.

Renal nerve stimulation (RNS) or mapping is a promising method to demonstrate interaction with the renal sympathetic nervous system *in vivo*. Initial animal study data first reported that rapid electrical stimulation of renal arterial nerves was associated with a transient rise in BP.⁷⁷ A recent experimental study demonstrated that transvascular pacing of aorticorenal ganglia might be useful as a procedural end point.⁷⁸ Subsequent studies also reported similar findings in humans.^{79,80} In one small study, de Jong et al⁸¹ demonstrated that completeness of RDN might be assessed by RNS, which in turn might predict the BP response to RDN. After RDN, a more blunted BP rise response with RNS was associated with greater reduction of ambulatory BP from 3 to 6 months.⁸¹ Interestingly, studies using RNS to predict response to RDN in treatment of atrial fibrillation⁸² and ventricular tachycardia⁸³ showed similar findings. These proof-of-concept studies involving RNS were often conducted with the use of conventional catheters designed for electrophysiology studies, followed by RDN using currently available RDN catheters. To facilitate the process of RNS, a dedicated device, the ConfidenHT system (Pythagoras Medical Ltd, Herzliya, Israel) has recently become available.⁸⁴ The SyMAP CATH ITM (SyMap Medical [Suzhou], Ltd, China) is another potential RNS, mapping and denervation device. The current SMART OFF-MED randomized controlled trial is enrolling hypertensive patients in the absence of antihypertensive medications, using SyMAP CATH ITM catheter and SYMPIONEER Stimulator/Generator for combined stimulation, mapping and denervation using one single device (URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02761811).

Procedural Efficiency

Preprocedural planning using magnetic resonance angiography or computed tomography angiography to identify any renal stenosis, location of renal artery ostia and presence of any accessory branches might be able to reduce procedural time. The RDN procedure is typically performed under local anesthesia and conscious sedation. Guiding catheters with appropriate configuration engaging the renal artery ostia should

be chosen after a nonselective aortogram. The use of second-generation multielectrode ablation catheters also helps to shorten the procedure time. If femoral access is chosen, the use of a vascular closure device should be considered to facilitate early mobilization and discharge from hospital. For the same purpose, the radial approach could also be considered if the selected device is radial approach compatible.

Summary

- Completeness of the RDN procedure should be ensured by increasing the number of ablations, ensuring circumferential lesion distribution, treating the main artery plus side branches, and even accessory branches when possible.
- Incorporating preprocedural imaging, electro-anatomic mapping, and using a radial access approach may reduce time and contrast use during the RDN procedure.
- Further research on RNS may help guide RDN procedure intraoperatively.

What Hypotheses Need to be Tested in New Clinical Trials?

Expanding Existing Indications and Usage

Reductions in BP after RDN can vary between patients, and there remains an unmet clinical need for ways to identify those who will have the best response. Some possible candidate conditions associated with sympathetic hyperactivity are shown in Figure 5.⁸⁵

Considering the unique characteristics of the Asian hypertension population, a new randomized controlled trial of RDN to target morning hypertension in the region could be valuable. Japanese observational studies including the community-based Ohasama population⁴² and the general practitioner-based HOMED-BP (the Hypertension Objective Treatment Based on Measurement by Electrical Devices of

Blood Pressure), J-HOP, and HONEST (The Home BP measurement with Olmesartan Naive patients to Establish Standard Target blood pressure) studies of antihypertensive medication^{43-46,86} clearly demonstrated that morning hypertension is significantly associated with the risk of CVD, especially stroke, regardless of office BP. The morning BP surge contributes to morning hypertension and is strongly associated with risk of stroke independent of 24-hour BP.⁸⁷ Morning BP surge and morning hypertension partly contribute to sympathetic hyperactivity in the morning.^{5,87} Morning hypertension is easily and accurately detected by home BP monitoring) and about half of medicated hypertensive patients are uncontrolled for morning hypertension in clinical trials (supplemental figure).⁷

The second target of RDN might be nocturnal uncontrolled hypertension. This could be especially important because the 24-hour BP-lowering effect of antihypertensive drugs may be partially limited by morning dosing habits. Nocturnal hypertension is closely associated with various diseases, including obstructive sleep apnea (OSA), chronic kidney disease, and diabetes mellitus.^{5,88} In particular, OSA is known as a cause of neurogenic hypertension with sympathetic hyperactivity triggered by hypoxic sleep apnea episodes.⁵⁰ The hypersympathetic drive induced by OSA episodes induces a BP surge during sleep.⁸⁸ In a post hoc analysis of patients enrolled in SYMPPLICITY HTN-3 who had OSA, averaged nighttime BP was not reduced by RDN, but significant reductions were seen in maximum and peak nighttime BP values (Figure 6).⁸⁹ In the direct study, which used recently developed hypoxia-trigger home BP monitoring in OSA patients, morning BP and peak nighttime BP triggered by OSA episodes were significantly reduced after RDN and by bedtime dosing of sympatholytic agents (α -blocker/ β -blocker),⁹⁰ indicating that the OSA-related sleep BP surge is triggered by sympathetic overdrive induced by obstructive apneas. The specific nighttime BP-lowering effect of RDN in OSA patients is an interesting area for research.

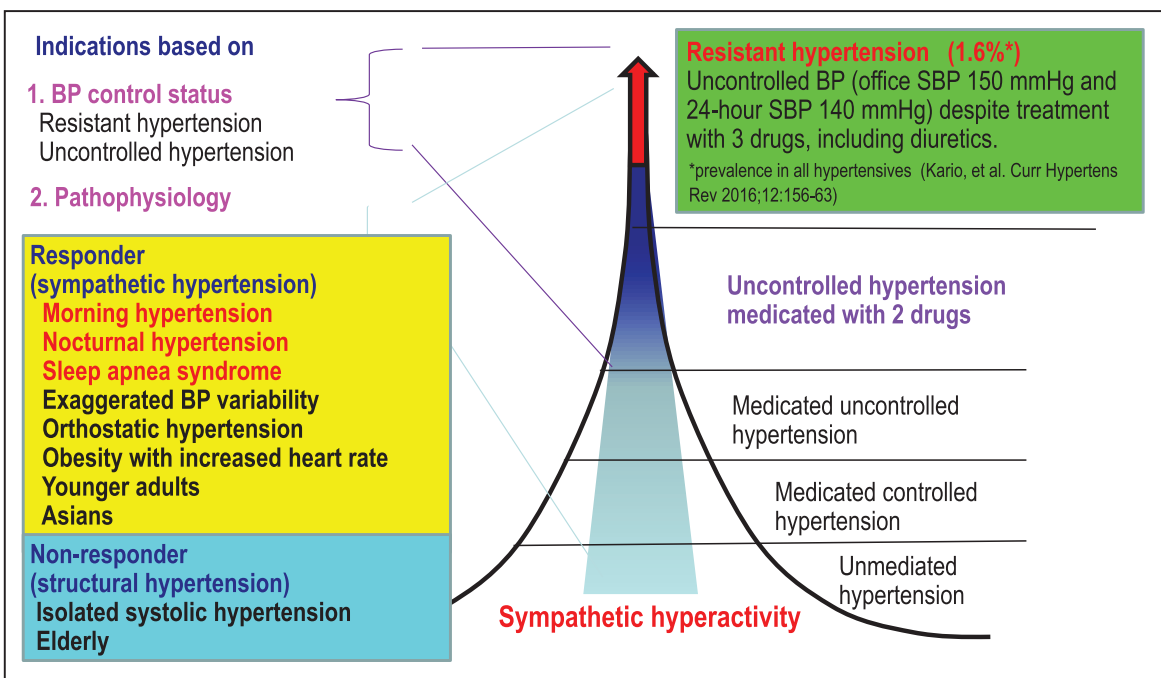


Figure 5. Possible indications for renal denervation. BP indicates blood pressure; and SBP, systolic blood pressure.⁸⁵

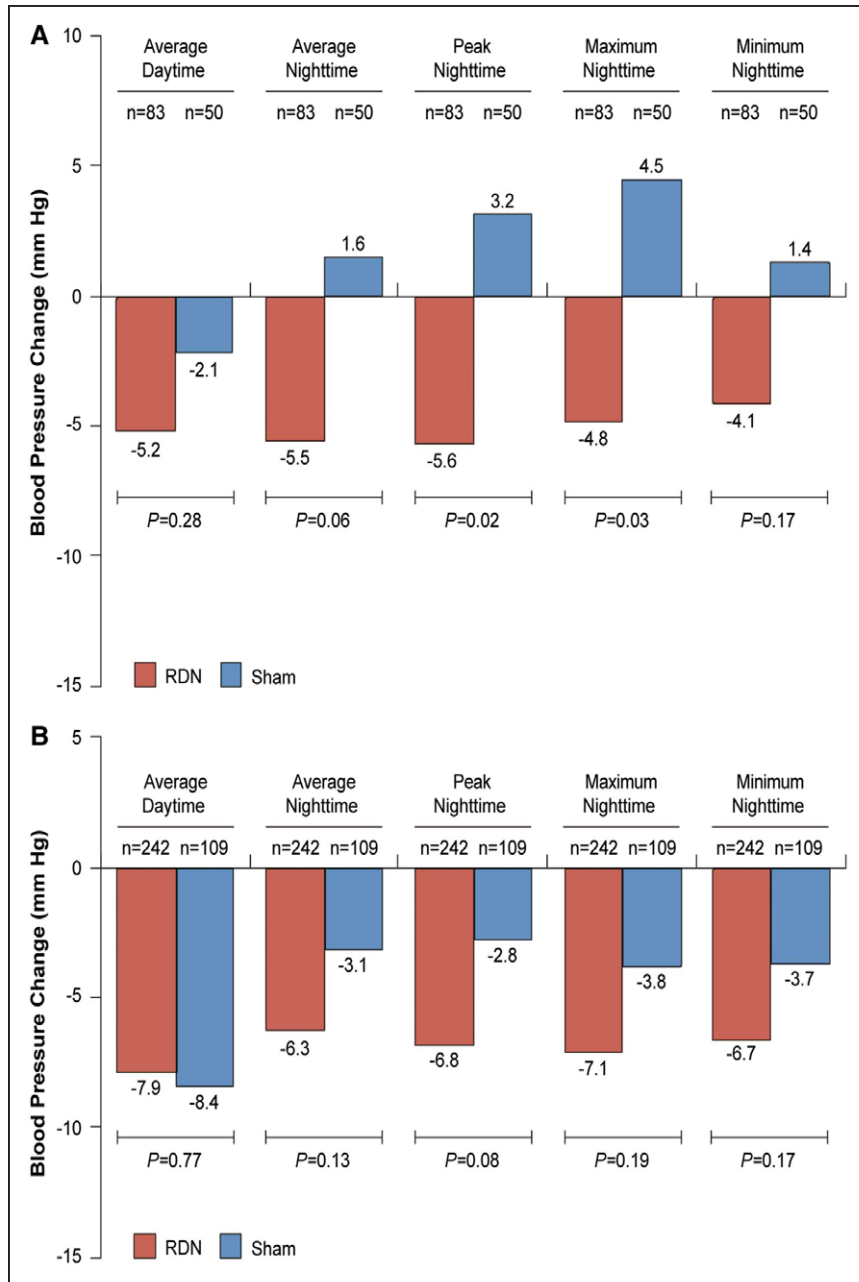


Figure 6. Impact of renal denervation (RDN) on nighttime blood pressure changes in patients with history of resistant hypertension and obstructive sleep apnea in the SYMPPLICITY HTN-3 trial. Changes in nighttime blood pressure reduction at 6 mo after RDN were predominant in the subgroup of patients with (A) vs without (B) obstructive sleep apnea.⁸⁹

Future clinical studies of RDN should continue to focus on the reduction of 24-hour SBP assessed by ambulatory BP monitoring as the primary end point. Visit-to-visit office, ambulatory, and home BP variability are all associated with CVD events, independently of average BP. Potentially, modern big data statistical techniques could be applied to new larger out-of-office BP data sets, obtained using home BP monitoring, ambulatory BP monitoring, and wearable BP monitoring devices, to more accurately detect the effects of RDN on average BP and BP variability.^{91,92} Recently, an advanced information communication technology-based ambulatory BP monitoring system has been developed that integrates an actigraph, thermometer, and barometer, allowing monitoring of home BP and environmental conditions in a single system.^{91,93} Using this system, the effect of RDN on sympathetic drive-induced BP variability during daily life could be evaluated.

Potential New Indications

In addition to uncontrolled hypertension, the potential of RDN has been evaluated in other clinical situations. These include metabolic syndrome,^{94,95} OSA,⁹⁶ atrial fibrillation,^{97,98} ventricular arrhythmias,^{99,100} heart failure,^{101–103} and chronic kidney disease.^{104–106} Based on positive results in pivotal trials, it is expected that there will be indications for RDN beyond hypertension. Evaluation of the effects of RDN on metabolic syndrome may be particularly important given the rapidly increasing prevalence of metabolic syndrome in East and South East Asian areas.¹⁰⁷ Likewise, OSA is a promising target for cardiovascular risk reduction via RDN because of its association with neurogenic hypertension. However, additional longer-term data are required.

Summary: RDN Future Research

- Uncontrolled morning hypertension and residual nocturnal hypertension despite antihypertensive pharmacotherapy are promising targets for the use of RDN in Asia.
- Cardiovascular diseases, including congestive heart failure, chronic kidney disease, and atrial and ventricular arrhythmias, are all associated with hypertension and sympathetic hyperactivity and might, therefore, benefit from RDN-associated reductions in BP and circulating volume; a direct effect on sympatholytic activity on target organs is also possible.
- OSA is a promising target for cardiovascular risk reduction via RDN because of its association with neurogenic hypertension.

Conclusion and Perspectives

The present recommendations seem both prudent and timely considering the unmitigated cardiovascular risk currently facing the large population with uncontrolled hypertension in Asia. Because of the unique manifestations of hypertension-related CVD and higher rates of uncontrolled hypertension, Asian patients could particularly benefit from RDN therapy. Available evidence suggests that RDN should not be considered a therapy of last resort but as an initial therapy option that may be applied alone or as a complementary therapy to antihypertensive medication. Furthermore, the therapy should not necessarily be restricted to clinical trials or centers of excellence, as long as proper procedural training and internal cooperation between referring physicians, hypertension specialists, and operators has been achieved. Evidence also supports consideration of RDN for sympathetically driven hypertension, including resistant hypertension, and any patient preference for device therapy should be factor in shared clinical decisions. New randomized clinical trials of RDN in Asia focusing on uncontrolled morning hypertension and, ultimately, clinical outcomes are needed to further optimize treatment.

Summary of ARDeC Consensus Panel Recommendations

- RDN could serve as a BP-lowering strategy alone or in combination with pharmacotherapy for Asian patients in situations where BP targets are difficult to achieve and maintain.
- The decision to perform RDN should consider patient preference as part of a patient-physician shared decision-making process.
- RDN should be considered for hypertensive patients with higher cardiovascular risk including the following:
 - Resistant or masked uncontrolled hypertension
 - Uncontrolled hypertension with established atherosclerotic cardiovascular disease such as stroke, coronary artery disease, aortic dissection, as well as heart failure
 - Intolerant of, or nonadherent to, antihypertensive drug therapy
 - Combined uncontrolled hypertension or lower pulse pressure (<100 mm Hg)
 - Increased 24-hour ambulatory heart rate (>74 beats/min)
- Therapy should not necessarily be restricted to clinical trials or centers of excellence if proper procedural training

and internal cooperation between referring physicians, hypertension specialists and proceduralists is achieved.

- Completeness of the RDN procedure should be ensured by increasing the number of ablations, ensuring circumferential lesion distribution, treating the main artery plus side branches, and even accessory branches when possible.
- RDN should be considered in uncontrolled morning hypertension and residual nocturnal hypertension treated with antihypertensive pharmacotherapy.
- A randomized controlled trial of RDN targeting morning hypertension in Asia is recommended to identify patients with increased procedural benefit.

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