2023 Philippine Working Group Consensus Statement on Renal Denervation Therapy for the Management of Hypertension

Philippine Renal Denervation Consortium Group
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Statement of Intent: This consensus statement is meant for the clinical management of hypertension using device based-therapies, based on the best available evidence at the time of its development, and is designed to be a guide for clinicians in managing hypertension for the Filipino patient. This, however, should not replace sound clinical judgment by doctors, and the ultimate decision for treatment should involve both the clinician and the patient.

These guidelines issued in June 2023 will be reviewed if significant new evidence becomes available.

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Abstract

BACKGROUND: Hypertension is the most common risk factor for cardiovascular disease in the Philippines. Despite the availability of antihypertensive medications that are effective, safe, and tolerated by Filipino patients, the numbers of uncontrolled hypertensives are still increasing. Several factors play in the poor control of blood pressure, particularly resistant hypertension and hyperactive sympathetic nervous system. Renal denervation therapy is a novel device that has been shown to lower blood pressure in patients with resistant and difficult-to-treat hypertension and is deemed safe in clinical trials. A Philippine Working Group composed of specialists in cardiology, hypertension, vascular surgery, and clinical epidemiology has come up with consensus statements in identifying patients who will benefit from the procedure. Locally, there is a need to have hypertension centers treating uncontrolled and resistant hypertension and offer renal denervation therapy to appropriate Filipino patients.

KEYWORDS: blood pressure, difficult-to-treat hypertension, renal denervation therapy, resistant hypertension

INTRODUCTION

Hypertension remains to be the most common modifiable risk factor for cardiovascular disease. According to the World Health Organization, hypertension causes seven million deaths every year, whereas 1.5 billion people suffer from the complications of elevated blood pressure (BP). In the Philippines, the prevalence of hypertension is increasing. In the latest Philippine Heart Association Council on Hypertension Report (PRESYON-4) report,[1] the prevalence rate of hypertension is 37% and is higher in the previous surveys.[2] Several factors may have caused this surge, including increasing comorbidities, poor control rate, and disease progression. Despite being prescribed with antihypertensive medications and with good patient compliance, 68% of Filipinos with hypertension have uncontrolled BP.

Uncontrolled hypertension is the inability to reach the target BP, defined in the 2022 Clinical Practice Guidelines of the Philippines as target BP of less than 130/80 mm Hg.[3] Several factors may play a role in failure to reach the target BP, notably inadequate antihypertensive regimen, nonadherence, clinical inertia, and resistant hypertension,[4] especially in patients receiving pharmacotherapy. According to the latest American Heart Association definition, resistant hypertension is defined as above-goal elevated BP in a patient despite the concurrent use of more than three antihypertensive medications, commonly including a calcium-channel blocker, a renin-angiotensin-aldosterone blocker, and a diuretic, which should be administered at maximum or maximally tolerated daily doses. This may also include patients whose BP achieves target values on four or more antihypertensive medications.[5,6] Addressing these factors may lead to good BP control. Renal denervation (RDN) therapy, a novel treatment, may be a viable option for these types of patients.

Statement 1. Renal denervation therapy may be an option for uncontrolled blood pressure by reducing central sympathetic hyperactivity.

Hyperactivity of the sympathetic nervous system has been implicated to be one of the causes of hypertension. This may contribute to the development and maintenance of chronic BP elevation and may modulate nocturnal BP dipping. It was also seen that increased adrenergic activity is more pronounced in patients with hypertension-mediated organ damage, independent of BP levels, suggesting a pathogenic role of the sympathetic nervous system in hypertensive complications. In the kidneys, the efferent sympathetic outflow to the kidneys leads to decreased blood flow, renin release, and sodium retention, whereas the afferent sympathetic fibers send signals to the brain to stimulate central sympathetic activity contributing to neurogenic hypertension.[7,8]

Renal denervation is a catheter-based radiofrequency ablation of the afferent and efferent sympathetic nerves within the wall of the renal arteries. It was shown in preclinical models that specifically targeting afferent nerves or efferent nerves lowers BP.[8]

Statement 2. Renal denervation therapy may lower ambulatory and office blood pressure.

For this consensus statement, eight clinical trials[9–16] and two meta-analyses[17,18] were reviewed to show the efficacy and safety of RDN technique (Table 1). First-generation sham-controlled randomized clinical trials have shown mixed results. Unfortunately, results were mixed and did not translate in human trials.[9-13] The biggest clinical trial, the SYMPLICITY-HTN 3,[13] which included more than 500 patients with resistant hypertension, failed to reach the primary outcome, which is the mean change in office BP and 24-hour ambulatory BP monitoring. Results showed no statistical difference in the reduction of BP in the RDN arm and sham-controlled group: 24-hour mean ambulatory blood pressure monitoring RDN: –4.3 (–6.8 to –1.8), sham: 2.5 (–5.0 to –0.1), $P = 0.32$.

A Clinical Consensus Conference on device-based hypertension[19] was produced after the results of the first-generation trials. Recommendations allowed for a more consistent and more complete circumferential ablation. Stricter criteria for including study patients were also recommended during this time. Newer multielectrode catheter should also be used to reduce procedure duration and allow for simultaneous and uniform delivery of radiofrequency energy. It was also recommended that renal nerve denervation be done in an experienced center under an expert technician.

Thus, recent clinical trials addressed the issues of previous clinical trials, especially by targeting the neuroanatomy with more advanced catheter designs, thus improving the approach

Table 1. Renal Denervation Therapy Experience in Filipino Hypertensive Individuals

Case	Average BP Before the Procedure, mm Hg	No. of Antihypertensives Before the Procedure	Average BP After the Procedure, mm Hg	No. of Antihypertensives After the Procedure
Patient 1	180/110	6	130/70	2
Patient 2	160/90	3	120/80	3
Patient 3	140/90	3	120/80	3
Patient 4	160/90	4	120/80	2
Patient 5	150/90	4	130/80	2

BP=blood pressure.

to RDN technique. We also saw changes in the design and conduct of second-generation randomized controlled trials (RCTs) of RDN therapy. The primary objective for these studies was the change in ambulatory BP, as this would be the best method to assess the BP load on cardiovascular, cerebrovascular, and renal system. The SPYRAL HTN-OFF MED[14] pivotal trials showed that the difference in the 24-hour ambulatory systolic BP between the two groups, although modest in magnitude, is statistically significant favoring the RDN treatment. Aside from reducing the 24-hour BP in these second-generation sham-controlled RCTs, it is noteworthy to show that nighttime BP was also significantly reduced in the clinical trials. Nighttime BP has been found in post hoc analyses to be a more prognostic predictor of cardiovascular outcomes compared with daytime BP. In a meta-analysis, Ahmad et al[20] showed favorable outcomes in the use of RDN therapy in both ambulatory systolic and diastolic BP reduction. In a subgroup analysis in sham-controlled studies, it showed modest benefit of 24-hour systolic BP reduction with RDN at 6 months. Office BP was also significantly reduced in the second-generation RDN trials. Reduction ranged from 9 to 10.8 mm Hg systolic BP to 0.5 to 5.0 mm Hg diastolic BP.

Only one clinical trial, the RADIANCE SOLO,[16] a multicenter, single-blind, sham-controlled randomized trial, produced efficacy endpoint of lowering 24-hour systolic BP after 12 months. The study design allowed for stepped-care antihypertensive medication due to ethical reasons after primary endpoint collection after 2-month follow-up. Nevertheless, after 12 months, fewer medications were prescribed in the RDN group compared with the sham group. After adjustment for the number of medications, the RDN group had better BP control (reduction of 8.5 ± 9.3 mm Hg) compared with the sham group (–2.2 ± 10 mm Hg).

There is a recent study published using ultrasound RDN that was a sham-controlled, randomized trial with 150 hypertensive individuals undergoing the procedure. Results showed reduction of daytime BP with the ultrasound RDN procedure (mean, –7.9 mm Hg) as compared with the same procedure (mean, –1.8 mm Hg). They also looked at 24-hour ambulatory systolic BP, home systolic BP, office systolic BP, and diastolic BP, and among these secondary endpoints, the ultrasound RDN procedure had better BP outcomes.[22]

Long-term studies and follow-up are needed to evaluate cardiovascular outcomes because there are still no randomized clinical trials looking at cardiovascular outcomes with RDN therapy. The International Global SYMPLICITY Registry,[23] with a population of more than 2000 patients who underwent the procedure with 3-year follow-up, showed that the 24-hour SBP at 3 years was –8.9 mm Hg, and that for resistant hypertension was –8.7 mm Hg. The follow-up was utilized to estimate a cardiovascular event reduction at 3 years. The absolute risk reduction of major cardiovascular events and stroke was estimated to be 5.2% and 3.8% for patients with type 2 diabetes mellitus.

We have local experience using the procedure on five Filipinos with resistant and difficult-to-treat hypertension. Average BPs were 160/90 mm Hg before the procedure and were on target after the RDN therapy was done (Table 1). There was also a significant decrease in the antihypertensive medications after the procedure in majority of the patients who underwent the procedure (Table 2).

Statement 3. Renal denervation therapy is safe in clinical trials.
In both first-generation[9–13] and second-generation trials[14–16] on RDN, most adverse events include vascular access site–related complications and unexpected events within 30 days after the procedure. The use of radial artery access instead of femoral artery has the potential to further diminish any complications on the vascular site. In the sham-controlled trials, adverse events were similar in the RDN and the sham group. A meta-analysis by Agasthi et al[21] showed no statistical significance in the reduction of estimated glomerular filtration rate (eGFR). Sequelae of renal artery stenoses were estimated to be 0.2%, which is comparable to the natural incidence of events in a population with untreated hypertension. Patients who have significant reduction in eGFR (<45 mL/min per 1.73 m^2) were excluded in the clinical trials, although initial pilot data with reduced eGFR reported no safety issues with RDN. In the Global SYMPLICITY Registry,[23] no long-term safety signal has been reported so far. In the local experience, no severe adverse events were reported by the patients who underwent RDN. Long-term follow-up and local experience are needed to assess safety of therapy for Filipino patients.

Statement 4. Filipinos with hypertension who may be eligible for the procedure include uncontrolled or resistant hypertension and are willing to undergo the procedure.
The inclusion criteria of RCTs include patients with office systolic BP of ≥150 and <180 mm Hg, office diastolic BP of ≥90 mm Hg, 24-hour ambulatory systolic BP of ≥140 and <170 mm Hg, who are on at least three antihypertensive medications, one of which is a diuretic for at least 6 months, with adequate renal artery anatomy, and who are willing to undergo the procedure.[16] In SYMPLICITY-HTN Japan,[24] the first controlled trial for RDN in Asian patients, patients included in the trial had a lower body mass index, less history of obstructive sleep apnea (OSA), and fewer antihypertensive medication changes compared with the Caucasian counterparts. Unfortunately, this study was underpowered for the primary endpoint analysis and thus was not included in our analysis.

The Malaysian consensus statement[25] for RDN therapy was published in 2022 and identified potential patients for the procedures. These are patients whose BP remains high despite full adherence to medications, with resistant hypertension, with history of repeated nonadherence despite numerous counseling sessions, on polypharmacy for multiple comorbidities, with multiple end-organ damage with high cardiovascular risk, unwilling to take long-term pharmacotherapy, intolerant to medications, with hypertension due to hyperactive sympathetic system, and had repeated admissions for hypertensive crises.

These factors may help in selecting the Filipino patient who needs to undergo therapy.

It is also important to highlight not only the physicians' knowledge in hypertension control, but also the patients' perspective in selecting their preferred treatment in controlling their hypertension. Thus, the European consensus statement suggested implementing a standardized shared decision-making process in selecting the best treatment for BP control including RDN therapy.

In the local experience, Filipino patients who underwent RDN did not experience any vascular access problem or an increase in creatinine even after 6 months of follow-up.

Resources Needed for Renal Denervation Treatment

Philippine health care is a fragmented, complex, multilayered system, with the population paying out-of-pocket or relying on private insurance. We need local cost-effectiveness studies to assess the ability of the population to afford the procedure. Two recent studies determined the cost-effectiveness of RDN therapy to the treatment of resistant hypertension. In a German study,[26] RDN gained 0.98 quality-adjusted life-years (QALYs) in men and 0.88 QALY in women 60 years of age. Considering a willingness-to-pay threshold of 35,000 euros/QALY, there was a 95% probability that the treatment would be cost-effective. The cost-effectiveness was influenced on its effect on systolic BP, the rate of nonresponders, and the procedure costs of the treatment. It was also shown that earlier treatment with RDN produced better cost-effectiveness ratios. In an Australian population,[27] RDN was shown to be more cost-effective for BP reduction compared with standard treatment of care. It was cost-effective in patients with a 10-year predicted cardiovascular risk of 13.2% initially. The incremental cost-effectiveness ratios were AU $49,519 per year gained and AU $47,130 per QALY gained.

A multidisciplinary approach is needed in the management of uncontrolled and resistant hypertension. Primary care specialists, hypertension specialists, cardiologists, nephrologists, neurologists, vascular surgeons, endocrinologists, and physicians of other specialties who handle resistant hypertension should work together in the management of these patients. The effectiveness of the RDN therapy also relies on the hands of expert vascular surgeons and interventional cardiologists who are adept in doing the technique. We recommend the establishment of hypertension centers that manage these types of patients, and part of their treatment management for appropriate patients is RDN therapy.

CONCLUSIONS

Renal denervation therapy may be an option for patients who have uncontrolled or resistant hypertension. The intervention has been shown to be effective and safe; however, long-term follow-up is necessary to determine cardiovascular outcomes. A registry of local cases may be needed to monitor these individuals long term. The option of offering RDN procedure to individuals who have difficult-to-control and resistant hypertension should be a discussion with the Filipino physician and patient to provide utmost care to control the hypertension and its complications.

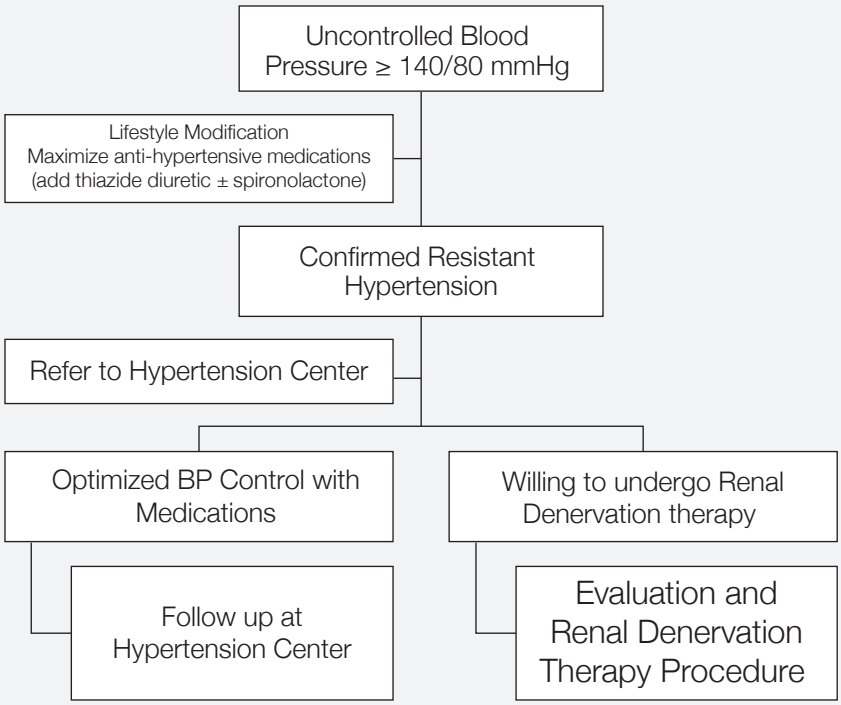

Figure 1. Proposed algorithm for renal denervation therapy.

Table 2. Renal Denervation Therapy Trials

Study Parameter	DENERHTN 2015 (Azizi et al[9])	Desch et al,[10] 2015	Prague-15 Study (Rosa et al[11])	SYMPLICITY 2 (Esler et al[12])	SYMPLICITY 3 (Bakris et al[13])	SPYRAL HTN-OFF (Townsend et al[14])	SPYRAL HTN-ON (Kandzari et al[15])	RADIANCE-HTN Solo (Azizi et al,[16] 2018)
Population	Resistant HTN patients 18–75 y old	Resistant HTN and mildly elevated BP[1] 18–75 y	True resistant HTN	Uncontrolled HTN	Resistant HTN	Nonmedicated patients with mild to moderate hypertension	Uncontrolled HTN	Mild to moderate HTN with no medications
Intervention	Renal Nerve Denervation (53) using Medtronic (bilateral RDN)	RDN (32 ITT, 29 PP)	RDN (n = 52)	RDN (49)	RDN (364)	RDN (38)	RDN (38)	RDN (74)
Comparator	Sham ± SSAHT (53)	Sham (32 ITT, 34 PP)	Intensified anti-HTN including spironolactone (n = 54)	Control (51), medication only, crossover after 6 mo	Sham (171)	Sham (42)	Sham (42)	Sham (72)
Type of RCT	Open-label, prospective, multicenter (French) RCT, ITT (phase 4) 6 mo extended to 1 y	Single-blind, parallel, single-center (Germany) RCT (phase 4), 6 mo	Open-label, prospective, randomized 6 mo	Multicenter, open label, RCT, 24 centers across Europe, Australia, and NZ	Multicenter, prospective, single-blind, RCT	Multicenter, international, single-blind, RCT Follow-up 3 mo	Single-blind, sham-controlled, RCT, multicenter Follow-up 36 mo	Multicenter, single-blind, sham-controlled, RCT
Anti-HTN medications	Indapamide 1.5 mg, ramipril 10 or irbesartan 300, amlodipine 10 mg May add spironolactone 25, bisoprolol 10, prazosin 5 mg, rilmenidine 1 mg	3 or more antihypertensive plus a diuretic	5.1 drugs—reduced to 5.0 drugs after 6 mo 5.4–5.6 drugs (intensive treatment)	3 or more antihypertension medications	3 or more (~5.1) antihypertension medications with diuretic	NA	2 or more medication burden (2.13 vs 2.55)	NA
Baseline BP	>135/85	135–149/90–94 mm Hg on 24-h ABPM Ave: 143–144 systolic BP	159 ± 17 and 155 ± 17 mm Hg	SBP > 160 mm Hg (>150 mm Hg if with T2DM, 18–85 y old	Baseline: 180 mm Hg	Office SBP ≥150 to <180, office DBP ≥90 mm Hg, and a mean 24-h SBP ≥140 and <170	ABPM 140 to less than 170 mm Hg, while on 1–3 medications	ABPM 135–170/85–105 mm Hg

Primary outcomes	Mean diurnal SBP	24-h systolic BP	24-h systolic BP	Office SBP after 6 mo then may do crossover after 1 y	Change in office SBP Change in 24-h SBPM	Change in 24-h ABPM in 3 mo	Change in 24 HR SBPM	Change in daytime SBPM
Results	RDN: −15.8 (−19.7 to −11.9 mm Hg) SSAHT alone: −9.9 mm Hg (−13.6 to −6.2) Mean diff: −5.9 mm Hg (−11.3 to −0.5), *P* = 0.0329	24Hr SBP RDN: −7.0 (−10.8 to −3.2) Sham: −3.5 (−6.7 to −0.2) 24 DBP RDN: −2.8 (−4.8 to −0.9) Sham – 2.1 (−3.9 to −0.2) 24-h Mean RDN: −4.3 (−6.8 to −1.8) Sham: 2.5 (−5.0 to −0.1), P = 0.32	24-h SBP RDN: −9.6 (−11.8 to −5.3) IP: −8.1 (−12.7 to −3.4) MD: −0.5 (−6.1 to −5.2), *P* = 0.87 Office SBP MD 1.9 (−5.2 to 9.0), *P* = 0.60	RDN 6 mo: −31.7 (−38.3 to −25.0) 1 y: −28.1 (−35.4 to −20.7) Crossover: Mean change: −23.7 ± 27.5 (from 190 ± 19.6 to 166.3 ± 24.7 mm Hg)	RDN −14.13 ± 23.93 (*P* < 0.001) Sham: −11.74 ± 25.94 (*P* < 0.001) Mean change: −2.39 (−6.89 to 2.12), *P* = 0.26 24-h SBP RDN: −6.75 ± 15.11 (*P* < 0.001) Sham: −4.79 ± 17.25 (*P* < 0.001) Diff: −1.96 (−4.97 to 1.06), *P* = 0.98	RDN 24H SBP: −5.5 (−9.1 to −2) 24HDBP −4.8 (−7.0 to −2.6) OSBP −10 (−15.1 to −4.9) ODBP −4.8 (−7.0 to −2.6) Sham 24HSBP −0.5 (−3.9 to 2.9) 24 H DBP −0.4 (−2.2 to 1.4) OSBP −2.3 (−6.1 to 1.6) ODBP −0.3 (−2.9 to 2.2 Mean diff: 24HSBP: −5.0 (−9.9 to −0.2) 24H DBP: −4.4 (−7.2 to −1.6) OSBP −7.7 (−14 to −1.5) ODBP −4.9 (−8.5 to −1.4)	24HSBPM- RDN: 18.7 ± 12.4 mm Hg Sham: −8.6 ± 14.6 mm Hg MD: −10.0 (−16.6 to −3.3), *P* = 0.0039 Mean diff: 24HDBPM −5.9 (−10 to −1.8), *P* = 0.0055 Morning SBP −11 (−19.8 to −2.1), *P* = 0.016 Night SBPM −11.8 (−19 to −4.7), *P* = 0.0017	RDN −8.5 ± 9.3 Sham −2.2 ± 10 Mean diff: −6.3 (−9.4 to −3.1), *P* = 0.0001
Safety events	Lumbar pain, mild groin hematoma			Renal artery dissection	Appeared to be safe, increased in serum creatinine >50% of baseline, stroke, hospitalization from HF	No major adverse events	No short-term or long-term safety issues	No major adverse events

24HDBP=24-hour diastolic blood pressure; 24HSBP=24-hour systolic blood pressure; ABPM=ambulatory blood pressure monitoring; BP=blood pressure; DBP=diastolic blood pressure; HF=heart failure; HTN=hypertension; ITT=intention to treat; MD=mean difference; ODBP=office diastolic blood pressure; OSBP=office systolic blood pressure; RCT=randomized controlled trial; RDN=renal denervation; SBP=systolic blood pressure; SSAHT=standardized, stepped-care antihypertensive treatment; T2DM=type 2 diabetes mellitus.

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