Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control After Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial

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ORIGINAL RESEARCH ARTICLE

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BACKGROUND: The multicenter, international, randomized, blinded, sham-controlled RADIANCE-HTN SOLO trial (A Study of the ReCor Medical Paradise System in Clinical Hypertension) demonstrated a 6.3 mm Hg greater reduction in daytime ambulatory systolic blood pressure (BP) at 2 months by endovascular ultrasound renal denervation (RDN) compared with a sham procedure among patients not treated with antihypertensive medications. We report 6-month results after the addition of a recommended standardized stepped-care antihypertensive treatment to the randomized endovascular procedure under continued blinding to initial treatment.

METHODS: Patients with a daytime ambulatory BP ≥135/85 mm Hg and <170/105 mm Hg after a 4-week discontinuation of up to 2 antihypertensive medications, and a suitable renal artery anatomy, were randomized to RDN (n=74) or sham (n=72). Patients were to remain off antihypertensive medications throughout the first 2 months of follow-up unless safety BP criteria were exceeded. Between 2 and 5 months, if monthly measured home BP was ≥135/85 mm Hg, a standardized stepped-care antihypertensive treatment was recommended consisting of the sequential addition of amlodipine (5 mg/d), a standard dose of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and hydrochlorothiazide (12.5 mg/d), followed by the sequential uptitration of hydrochlorothiazide (25 mg/d) and amlodipine (10 mg/d). Outcomes included the 6-month (1) change in daytime ambulatory systolic BP adjusted for medications and baseline systolic BP, (2) medication burden, and (3) safety.

RESULTS: A total of 69/74 RDN patients and 71/72 sham patients completed the 6-month ambulatory BP measurement. At 6 months, 65.2% of patients in the RDN group were treated with the standardized stepped-care antihypertensive treatment versus 84.5% in the sham group (P=0.008), and the average number of antihypertensive medications and defined daily dose were less in the RDN group than in the sham group (0.9±0.9 versus 1.3±0.9, P=0.010 and 1.4±1.5 versus 2.0±1.8, P=0.018; respectively). Despite less intensive standardized stepped-care antihypertensive treatment, RDN reduced daytime ambulatory systolic BP to a greater extent than sham (−18.1±12.2 versus −15.6±13.2 mm Hg, respectively; difference adjusted for baseline BP and number of medications: −4.3 mm Hg, 95% confidence interval, −7.9 to −0.6, P=0.024). There were no major adverse events in either group through 6 months.

CONCLUSIONS: The BP-lowering effect of endovascular ultrasound RDN was maintained at 6 months with less prescribed antihypertensive medications compared with a sham control.

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Clinical Perspective

What Is New?

- This is the first trial to report 6-month results after the addition of a recommended standardized stepped-care antihypertensive treatment to endovascular ultrasound-based renal denervation or sham procedure patients with uncontrolled combined systolic and diastolic hypertension who were initially off medications for 2 months after randomization.
- Although the majority of the patients needed the addition of the standardized stepped-care antihypertensive treatment, fewer medications were administered in the renal denervation group, and after accounting for these medication differences, ultrasound-based ablation of the main renal arteries in addition to standardized stepped-care antihypertensive treatment had greater ambulatory blood pressure–lowering efficacy than a sham procedure in addition to standardized stepped-care antihypertensive treatment at 6 months.

What Are the Clinical Implications?

- If safety is maintained in larger studies with longer follow-up, renal denervation is a promising adjunctive therapy for patients with hypertension.
- Identification of ideal responders to renal denervation is required.

The international, multicenter, RADIANCE-HTN trial was designed to compare the blood pressure (BP)–lowering efficacy and safety of an endovascular ultrasound renal denervation (RDN) system with a sham procedure in 2 separate cohorts: (1) patients with mild-to-moderate hypertension, randomized while off antihypertensive medications (SOLO cohort); and (2) patients with uncontrolled resistant hypertension, despite receiving 3 antihypertensive medications (TRIO cohort).[1] Each cohort was independently powered to detect a difference between RDN and a sham procedure on the primary end point of change in daytime ambulatory systolic BP (SBP) at 2 months.

We previously reported the 2-month BP and safety results of the SOLO cohort.[2] In the strictly controlled conditions of the trial, among patients with combined systolic-diastolic hypertension who were not taking, or were withdrawn from, antihypertensive medications, endovascular ultrasound RDN achieved a greater average reduction in daytime ambulatory SBP at 2 months compared with a sham procedure, and patients undergoing RDN were more likely to achieve daytime ambulatory BP control than patients undergoing the sham procedure (21.9% versus 3.4%, respectively, P=0.003).

For safety reasons, we limited the duration of patients being off antihypertensive medications to 2 months before starting or reinstituting a standardized drug titration protocol in order to lower BP to clinically recommended levels. In this setting, longer-term and standardized follow-up was planned to assess the durability and longer-term BP-lowering effects of RDN in conjunction with titrated medications in patients included in the RADIANCE SOLO trial. Some studies have reported increasing antihypertensive effects of RDN over time,[3,4] whereas preclinical studies have demonstrated that renal nerve regeneration may occur,[5] but only with partial restoration of functional renal nerve activity.[6] Whether the magnitude of the BP-lowering effect of endovascular ultrasound RDN remains stable, is amplified or is decreased over time, and further, whether safety is maintained especially in a cohort of patients who were not taking or were withdrawn from antihypertensive medications, remains unknown.

The objectives of this analysis of the SOLO cohort was to report the 6-month BP-lowering efficacy and safety of endovascular ultrasound RDN and antihypertensive medication burden while both patients and clinical staff following those patients remained blinded to the initial study randomization.

METHODS

Study Design

The international, multicenter, randomized, sham controlled, RADIANCE-HTN trial design has been described previously.[1] The study was approved by local ethics committees or institutional review boards and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent to complete up to 3 years follow-up. Between March 28, 2016, and December 28, 2017, participants were recruited into the SOLO cohort of the RADIANCE-HTN trial from 21 centers in the United States and 18 in Europe (located in France, Germany, the Netherlands, Belgium, and the United Kingdom). For the purposes of reproducing the analysis generated here, the data that support the findings of this study will be available from the corresponding author and study steering committee on reasonable request at the end of the study.

Study Population and Procedures

Eligible patients were aged 18 to 75 years with office systolic and diastolic BP (DBP) ≥140/90 mm Hg but <180/110 mm Hg on 0 to 2 hypertensive medications (uncontrolled) or with office BP <140/90 mm Hg (controlled) on 1 to 2 antihypertensive medications, had no history of cardiovascular or cerebrovascular events, and had an estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73 m2 (Modification of Diet in Renal Disease formula). After a 4-week discontinuation of antihypertensive medications, a total of 146 patients with daytime ambulatory SBP ≥135 and <170 mm Hg, and DBP ≥85 and <105 mm Hg, and with suitable renal artery anatomy on a prerandomization renal computed tomography

or magnetic resonance angiography were randomized (1:1) to endovascular ultrasound RDN (n=74) with the Paradise RDN system (ReCor Medical, Inc, Palo Alto, CA) or a sham procedure (restricted to the renal angiogram only, n=72). The randomization sequence was computer generated and stratified by centers with randomized blocks of 4 or 6 and permutation of treatments within each block.[2] Patients in the RDN group received a total average of 5.4±1.0 ultrasound emissions restricted to the main renal arteries in the majority of the cases; in addition, 9 patients with accessory renal arteries of at least 4 mm in diameter were also treated with 1.2±0.4 ablations in the accessories.[2] Two or more bilateral ultrasound emissions were performed in 71 (95.9%) patients; 1 patient received only unilateral treatment because of renal artery tortuosity; 2 patients received no RDN because of either renal artery tortuosity or generator failure.[2] There was no difference between groups in postprocedure pain and blinding indices.[2]

The randomization assignment was masked for 6 months after randomization for patients and for clinical and research staff responsible for follow-up. From randomization to 6 months, patients were seen at monthly outpatient visits scheduled at approximately 08:30 AM, prior to ingestion of their morning antihypertensive treatment, to (1) undergo seated office BP, heart rate, and laboratory assessments; (2) analyze their home BP results; and (3) record adverse events and concomitant medications. Seated office BP and home BP were measured with the same validated electronic device (Omron M10-IT, Kyoto, Japan) as previously described.[1,2] Serial ambulatory BP measurements were performed to assess initial eligibility at baseline after a 4-week discontinuation of all antihypertensive treatments and also at 2- and 6-months postrandomization as previously described (Microlife WatchBP, Taipei, Taiwan).[1,2] At 6 months, ambulatory BP measurements were obtained after witnessed pill ingestion in patients prescribed antihypertensive medications. The ambulatory BP measurement was repeated if the number of daytime BP measurements was <21. All ambulatory BP recordings were sent to a core laboratory (dabl Ltd, Dublin, Ireland), with treatment assignment masked. Noninvasive renal artery imaging by duplex ultrasound, renal computed tomography or magnetic resonance angiogram was performed at 2 and 6 months to detect renal artery stenosis, as previously described.[1,2]

Patients were to remain off antihypertensive medications throughout the initial 2 months of follow-up unless specified office or home BP criteria were exceeded (180/110 mm Hg or 170/105 mm Hg, respectively.[1,2] Of note, 5 patients in the RDN group and 13 in the sham group were started on antihypertensive medications prior to the 2-month visit by physicians blinded to the randomization.[2] From the 2nd to the 5th month after randomization, a specified and standardized stepped-care antihypertensive treatment (SSAHT)[7] with drug titration protocol was recommended in both randomized groups, consisting of the sequential addition of (1) a mid-dose of a long-lasting dihydropyridine calcium channel blocker (preferentially amlodipine 5 mg/d); (2) a standard dose of an angiotensin-converting enzyme inhibitor (preferentially lisinopril 20–40 mg/d or ramipril 10–20 mg/d) or an angiotensin receptor blocker (preferentially valsartan 160–320 mg/d or olmesartan 20–40 mg/d); and (3) a low dose of a thiazide diuretic (eg, hydrochlorothiazide 12.5 mg/d) followed by the sequential uptitration to a full dose of the thiazide diuretic (eg, hydrochlorothiazide 25 mg/d) and of the calcium channel blocker (eg, amlodipine 10 mg/d) if the average BP at home measured monthly was ≥135 mm Hg systolic, or ≥85 mm Hg diastolic (Figure I in the online-only Data Supplement). After the 6-month follow-up visit antihypertensive medications could be modified at physician's discretion after unblinding both patients and clinical staff.

Outcomes

The main efficacy end point was the baseline and covariate-adjusted change in daytime ambulatory SBP at 6 months. Other efficacy end points included baseline and covariate-adjusted change at 6 months in all other ambulatory, home, and office BP measurements and in ambulatory heart rate; the proportion of patients with a decrease in daytime ambulatory SBP from baseline to 6 months of at least 10, 15, or 20 mm Hg; and the proportion of patients with controlled BP at 6 months (defined as <135/85 mm Hg for daytime ambulatory and <130/80 mm Hg for 24-hour ambulatory BP); and change in eGFR at 6 months. Medication burden was also assessed from 2 to 6 months expressed as the number of antihypertensive medications prescribed, the sum of defined daily dose of each individual antihypertensive medication to assess and compare total drug consumption between the groups[8] and the antihypertensive load calculated percentage of the maximum dose of each drug

$$\left(\sum_{\text{antihypertensive medications}} \frac{(\text{prescribed daily dosage})}{(\text{maximum daily dosage})}\right).^{9}$$

Safety assessments were performed as previously reported.[1,2] All prespecified potential device or procedural and/or serious adverse events up to the 6-month visit reported by study sites were sent for independent adjudication as previously reported.[1,2] An independent data safety and monitoring board reviewed study data quarterly for all enrolled patients.

Statistical Analysis

The primary efficacy end point previously reported was the mean change in daytime ambulatory SBP from baseline to 2 months and the primary statistical analysis on this end point was performed on the intention-to-treat population (RDN, n=74 and sham, n=72).[2] This secondary end point analysis at 6-months was performed on the analysis population that included all patients with complete baseline and 6-month ABP (69 and 71 patients in the RDN and sham groups, respectively). Five of 74 patients allocated to the RDN group and 1 of 72 patients allocated to the sham group had a missing ambulatory BP measurement at 6 months (Figure II in the online-only Data Supplement). Hypothesis tests for these secondary end points will not be used to make labeling claims and reported *P* values are reported on nominal values not adjusted for multiple comparisons, as previously reported.[2]

Continuous variables are expressed as mean±SD, unless otherwise specified, and between-group differences are expressed as mean and corresponding 2-sided 95% CI. Comparisons between groups at baseline and 6 months were made using unpaired Student *t* tests for continuous variables and Fisher exact test for categorical variables. Bang and James blinding indices were calculated.[10,11] All analyses were

performed using statistical analysis system (SAS) software version 9.4 (SAS Institute, Cary, NC). A *P* value lower than 0.05 (2-sided) was considered significant.

Treatment effects (change in BP parameters, heart rate, or eGFR from baseline) were assessed using analysis of covariance with RDN versus sham as the main effect, including the baseline value as a covariate, and also including the number of antihypertensive medications at 6 months as a covariate. When the change in BP parameters, heart rate, or eGFR from baseline was not normally distributed, an adjusted analysis of covariance based on ranks was also performed. Treatment interactions were assessed using linear regression models adjusting for baseline daytime ambulatory SBP for subgroups prespecified in the statistical analysis plan (ethnicity, age, sex, baseline daytime ambulatory systolic BP, abdominal obesity, and presence of accessory renal arteries on renal angiogram). Abdominal obesity was defined as a waist circumference >102 cm for men and >88 cm for women. Repeated measures analyses of the change in ambulatory and home BP from baseline to 6 months were also performed as supportive analyses using linear mixed models adjusting for baseline values and including the number of antihypertensive medications at each visit as covariate. Additionally, the interaction between treatment arm and visit (categorical) were included as fixed effects; in these cases, *P* values were adjusted for multiple comparisons using the Tukey-Kramer test.

RESULTS

Study Population

Between March 28, 2016, and Dec 28, 2017, 803 patients with a history of hypertension were enrolled. One-hundred and seventy patients met both daytime ambulatory BP and noninvasive imaging criteria and thus underwent subsequent renal angiography; of them, 146 were randomized to RDN or sham procedure.[2] The analysis population included 69 patients in the RDN group and 71 in the sham group at 6 months (Figure II in the online-only Data Supplement). Baseline characteristics were similar across both study groups (Table 1) and did not differ from those of the original intention-to-treat population (including all patients irrespective of availability of 6 month ambulatory BP monitoring data).[2] At the time of initial enrollment, 28 patients (20.0%) were not receiving any antihypertensive medications, and 58 (41.4%) and 54 (38.6%) were receiving 1 or 2 or more medications, respectively (Table 1).

Burden of Medications

At completion of the 6-month ambulatory BP measurement, the overall proportion of patients receiving antihypertensive medications (45/69 [65.2%] versus 60/71 [84.5%], respectively, *P*=0.008), the proportion of patients on 1, 2, or at least 3 antihypertensive medications, and the total number of antihypertensive medications prescribed were lower in the RDN group than in the sham group (Table 2 and Figure 1). Medication burden at 6 months were both less in the RDN group than in the sham group (Table 2). Moreover, medication burden was significantly lower at 3, 4, and 5 months in the RDN group than in the sham group (Figure 1 and Table I in the online-only Data Supplement). Among patients on antihypertensive medications, 33/45 patients in the RDN group (73.3%), and 47/60 patients in the sham group (78.3%) were prescribed their medication according to the specified and standardized stepped-care antihypertensive treatment protocol (*P*=0.645). The class of antihypertensive drugs prescribed among patients receiving antihypertensive medications at 6 months was similar in the 2 groups (Table 2). Notably, there was no difference between groups in blinding indices at 6 months (data not shown).

Efficacy End Points

The overall decrease in daytime ambulatory SBP at 6 months was −18.1±12.2 mm Hg with RDN versus −15.6±13.2 mm Hg with sham (between-group difference adjusted for baseline value: −2.3 mm Hg; 95% CI, −6.0 to 1.5; between-group difference adjusted for baseline value and number of medications at 6 months: −4.3 mm Hg; 95% CI, −7.9 to −0.6 mm Hg; *P*=0.024; Table 3). The adjusted between-group differences, in changes in daytime ambulatory DBP and 24-hour and nighttime ambulatory SBP and DBP at 6 months, were consistent and all in favor of the RDN group (Table 3). In the linear mixed model including baseline and 2 and 6-month daytime ambulatory SBP, the overall between-group difference was −5.8 mm Hg, 95% CI, −8.6 to −3.0 mm Hg (treatment in the model including treatment×time interaction *P*<0.001, Table II in the online-only Data Supplement). The additional decrease in daytime ambulatory SBP from the 2nd to the 6th month was −9.3 mm Hg (95% CI, −12.4 to −6.1 mm Hg) in the RDN group versus −13.0 mm Hg (95% CI, −16.4 to −9.7 mm Hg) in the sham group (*P*=0.116), reflective of the greater use of medications during this phase of the trial. The consistency of the larger BP-lowering effect over the circadian cycle at both 2 and 6 months in the RDN group compared with the sham group is shown on the ambulatory BP profiles (Figure 2). Individual patient changes in daytime ambulatory SBP are shown according to treatment group in Figure III in the online-only Data Supplement. The proportion of patients with a decrease in daytime ambulatory SBP from baseline to 6 months of at least 10 mm Hg (78.0% versus 62.0%; *P*=0.036), 15 mm Hg (62.0% versus 45.0%; *P*=0.041), or 20 mm Hg (49.0% versus 34.0%; *P*=0.063), was larger in the RDN group than in the sham group, respectively (Figure IV in the online-only Data Supplement). BP control rate at 6 months was 56.5% as as-

Table 1. Baseline Demographic and Clinical Characteristics of the Analysis Population

Characteristic	Renal Denervation (n=69)	Sham Procedure (n=71)
Age (years)	54.1±10.2	53.8±10.1
Female sex	37.7% (26/69)	45.1% (32/71)
Race		
White	81.2% (56/69)	71.8% (51/71)
Black	15.9% (11/69)	18.3% (13/71)
Other	2.9% (2/69)	9.9% (7/71)
Body mass index, kg/m^2	29.9±5.9	29.0±5.0
Abdominal obesity*	57.4% (39/68)	60.6% (43/71)
eGFR, ml/min/1.73 m^2	84.2±15.7	82.9±16.1
eGFR <60 mL/min/1.73 m^2*	1.4% (1/69)	4.3% (3/70)
Diabetes mellitus		
Type 1	0	0
Type 2	2.9% (2/69)	7.0% (5/71)
Obstructive sleep apnea	8.7% (6/69)	11.3% (8/71)
Office SBP prior to antihypertensive medication washout (mm Hg)	142.8±14.8	144.7±16.0
Office DBP prior to antihypertensive medication washout (mm Hg)	92.4±9.8	93.6±8.4
Office heart rate prior to antihypertensive medication washout (bpm)	72.6±11.8	73.1±12.4
Number of antihypertensive medications at screening		
0†	17.4% (12/69)	22.5% (16/71)
1	43.5% (30/69)	39.4% (28/71)
2	37.7% (26/69)	36.6% (26/71)
3‡	1.4% (1/69)	1.4% (1/71)
Types of medication at screening within patients on medications		
Renin angiotensin system blockers	70.2% (40/57)	72.7% (40/55)
Angiotensin-converting enzyme inhibitor	47.4% (27/57)	50.9% (28/55)
Angiotensin receptor blocker	21.1% (12/57)	21.8% (12/55)
Direct renin inhibitor	1.8% (1/57)	0% (0/55)
Calcium channel blocker	35.1% (20/57)	38.2% (21/55)
Diuretic	14.0% (8/57)	9.1% (5/55)
β Blocker	7.0% (4/57)	12.7% (7/55)
α-1 receptor blocker	5.3% (3/57)	1.8% (1/55)
Spironolactone	0% (0/57)	1.8% (1/55)

Data displayed as percentage (n/N) and mean±SD. There were no significant differences between the two groups in baseline characteristics. bpm indicates beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and SBP, systolic blood pressure.

*Abdominal obesity status not available in 1 patient in the renal denervation group. eGFR data unavailable in 1 patient in the sham group.

†Nine patients were drug naïve in the renal denervation and sham groups (3 and 6, respectively), and 19 were drug intolerant or had chosen not to take antihypertensive medications (9 and 10, respectively).

‡Two patients were discovered to have been on 3 antihypertensive medications at screening.

sessed for daytime, and 58.0% for 24-hour ambulatory BP in the RDN group compared with 43.7% for daytime (*P*=0.128), and 42.3% for 24-hour ambulatory BP (*P*=0.063) in the sham group (Table III in the online-only Data Supplement).

The decrease in home SBP from baseline to 2, 3, 4, 5, and 6 months is shown in Figure 3 and was greater in the RDN group than in the sham group (overall between-group difference −6.9 mm Hg; 95% CI, −9.6 to −4.1 mm Hg; *P*<0.001 for treatment in the model including treatment×time interaction; Table IV in the online-only Data Supplement). The changes in home and office SBP and DBP at 6 months are shown in Table 3. The overall between-group difference in office SBP from baseline to 6 months including all visits was −4.5 mm Hg (95% CI, −7.9 to −1.1 mm Hg; *P*=0.010 for treatment in the model including×time interaction; Table V in the online-only Data Supplement). There was no within-group or between-group difference in office or ambulatory heart rate (Table VI in the online-only Data Supplement) or in body weight at 6 months (not shown).

The effect of RDN on the main efficacy end point was consistent across several prespecified subgroups, with the exception of the subgroup of patients aged <55 years where a greater treatment effect was observed (*P* for interaction=0.0233, Figure V in the online-only Data Supplement). In patients aged <55 years there was a large between group difference in daytime ambulatory SBP adjusted for baseline value and medications in favor of RDN (−7.0 mm Hg; 95% CI, −12.0 to −2.0; *P*=0.007) with a lower number of medications prescribed at 6 months (RDN: 0.9±0.9 versus sham: 1.2±0.9; *P*=0.043). In contrast, among patients aged ≥55 years, there were no differences in daytime ambulatory SBP (between group difference in daytime ambulatory SBP adjusted for baseline value and medications: 1.8 mm Hg; 95% CI, −3.8 to 7.3 mm Hg; *P*=0.533), perhaps because of the prescription of a greater number of antihypertensive drugs in the sham group (RDN: 1.0±0.9 versus sham: 1.4±0.9, respectively; *P*=0.031).

Safety Outcomes

There were no major adverse events in either group at 6 months (Table VII in the online-only Data Supplement). Six-month imaging was available in 72 RDN patients and 68 sham patients. At 6 months, 1 patient in the RDN group, who had a mild progression of a preexisting ostial renal artery stenosis (which would have met criteria for exclusion but was not recognized at the time of randomization), underwent renal artery stent placement as previously reported. This stenosis was not located at the site of a prior ultrasound emission.[2] No new renal artery stenosis >70% was detected on noninvasive renal artery imaging in either group at 6 months or in the 38 patients of the RDN arm who underwent the protocol-required computed tomography or magnetic resonance angiography of the renal arteries at 12 months. Finally, a small and similar increase

Table 2. Number and Type of Antihypertensive Medications, Defined Daily Dose and Antihypertensive Medication Load at 6 Months in the Analysis Population

Characteristic	Renal Denervation (n=69)	Sham Procedure (n=71)	*P* Value
Total number of antihypertensive medications at 6 mo			
Median (interquartile range)	1.0 [0.0, 1.0]	1.0 [1.0, 2.0]	0.010*
Mean (range)	0.9 (0.0, 3.0)	1.3 (0.0, 4.0)	
Number of antihypertensive medications at 6 mo, % (n/N)			
0	34.8% (24/69)	15.5% (11/71)	0.055† 0.008‡
1	42.0% (29/69)	47.9% (34/71)	
2	17.4% (12/69)	26.8% (19/71)	
3 or more	5.8% (4/69)	9.9% (7/71)	
Types of medication at 6 mo within patients on medications, % (n/N)			
Calcium channel blocker§	73.3% (33/45)	83.3% (50/60)	0.234†
Renin angiotensin system blockers	51.1% (23/45)	46.7% (28/60)	0.696†
Angiotensin-converting enzyme inhibitor	28.9% (13/45)	21.7% (13/60)	0.494†
Angiotensin receptor blocker	22.2% (10/45)	25.0% (15/60)	0.819†
Diuretic	20.0% (9/45)	20.0% (12/60)	1†
β Blocker‖	0% (0/45)	1.7% (1/60)	1†
Aldosterone antagonist‖	0% (0/45)	5.0% (3/60)	0.258†
Medication dose burden			
Defined daily dose, mean±SD	1.4±1.5	2.0±1.8	0.018*
Antihypertensive medication load index, mean±SD	0.5±0.5	0.7±0.6	0.014*

Medication dose burden at 6 mo expressed as the sum of defined daily dose of each individual antihypertensive medication.[8] The antihypertensive medication load index calculated percentage of the maximum dose of each drug

$$\left(\sum_{\text{antihypertensive medications}} \frac{(\text{prescribed daily dosage})}{(\text{maximum daily dosage})}\right).^{9}$$

**P* value from Wilcoxon test comparing the renal denervation group to the sham group.

†Fisher exact test.

‡Chi-squared test comparing no medications to medications between groups.

§Even though a calcium channel blocker was recommended as first-line therapy in the protocol, physicians prescribed another first-line antihypertensive treatment using other agents included in the protocol, including a renin angiotensin system blocker (angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker), a thiazide diuretic, or in one case, an aldosterone antagonist (outside of the protocol) in 12 patients in the renal denervation group and 10 patients in the sham group.

‖A β blocker or an aldosterone antagonist was prescribed on physician decision outside of the recommended protocol.

in eGFR was observed in both the RDN group and the sham group at 6 months (Table VIII in the online-only Data Supplement).

DISCUSSION

Among patients with combined systolic-diastolic hypertension included in the RADIANCE-HTN SOLO trial, we show that the BP-lowering effect of endovascular ultrasound RDN demonstrated at 2 months while patients were off antihypertensive medications[2] was maintained throughout the 6-month follow-up, not only after initiation of the recommended SSAHT but also in the setting of more antihypertensive medications and at higher doses in the sham group. The decrease in home BP was also consistently greater at 2, 3, 4, and 5 months in the RDN group than in the sham group, leading physicians—who were kept blinded to randomization assignment up to 6 months—to initiate later, and to add and to subsequently uptitrate oral antihypertensive medications less frequently in the RDN group than in the sham group as suggested by the drug titration protocol. Consequently, the proportion of patients receiving antihypertensive medications at 6 months was smaller in the RDN group (65.2%) than in the sham group (84.5%). In addition, among patients treated with antihypertensive medications, a greater proportion received drug monotherapy in the RDN group (29/45, 64.4%), mainly a long acting calcium channel blocker, than in the sham group (34/60, 56.7%). The more rapid BP control and the lower medication burden over the 6 months led to a numerically greater daytime and 24-hour ambulatory BP control rate in the RDN group (56.5% and 58.0%, respectively) than in the sham group (43.7% and 42.3%) at 6 months. Furthermore, the BP-lowering ef-

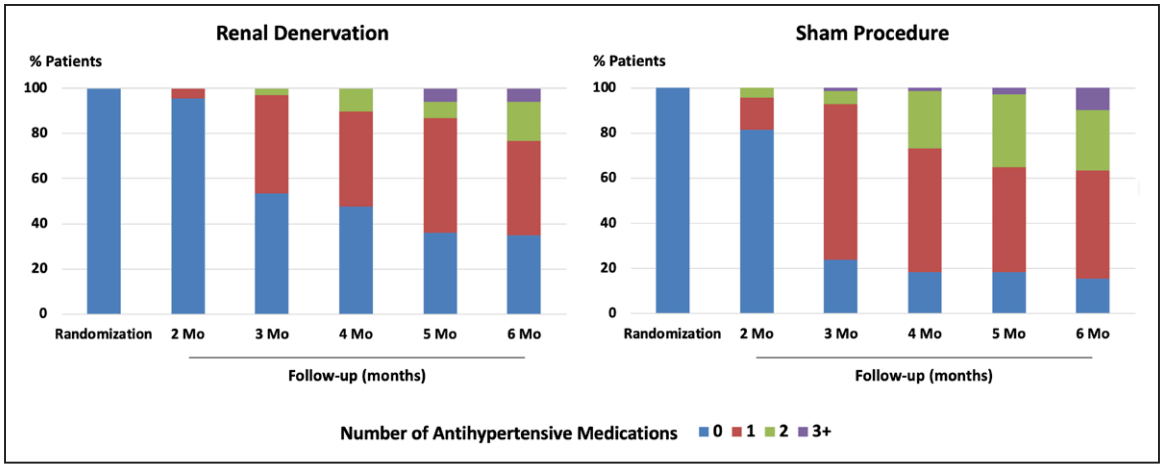

Figure 1. Percentage of patients on 0, 1, 2, or ≥3 antihypertensive medications at each monthly visit from randomization to 6 months in the renal denervation group (n=69, left) and the sham procedure group (n=71, right) in the analysis population.

fect in favor of RDN+SSAHT was consistent for daytime, 24-hour, and nighttime ambulatory systolic/diastolic BP (between-group adjusted difference of ≈4.0–5.0/2.0–3.0 mm Hg), as well as for home systolic BP (between-group adjusted difference of ≈4.5 mm Hg).

Despite the potential confounding effect of the drug titration protocol prescribed to both the RDN and the sham groups, our results confirm the sustained durability of the BP-lowering effect of ultrasound-based RDN at 6 months. According to international guidelines[12,13] and with the approval of health authorities and ethics committees, we favored safety of the participants during the trial by (1) restricting the duration of patients being off medications to 2 months, (2) recommending a drug titration protocol in both groups from the 2nd months onwards, and (3) using home rather than office BP to adjust the SSAHT, with the same treatment algorithm used for both study groups. However, a potential drawback of this study design could have been to reduce the BP difference between the 2 groups at 6 months. We observed a larger SSAHT-induced decrease in daytime ambulatory SBP in the sham group from 2 to 6 months (–13.0 mm Hg) than in the RDN group (–9.3 mm Hg, *P*=0.116), attributable to both the earlier initiation and use of more antihypertensive medications and at higher doses, and the higher BP at 2 months in the sham group (Figure 2). Despite this potential pitfall, the proportion of patients with at least 10, 15, and 20 mm Hg decrease in daytime ambulatory SBP at 6 months was much greater in the RDN group, even though the proportion of patients on 1, 2, or at least 3 antihypertensive medications, the defined daily dose, and the antihypertensive load index was lower in the RDN group than in the sham group, respectively. There was no significant increase in adverse effects with RDN as compared to the sham procedure. Together, the 2- and 6-month data demonstrate the safety and efficacy of endovascular RDN both in the absence (2-month) and presence (6-month) of background antihypertensive medications. These data suggest that in patients with uncontrolled systolic-diastolic blood pressure, endovascular ultrasound RDN may be an alternative to uptitrating antihypertensive medication without increasing the risk of side effects to pharmacological therapy.

A nominally larger decrease in office BP at 6 months was observed in the RDN group compared with the sham group that was consistent with the difference in the ambulatory BP changes. This is in contrast with the 2-month results where the difference between the RDN and the sham groups was of the same magnitude for both office and daytime ambulatory BP.[2] This is explained by (1) the smaller difference in office BP between the 2 groups at 6 months (–3.7 mm Hg) than at 2 months (–6.5 mm Hg),[2] attributable to the SSHAT prescribed from the 2nd month onwards especially in the sham group; and (2) the larger between-patient variability in office BP than ambulatory BP measurements, despite the precautions taken to decrease it. This emphasizes the importance of using ambulatory BP monitoring that provides more stable and reproducible BP values than office measurements to assess the BP-lowering effect of RDN, especially when antihypertensive medications are used concomitantly.[14,15]

Comprehensive examination of the 24-hour ambulatory BP profiles highlights consistently lower BP with RDN than with the sham procedure throughout the circadian cycle when patients were off medications at 2 months, this effect being amplified at 6 months despite the RDN group receiving fewer and lower doses of antihypertensive medications than the sham group (Figures 2 and 3). If maintained over the long-term, a greater reduction in both daytime and nighttime ambulatory BP may occur when combining antihypertensive medications with RDN and may favorably impact cardiovascular risk.[16,17] The immediate clinically meaningful benefit of RDN would be to minimize the potential negative consequences of episodic, temporary gaps in dosing, which may occur in ambulatory patients by prolonging the BP-

Table 3. Efficacy Endpoints: Change in Ambulatory, Office, and Home Blood Pressure at 6 Months Following Renal Denervation or Sham Procedure (Analysis Population)

	Renal Denervation			Sham Procedure			Mean Between-Group Difference Adjusted for Baseline Value (95% CI)	*P* Value*	Mean Between-Group Difference Adjusted for Baseline Value and Number of Antihypertensive Medications at 6 mo (95% CI)	*P* Value†
	Randomization	6 mo	Difference	Randomization	6 mo	Difference				
Daytime ABP (mm Hg)	(n=69)	(n=69)	(n=69)	(n=71)	(n=71)	(n=71)				
SBP	150.2±7.9	132.2±12.1	−18.1±12.2	149.9±9.8	134.3±11.2	−15.6±13.2	−2.3 (−6.0, 1.5)	0.242	−4.3 (−7.9, −0.6)	0.024
DBP	93.0±4.6	82.3±7.5	−10.7±7.8	93.4±5.4	83.7±7.9	−9.7±8.1	−1.3 (−3.7, 1.2)	0.321	−2.8 (−5.1, −0.5)	0.018
24-hour ABP (mm Hg)	(n=69)	(n=69)	(n=69)	(n=71)	(n=71)	(n=71)				
SBP	142.4±8.2	126.0±11.2	−16.5±11.8	143.7±10.4	128.8±10.6	−14.9±12.8	−2.4 (−6.0, 1.1)	0.178 (0.108‡)	−4.3 (−7.7, −1.0)	0.012 (0.007‡)
DBP	87.3±4.9	77.6±7.0	−9.7±7.3	88.5±5.7	79.2±7.4	−9.4±7.8	−1.0 (−3.3, 1.3)	0.383 (0.251‡)	−2.6 (−4.6, −0.5)	0.017 (0.010‡)
Nighttime ABP (mm Hg)	(n=69)	(n=69)	(n=69)	(n=70)	(n=70)	(n=70)				
SBP	130.0±12.0	116.1±12.0	−13.9±13.6	132.5±13.7	119.7±12.1	−12.8±13.5	−2.7 (−6.4, 1.0)	0.157	−4.7 (−8.2, −1.2)	0.009
DBP	78.1±8.1	70.2±8.1	−7.9±9.1	80.0±8.2	71.7±8.0	−8.3±8.7	−0.8 (−3.3, 1.7)	0.534	−2.4 (−4.7, −0.1)	0.042
Office BP (mm Hg)	(n=69)	(n=69)	(n=69)	(n=71)	(n=71)	(n=71)				
SBP	154.7±12.8	136.4±14.1	−18.2±14.2	153.5±15.8	137.6±15.1	−15.9±17.2	−1.6 (−6.1, 2.8)	0.471	−3.7 (−8.1, 0.7)	0.102
DBP	99.7±7.9	89.6±9.8	−10.1±9.6	99.2±9.5	89.6±9.1	−9.5±10.1	−0.3 (−3.2, 2.6)	0.847	−1.7 (−4.5, 1.1)	0.228
Home BP (mm Hg) §	(n=66)	(n=66)	(n=66)	(n=69)	(n=69)	(n=69)				
SBP	147.3±8.8	130.8±11.4	−16.5±12.3	147.4±12.1	133.9±10.3	−13.5±12.2	−3.0 (−6.5, 0.4)	0.086 (0.030‡)	−4.5 (−8.1, −1.0)	0.012 (0.003‡)
DBP	94.8±7.1	85.1±6.7	−9.8±7.8	94.7±7.1	85.5±7.0	−9.1±7.1	−0.5 (−2.7, 1.6)	0.613	−1.8 (−3.9, 0.3)	0.091

Data are displayed as mean±SD unless otherwise noted. ABP indicates ambulatory blood pressure; BP, blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

**P* value by analysis of covariance, adjusting for baseline value.

†*P* value by analysis of covariance, adjusting for baseline value and number of antihypertensive medications at 6 months.

‡*P* value by adjusted analysis of covariance on the ranks.

§Three out of 69 patients in the renal denervation group and 2/71 patients in the sham group had missing 6-month home BP measurements. For months 2 to 5, if a patient was missing home BP, medications were titrated based on their office BP value using a seated office BP threshold of 140/90 mm Hg instead of the 135/85 mm Hg home BP threshold.

lowering efficacy of once-daily administration of antihypertensive medications. This may occur especially in the early morning when plasma drug concentrations are at their lowest.[18] The maintenance of the BP-lowering effect of RDN would thus theoretically limit the negative consequences of partial and even full nonadherence on clinical outcomes in hypertensive patients.[19]

Similar to previous reports,[4,20,21] we observed large between-patient variability in the daytime ambulatory SBP response in both the RDN and the sham groups at 6 months. Such large variability was already present at 2 months when patients were off medications; it was possibly explained by variability in the completeness of renal nerve ablation especially in the presence of accessory arteries, and in the prevailing renal sympathetic nerve activity in the RDN group.[22,23] The large variability observed at 6 months may have been driven by the variable response to the SSAHT added from the 2nd month

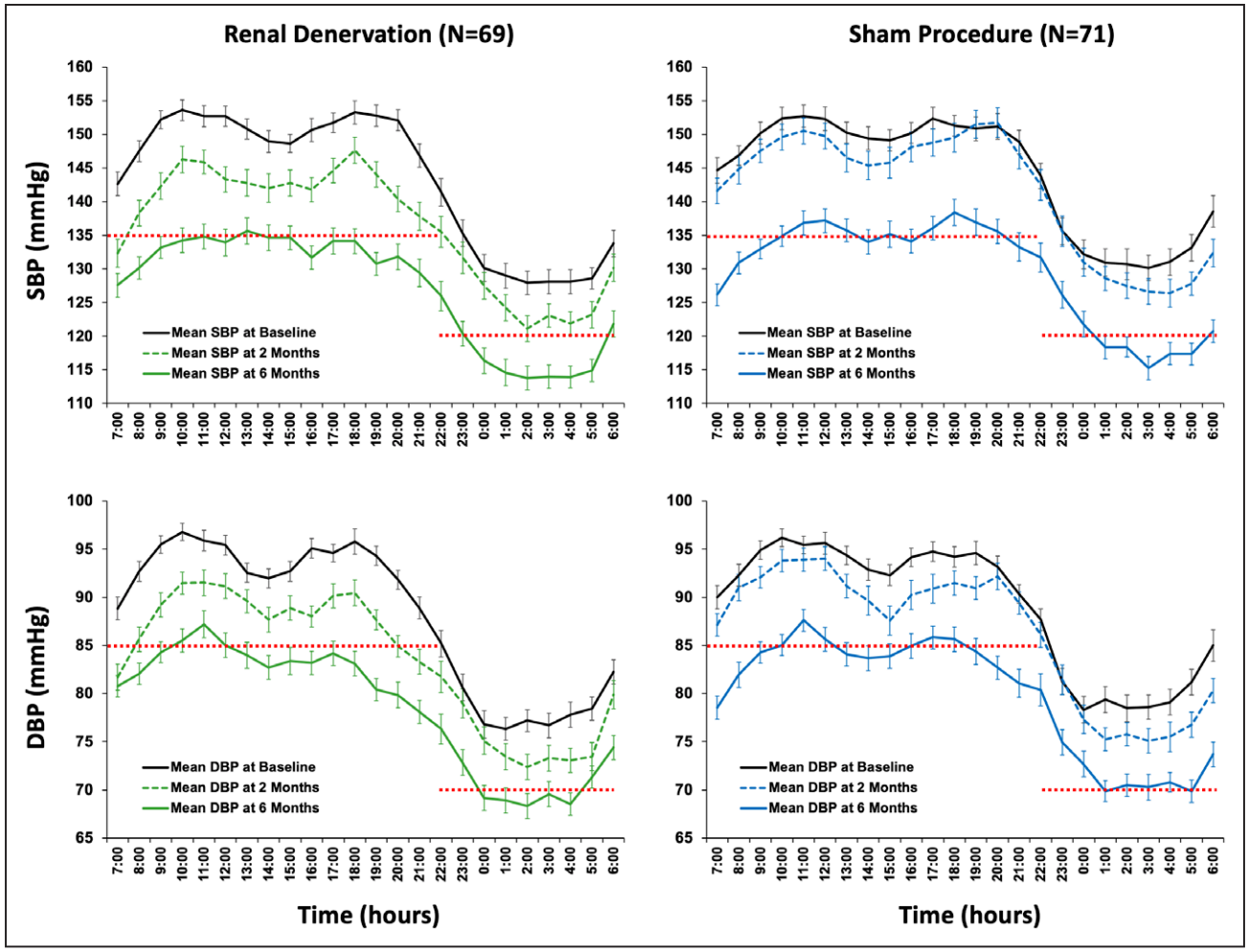

Figure 2. Twenty-four–hour ambulatory profiles at baseline, 2, and 6 months in the renal denervation group (left) and the sham group (right) in the analysis population.

Systolic blood pressure (SBP) is shown on the **top** and diastolic blood pressure (DBP) on the **bottom**; error bars represent SE. Red dotted lines show the upper limit of normal daytime and nighttime systolic (135 and 120 mm Hg, respectively; **top**) and diastolic blood pressure (85 and 70 mm Hg, respectively; **bottom**).

onward. Alternatively, we cannot exclude variability in adherence to the SSAHT, since we did not measure drug levels in patients' plasma or urine; however, both patients and study physicians were kept blind to the randomization up to 6 months, patients did not predict the randomization code up to 6 months follow-up, and ambulatory BP measurements were obtained after witnessed pill ingestion.

We also looked to predictors of the ambulatory BP response to RDN+SSAHT in the multiple linear regression analysis. Younger age (<55 years) was the main independent contributor to the BP response to RDN+SSAHT at 6 months, but not sex, ethnicity, obesity, or baseline ambulatory BP. Although patients in the RDN group had amplified reductions in daytime ambulatory SBP at 6 months regardless of age, we observed a larger than expected daytime ambulatory SBP reduction in patients aged >55 years in the sham group because of the prescription of more antihypertensive drugs than in the RDN group (1.4±0.9 versus 1.0±0.9, respectively; P=0.031). However, patients aged <55 years benefited the most from the RDN procedure since they displayed the largest between-group differences in ambulatory SBP in favor of RDN (≈7.0 mm Hg) with prescription of similar number of medications at 6 months (0.9±0.9). We previously observed a similar tendency toward a greater BP response to RDN in younger patients while off medications at 2 months, but it did not reach statistical significance.[2] A larger response to RDN in younger patients has been reported in different trials.[24,25] This observation is also consistent with the larger BP response to RDN in patients of the DENERHTN trial (Renal Denervation for Resistant Hypertension) in younger patients with less vascular remodeling,[26] and may reflect the predominant contribution of the renal sympathetic drive to the pathophysiology of hypertension in younger patients, consistent with the results of renal norepinephrine spillover experiments.[27] Finally, the number of ultrasound emissions was not a predictor of the BP response to RDN at 2 months, as previously reported.[2,22]

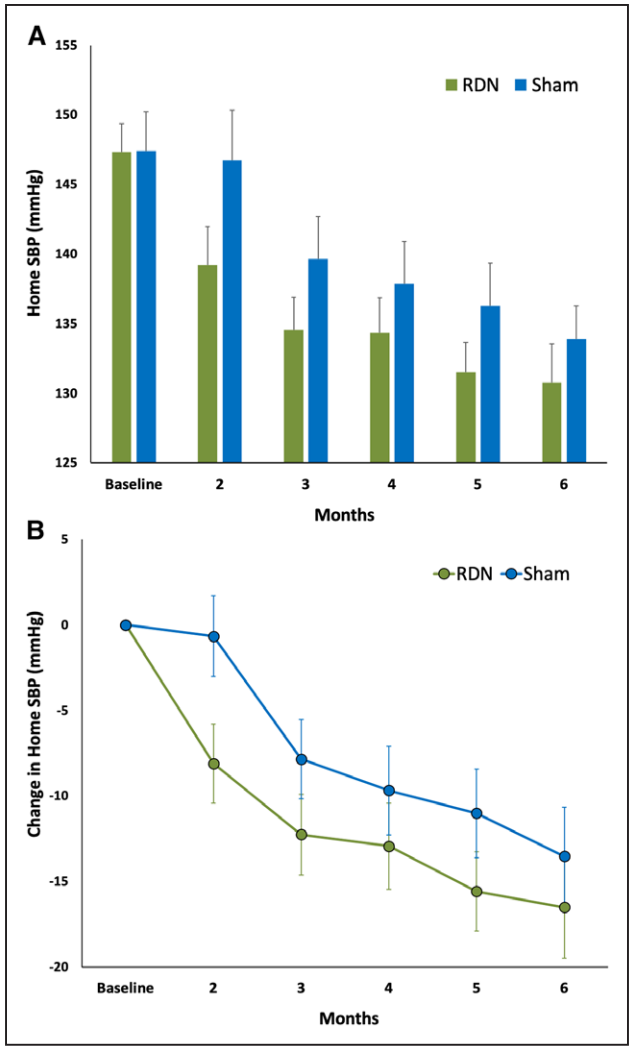

Figure 3. Home systolic blood pressure (SBP) values (top) and changes from baseline to 2, 3, 4, 5, and 6 months (bottom) in the renal denervation (RDN) group (green bars and dots) and the sham group (blue bars and dots) on evaluable patients.

For the change in home SBP, mean values and 95% CI are presented. The decrease in home SBP was significantly larger in the renal denervation group than in the sham group (overall between-group difference −6.9 mm Hg; 95% CI, −9.6 to −4.1 mm Hg; $P<0.001$ for the treatment×time interaction by linear mixed model).

Our BP results at 6 months with the majority of our patients being on medications are consistent with the results of a meta-analysis, including all sham-controlled trials, showing that RDN was associated with a significant decrease in daytime ambulatory SBP (weighted mean difference of −4.07 mm Hg; 95% CI, −6.46 to −1.68; $P<0.001$) compared with sham.[28] Nevertheless, our results expand those of the SPYRAL OFF- (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypentensive Medications) and ON-med (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy) studies,[4,21] since we used a different study design and ultrasound-based rather than radiofrequency-based renal nerve ablation. Moreover, endovascular ultrasound-based RDN in the main renal artery was found to decrease ambulatory BP to a greater extent than radiofrequency-based ablation of the main renal arteries and similarly to a combined radiofrequency ablation of the main arteries, accessories and side branches.[29]

Our study has limitations, some of which have been discussed previously.[2] These include (1) the short-intermediate duration of follow-up to establish the efficacy and safety of RDN; (2) the absence of a periprocedural marker for successful renal nerve ablation, common to all methods of RDN; (3) the small sample size of the study that cannot exclude rare adverse events; and (4) the limited applicability of our results to other RDN catheters, which may achieve different degrees of renal nerve ablation.[29] Longer-term follow-up of the treatment effect and safety is planned up to 3 years from within this trial cohort.

CONCLUSIONS

In the strictly controlled conditions of the RADIANCE-HTN SOLO trial, we showed that in patients with combined systolic and diastolic hypertension, although the majority of patients needed the addition of the SSAHT in order to improve BP control, fewer medications were administered in the RDN group, and the BP-lowering effect of endovascular ultrasound RDN was maintained at 6 months without adverse safety signals.

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